Provisional Translation (as of March 16, 2009) *

PFSB/ELD (*Yakushokushinsa*) Notification No. 0330006
PFSB/CND (*Yakushokukanma*) 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 Conformity Audit

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 in 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 "Partial Revision 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 Concerning 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 has made its decision to handle applications for GMP conformity audit as described below. You are requested to fully notify relevant business parties and organizations under your

* 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 Japanese text shall prevail.

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 Conformity Audit Required for Application for Marketing Approval or Approval for Partial Changes in Approved Information, or the Manufacturing of Drugs for Export etc.

   (1) When an application for GMP conformity audit is submitted to obtain marketing approval or approval to make partial changes in 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., an applicant shall, in principle, submit the application for each product for which the applicant intends to obtain marketing approval or partial change approval , or which the applicant intends to manufacture. In principle, an application for GMP conformity audit must be submitted to the corresponding entity that will conduct the GMP conformity audit (hereinafter referred to as “conformity audit authority”) for each manufacturing site etc. indicated on the approval application form (including manufacturing sites of drug substances, manufacturing sites for packaging, external testing laboratories, and laboratories that perform design and development control (hereinafter referred to as “design and development control”); the same shall apply hereinafter).

   (2) When applying for GMP conformity audit for multiple products that are manufactured using the same drug substances (refers to those manufactured at the same manufacturing site, by the same manufacturing method, manufacturing process, or manufacturing facility, or according to the same specifications, etc.; the same shall apply hereinafter), a single application may cover all the multiple products applied for, provided that the GMP conformity audit is performed 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 multiple products, and list all the applicable products.

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

(3) If sterilization of multiple products is only performed at a single manufacturing site, then a single application for GMP conformity audit 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 multiple products, and list all the applicable products.

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

(4) If tests and inspections on multiple products are performed by a single testing laboratory, then a single application for GMP conformity audit 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 multiple products, and list all the applicable products.

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

(5) If design and development control for multiple products are performed by a single design and development control organization, then a single application for GMP conformity audit may cover all the multiple products for 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 multiple products, and list all the applicable products.

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

(6) If multiple products are essentially a single product with different names (the content of the approval application is the same, excluding that only 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 the Minister of Health, Labour and Welfare in accordance with the provisions of Article 2, Paragraphs 5 through 7 of the Pharmaceutical Affairs Law [Ministry of Health, Labour and Welfare Ministerial Notification No. 298 of 2004]; the same shall apply hereinafter), those multiple products may be covered by a single application for GMP conformity audit. In this case, make a note on the application form to the effect that the application is made for multiple products, and list all the applicable products.

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

(7) A drug substance manufacturing site that holds the license for manufacturing or importing/marketing under the Pharmaceutical Affairs Law prior to the amendment by the partially revised Law and that is deemed to hold the license for manufacturers under the revised Pharmaceutical Affairs Law as of April 1, 2005 is not subject to GMP conformity audit for products that are manufactured using the drug substance until the manufacturing site is notified of the results of a periodic GMP conformity audit that it must undergo upon renewal of the license for manufacturing or importing/marketing. In this case, a copy of the license for manufacturing of and a copy of the license to add products of the drug substance manufacturing site must be attached to the application form submitted for the GMP conformity audit 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, for each product, the license for manufacturers for a drug substance that is used for manufacturing drugs etc. on or before March 31, 2005, the provisions under (7) shall apply to the drug substance until the applicant receives a copy of the GMP Conformity Audit Result Notification for the drug substance. In this case, a copy of the document (e.g., the relevant part of the product standard code) showing that the drug substance was used for manufacturing drugs etc. must be attached to the GMP conformity audit application form for the product that is manufactured using the drug substance. In addition, the GMP conformity audit for the drug substance shall be conducted promptly.

(9) A GMP conformity audit for a drug substance is not necessary when the GMP conformity of the same drug substance has already been confirmed by an audit conducted at the request of another marketing authorization holder, and copies of the GMP Conformity Audit Result Notification for the same drug substance and a document proving the equivalence of the two drug substances are submitted to a conformity audit authority and an approval authority, respectively (refers to the approval authority as stipulated in Article 23 of the Enforcement Ordinance of the Pharmaceutical Affairs Law [Ministry of Health and Welfare Ministerial Ordinance No. 11 of 1961]; however, submit to the Pharmaceuticals and Medical Devices Agency for

products that must be approved by the Minister; the same shall apply hereinafter). In this case, copies of the application form submitted for the GMP conformity audit, the GMP Conformity Audit Result Notification for the drug substance, and the document proving the equivalence of the two drug substances should be submitted to the approval authority without delay after the application. In this case, the copy of the GMP Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing the notification. When a copy of GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

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

In this case, the copy of the GMP Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing the notification. When a copy of the GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

(11) A GMP conformity audit is not necessary for a manufacturing site when the GMP conformity 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 specifications, etc.; the same shall apply hereinafter) has already been confirmed by an audit conducted at the request of another marketing authorization holder, and copies of the GMP Conformity Audit Result Notification for that same product and a document proving the equivalence of the two products are submitted to the conformity audit authority and approval authority. In this case, also submit these copies to the approval authority without delay.

In this case, the copy of the GMP Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing

the notification. When a copy of GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

(12) The application for the GMP conformity audit is not necessary for a manufacturing site when another marketing authorization holder has already submitted an application for the GMP conformity audit of the same product as the one manufactured at the site, and copies of the GMP Conformity Audit Result Notification after its issuance and a document proving the equivalence of the two products are submitted to the approval authority. In this case, also submit these copies to the approval authority without delay.

(13) A GMP conformity audit is not necessary for a testing laboratory to which the tests and inspections concerning the product applied for have been outsourced when the GMP conformity of the laboratory has already been confirmed by an audit conducted at the request of another marketing authorization holder or manufacturer of drugs etc. for export, and a copy of the GMP Conformity Audit Result Notification accompanies the application form. In this case, submit to the approval authority a copy of the application form submitted for the GMP conformity audit and a copy of the GMP Conformity Audit Result Notification for the testing laboratory without delay after the application.

In this case, the copy of the GMP Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing the notification. When a copy of GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

(14) A GMP conformity audit is not necessary for a design and development control organization to which the design and development control concerning the product applied for have been outsourced when the GMP conformity of the organization has already been confirmed by an audit conducted at the request of another marketing authorization holder or manufacturer of drugs etc. for export, and a copy of the GMP Conformity Audit Result Notification accompanies the application form. In this case, submit to the approval authority a copy of the application form submitted for GMP conformity audit and a copy of the GMP Conformity Audit Result Notification for the design and development control organization without delay after the application.

In this case, the copy of the GMP Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing

the notification. When a copy of GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

(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 conformity audit.

(16) Drug substances that are used to manufacture quasi-drugs are not subject to a GMP conformity audit.

(17) If accessories or components, etc. (limited to those subject to GMP) used to manufacture medical devices have been confirmed to conform to GMP through a GMP conformity audit of other products, such as a medical device using the same component, they are not subject to another GMP conformity audit.

(18) Drug substances that are used to manufacture in-vitro diagnostics are not subject to a GMP conformity audit.

(19) When submitting a partial change approval application, 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 conformity audit is not necessary. If the partial change affects the methods of manufacturing control or quality control of the product, however, out of the manufacturing sites listed in the marketing approval letter, those that may be affected must undergo the audit.

2. GMP Conformity Audit Application for Periodic Audit

(1) Application for GMP conformity audit that is conducted once every five years after obtaining marketing approval or every five years after the commencement of manufacture of drugs etc. for export (hereinafter referred to as “periodic audit”) shall be submitted for approved products or products for export manufactured at each manufacturing site, for each manufacturing site. Notwithstanding the foregoing, testing laboratories or design and development control organizations are not subject to GMP conformity audit for periodic audit. In addition, drug substance manufacturing sites etc. are not subject to GMP conformity audit for periodic audit, unless a periodic audit must

be conducted to meet the requirements under (4) below.

(2) Regarding the fee for a periodic GMP conformity audit conducted by the Pharmaceuticals and Medical Devices Agency, the basic unit price shall be based on the highest fee category at the facility and the product unit surcharge shall be derived by multiplying the unit price for each category by the number of products applied for in the category. The fee categories are, in the order from the highest to lowest 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 multiple products that are actually the same product with different names or multiple medical devices with same generic names, a single GMP conformity audit application may be submitted by regarding the number of applicable multiple products as one product applied for.

(4) When submitting an application for renewal of the license for manufacturers of a manufacturing site that manufactures drug substances, attach to the application form copies of the most recent GMP Conformity Audit 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 Conformity Audit Result Notification attached to the application form must, in principle, be dated within two years after the date of issuing the notification. When a copy of GMP Conformity Audit Result Report dated within two years after the date of the audit is also attached, however, the copy of the GMP Conformity Audit Result Notification may be dated within five years.

(5) When submitting a GMP conformity audit application for foreign manufacturing sites concerning periodic audit 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. The application shall be made for manufacturing sites for packaging that decide 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 derived by multiplying the basic unit price for each category by the number of products applied for in the category.

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

(7) A GMP conformity audit application for periodic audit of a marketed product may be submitted at the same time that the application for renewal of the license for manufacturers (renewal of the certification 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 conformity audit application under 1 or 2 above may be submitted at any time when the marketing authorization holder or manufacturer intends to undergo a GMP conformity audit, upon consultation with the conformity audit authority. This also applies to drug substances etc. that are used for manufacturing over-the-counter drugs.

(2) The GMP conformity audit results for a product that is marketed in Japan shall not be interpreted as the situation where the same product for export does not require a GMP conformity audit. Also, the GMP conformity audit results for a product for export shall not be interpreted as the situation where the same product marketed in Japan does not require a GMP conformity audit.

[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