

Provisional Translation (as of April 2010) *

PFSB/ELD (*Yakushoku-shinsa*) Notification No. 0330006

PFSB/CND (*Yakushoku-kanma*) Notification No. 0330005

March 30, 2005

To: Directors of Health Departments (Bureaus),
Prefectural Governments

From: Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Director of Compliance and Narcotics Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Re: Handling of Applications for GMP Inspections

The Good Manufacturing Practice (hereinafter referred to as "GMP") for drugs, quasi-drugs, and medical devices in accordance with the Pharmaceutical Affairs Law (Law No.145 of 1960) as amended by the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Control Law (Law No.96 of 2002; hereinafter referred to as "partially revised Law") has been notified to prefectural governors under PFSB (*Yakushoku*) Notification No.0330008 by the Director-General of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 30, 2005, "Establishment and Revision/Abolishment of Ministerial Ordinance and Ministerial Notification on the Good Manufacturing Practice and Quality Management System (GMP/QMS) of Drugs, Medical Devices, etc., Pursuant to the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Control Law." The Ministry of Health, Labour and Welfare (MHLW) has made its decision to handle applications for GMP inspections as described below. You are requested to fully notify relevant business

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

parties and organizations under your jurisdiction of the information below, and to provide them with your appropriate guidance to ensure the smooth handling of such applications.

Please note that copies of this Notification will be sent to the heads of the organizations shown in Appendix.

1. Application for GMP Inspection to Obtain Marketing Approval or Approval for Partial Changes in Approved Information, or to Manufacture Drugs for Export etc.

(1) When an applicant applies for a GMP inspection to obtain marketing approval or approval to make partial changes to the approved information (hereinafter referred to as “partial change approval”) for a drug (excluding drugs that are drug substances), quasi-drug, or medical device (hereinafter referred to as “drugs etc.”), or to manufacture drugs for export etc., the applicant shall, in principle, submit an application for a GMP inspection for each relevant product. As a rule, the application for a GMP inspection must be submitted to an inspection entity that will conduct the GMP inspection (hereinafter referred to as “competent inspection authority”) for all manufacturing sites and other relevant sites indicated in the product approval application (including manufacturing sites of drug substances, manufacturing sites for packaging, external testing laboratories, and organizations that perform design and development control [hereinafter referred to as “design and development control”]); the same shall apply hereinafter).

(2) When an applicant applies for GMP inspections for multiple products that are manufactured using the same drug substance (refers to that manufactured at the same manufacturing site, by the same manufacturing method, manufacturing process, or manufacturing facility, or according to the same specification, etc.; the same shall apply hereinafter), a single application for a GMP inspection may cover all the multiple products, provided that the GMP inspection is performed only for the manufacturing site of the drug substance. In this case, make a note on the application form to the effect that the application is made for an inspection in relation to multiple products, and list all the applicable products.

The inspection fee for multiple products is the same as that for a single product.

(3) If sterilization of multiple products is only performed at a single manufacturing site, then a single application for a GMP inspection may cover all the multiple products

sterilized at the manufacturing site. In this case, make a note on the application form to the effect that the application is made for an inspection in relation to multiple products, and list all the applicable products.

The inspection fee for the group of multiple products is the same as that for a single product.

- (4) If tests and inspections on multiple products are performed by a single testing laboratory, then a single application for a GMP inspection may cover all the multiple products tested and inspected at its facility. In this case, make a note on the application form to the effect that the application is made for an inspection in relation to multiple products, and list all the applicable products.

The inspection fee for the group of multiple products is the same as that for a single product.

- (5) If design and development control of multiple products are performed by a single design and development control organization, then a single application for a GMP inspection may cover all the multiple products of which design and development control are performed at its facility. In this case, make a note on the application form to the effect that the application is made for an inspection in relation to multiple products, and list all the applicable products.

The inspection fee for the group of multiple products is the same as that for a single product.

- (6) If multiple medical device applications are filed for actually a single product with different names (the contents of the medical device applications are the same, except that the brand name differs; the same shall apply hereinafter), or multiple medical devices are of the same generic name (refers to the names of specially controlled medical devices, controlled medical devices, and general medical devices that are designated by MHLW pursuant to Article 2, Paragraphs 5 through 7 of the Pharmaceutical Affairs Law [MHLW Ministerial Notification No. 298 of 2004]; the same shall apply hereinafter), the group of the multiple products may be covered by a single application for a GMP inspection. In this case, make a note on the application form to the effect that the application is made for an inspection in relation to multiple products, and list all the applicable products.

The inspection fee for the group of multiple products is the same as that for a single product.

- (7) The drug substance manufacturing site that holds the license for manufacturing or importing/distributing under the Pharmaceutical Affairs Law prior to the amendment by the partially revised Law is deemed to be a licensed manufacturer under the revised Pharmaceutical Affairs Law as of April 1, 2005. The manufacturing site is not subject to GMP inspections for products that are manufactured using the drug substance until the manufacturing site is notified of the results of a routine GMP inspection required for renewal of the license for manufacturing or importing/distributing. In this case, each copy of the license for manufacturing and the license to add products for the drug substance manufacturing site must be attached to the GMP inspection application form for each product that is manufactured using the drug substance. The foregoing shall not apply, however, if any problem is found in the methods of manufacturing control or quality control at the manufacturing site.
- (8) If an applicant has not obtained the license for manufacturing of a drug substance that is used for manufacturing drugs etc. on or before March 31, 2005, the provisions under (7) shall apply to the manufacturing site of the drug substance until the applicant receives the copy of the GMP Inspection Result Notification for the drug substance. In this case, a copy of the document (e.g., the relevant part of the product master formula) demonstrating that the drug substance was used for manufacturing drugs etc. must be attached to the GMP inspection application form for the product that is manufactured using the drug substance. In addition, an application for a GMP inspection of the manufacturer of the drug substance shall be made promptly.
- (9) A GMP inspection for a manufacturer of a drug substance of the product for review is not necessary when the GMP compliance of the manufacturer of the same drug substance has already been confirmed by an inspection conducted at the request of another marketing authorization holder, and if each copy of the GMP Inspection Result Notification for the same drug substance and a document proving the equivalence of the two drug substances is submitted to the competent inspection authority and competent approval authority (refers to the competent approval authority as stipulated in Article 23 of the Ordinance for Enforcement of the Pharmaceutical Affairs Law [Ministry of Health and Welfare Ministerial Ordinance No. 11 of 1961]; however, the Pharmaceuticals and Medical Devices Agency, for products that must be approved by the Minister; the same shall apply hereinafter). In this case, each copy of the submitted application form for the GMP inspection, the GMP Inspection Result Notification for

the drug substance, and the document proving the equivalence of the two drug substances should be submitted to the competent approval authority without delay after submission of the application.

In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the said application date is acceptable.

- (10) A GMP inspection is not necessary for a manufacturing site that only performs sterilization of the product as part of the manufacturing process when the GMP compliance of the manufacturing site has already been confirmed by an inspection conducted at the request of another marketing authorization holder and if a copy of the GMP Inspection Result Notification accompanies the application form. In this case, a copy of the submitted application form for the GMP inspection should be submitted to the competent approval authority without delay after submission of the application.

In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the said application date is acceptable.

- (11) A GMP inspection is not necessary for a manufacturing site when the GMP compliance of the same product as the one manufactured at the site (refers to those manufactured at the same manufacturing site, by the same manufacturing method, manufacturing process, or manufacturing facility, or according to the same specification, etc.; the same shall apply hereinafter) has already been confirmed by an inspection conducted at the request of another marketing authorization holder, and if each copy of the GMP Inspection Result Notification for the same product and a document proving the equivalence of the two products is submitted to the competent inspection authority and approval authority. In this case, also submit these copies to the competent approval authority without delay.

In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be

attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the said application date is acceptable.

(12) An application for the GMP inspection is not necessary for a manufacturing site when another marketing authorization holder has already submitted an application for the GMP inspection in relation to the same product as the one manufactured at the site, and if each copy of the GMP Inspection Result Notification and a document proving the equivalence of the two products is submitted to the competent approval authority. In this case, also submit these copies to the competent approval authority without delay.

(13) A GMP inspection is not necessary for a testing laboratory to which the tests and inspections concerning the relevant product have been outsourced when the GMP compliance of the laboratory has already been confirmed by an inspection conducted at the request of another marketing authorization holder or manufacturer of drugs etc. for export, and if a copy of the GMP Inspection Result Notification accompanies the application form.

In this case, submit to the competent approval authority each copy of the submitted application form for the GMP inspection and the GMP Inspection Result Notification for the testing laboratory without delay after submission of the application.

In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the same application date is acceptable.

(14) A GMP inspection is not necessary for a design and development control organization to which the design and development control concerning the relevant product have been outsourced when the GMP compliance of the organization has already been confirmed by an inspection conducted at the request of another marketing authorization holder or manufacturer of drugs etc. for export, and if a copy of the GMP Inspection Result Notification accompanies the application form. In this case, submit to the competent approval authority each copy of the submitted application form for GMP inspection and the GMP Inspection Result Notification for the design and development control

organization without delay after submission of the application.

In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the said application date is acceptable.

- (15) Drug substances that are used to manufacture over-the-counter drugs (excluding those approved as new drugs as stipulated in Article 14-4, Paragraph 1, Item (1) of the Law) are not subject to a GMP inspection.
- (16) Drug substances that are used to manufacture quasi-drugs are not subject to a GMP inspection.
- (17) If accessories or components, etc. (limited to those subject to GMP requirements) used to manufacture medical devices have been confirmed to comply with GMP through a GMP inspection for other products, such as a medical device using the same component, they are not subject to another GMP inspection.
- (18) Drug substances that are used to manufacture *in-vitro* diagnostics are not subject to a GMP inspection.
- (19) When a marketing authorization holder intends to submit a partial change application, and if the partial change constitutes an addition, change, or deletion of dosage and administration, or indications that do not affect the methods of manufacturing control or quality control, a GMP inspection is not necessary. However, if the partial change affects the methods of manufacturing control or quality control of the product, the manufacturing sites that are listed in the Marketing Approval Document and that may be affected by the change shall undergo the inspection.

2. Application for Routine GMP Inspection

- (1) An application for a GMP inspection that is conducted once every five years after granting marketing approval or every five years after the commencement of manufacture of drugs etc. for export (hereinafter referred to as “routine GMP inspection”) shall be submitted for each manufacturing site where approved products or

products for export are manufactured. Notwithstanding the foregoing, testing laboratories or design and development control organizations are not subject to routine GMP inspections. In addition, drug substance manufacturing sites etc. are not subject to routine GMP inspections, unless a routine GMP inspection is conducted to meet the requirements under (4) below.

- (2) Regarding the fee for a routine GMP inspection conducted by the Pharmaceuticals and Medical Devices Agency, the basic unit price shall be based on the highest fee category applicable to the facility and the product unit surcharge shall be given by multiplying the unit price for each category by the number of the products classified into the category. The fee categories are defined in the following order from the highest to lowest fee category: biological products category, sterile drugs and sterile medical devices category, over-the-counter drugs and medical devices category, and packaging manufacturing site category.
- (3) In the case of a medical device for which multiple product applications are filed under different names or multiple medical devices with the same generic name, a single application for a GMP inspection submitted by treating the group of multiple products as a single product.
- (4) When an application is submitted for renewal of the license for a drug substance manufacturing site, attach to the application form copies of the most recent GMP Inspection Result Notifications for all the drug substances that are used for the manufacture of the prescription drugs manufactured at the manufacturing site.
In this case, the copy of the GMP Inspection Result Notification issued not more than two years prior to the date of application for the inspection must, in principle, be attached to the application form. If the copy of the GMP Inspection Result Report issued not more than two years after the date of the inspection is also attached, however, the copy of the GMP Inspection Result Notification issued not more than five years prior to the said application date is acceptable.
- (5) When an application is submitted for a routine GMP inspection of foreign manufacturing sites for a product of which only packaging, labeling, or storage is conducted in Japan, a single application may cover multiple foreign manufacturing sites for the product. In this case, the application shall be filed for manufacturing sites for packaging etc. where the decision is made on whether to release the product. In this

case, the basic unit price shall be based on the highest fee category for the foreign manufacturing sites etc. The product unit surcharge shall be given by multiplying the basic unit price for each category by the number of the products classified into the category.

(6) The handling as stipulated under 1-(15) through (18) shall also apply to 2-(1) through (5) above.

(7) An application for a routine GMP inspection for a marketed product may be submitted with the application for renewal of the license for manufacturer (renewal of the accreditation of foreign manufacturers, in case of a foreign manufacturing site) is submitted, regardless of the timing of marketing approval.

3. Other Points to Consider

(1) The GMP inspection application under 1 or 2 above may be submitted from time to time, upon consultation with the competent inspection authority, when the marketing authorization holder or manufacturer intends to undergo a GMP inspection. This also applies to the cases of drug substances etc. that are used for manufacturing over-the-counter drugs.

(2) The GMP inspection results for a product marketed in Japan shall not be interpreted to mean that the same product for export does not require a GMP inspection. Also, the GMP inspection results for a product for export shall not be interpreted to mean that the same product marketed in Japan does not require a GMP inspection.

[Appendix]

Chairperson, Federation of Pharmaceutical Manufacturers' Associations of Japan

Chairperson, Japan Pharmaceutical Manufacturers Association

Chairperson, Japan Bulk Pharmaceutical Manufacturers Association

Chairperson, Japan Self-Medication Industry

Chairperson, Japan Pharmaceutical Traders' Association

Representative, Technical Committee in Japan, Pharmaceutical Research and Manufacturers of America

Chairperson, Pharmaceuticals Subcommittee, American Chamber of Commerce in Japan

Chairperson, Executive Committee in Japan, European Federation of Pharmaceutical Industries and Associations

Chairperson, Japan Federation of Medical Devices Associations

Chairperson, Pharmaceutical Manufacturers' Association of Tokyo

Chairperson, Osaka Pharmaceutical Manufacturers Association

Chairperson, Japan Association for Clinical Reagents Industries

Chairperson, Japan Medicinal Plant Federation

Chairperson, Japan Kampo Medicine Manufacturers Association

Chairperson, Japan Cosmetic Industry Association

Chairperson, Japan Hygiene Products Industry Association

Chairperson, Toiletries, Cosmetics and Fragrances Committee, American Chamber of Commerce in Japan

Chairperson, Medical Devices and Diagnostics Subcommittee, American Chamber of Commerce in Japan

Chairperson, Cosmetics Committee, European Business Council in Japan

Chairperson, Medical Equipment Committee, European Business Council in Japan

Chairperson, Medical Diagnostics Committee, European Business Council in Japan