

Tentative translation (as of October 7, 2008)

September 1, 2008

**Office of Compliance and Standards  
Pharmaceuticals and Medical Devices Agency**

**GMP Compliance Inspection concerning Pharmaceuticals (including APIs)  
of Foreign Manufacturers  
(Overview Guidance for Foreign Manufacturers)**

GMP Compliance Inspection concerning Pharmaceuticals of Foreign Manufacturers is a inspection on the compliance of manufacturing control and quality control methods at the relevant manufacturing sites with Japanese GMP (“Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs”, Ordinance of Ministry of Health, Labour and Welfare, No. 179, 2004), conducted by the Pharmaceuticals and Medical Devices Agency (hereinafter “PMDA”). GMP compliance is a requirement for marketing approval.

GMP Compliance Inspections include 1) Inspections that are conducted at the point of application for new marketing approval or of application for partial changes of approved information, and 2) Inspections that are conducted every five years following the obtainment of marketing approval. In the case of ethical drugs, packaging, labeling and storage facilities and external testing laboratories are included in the scope of GMP Inspection, in addition to the manufacturing sites of drug products, APIs (Active Pharmaceutical Ingredients) and intermediates. In the case of application for partial change approval, GMP Compliance Inspection is not required if the partial change is addition, change, or deletion etc. of administration and dosage, or indication that will not affect the methods for manufacturing control or quality control. While drug products for over-the-counter drugs are included in the scope of GMP compliance Inspection, APIs for over-the-counter drugs are excluded from the inspection (however APIs of over-the-counter for new marketing approval are in the scope of GMP compliance Inspection).

A marketing authorization holder that applies for the marketing approval of pharmaceutical, or an appointed marketing authorization holder designated by a manufacturer that seeks to obtain foreign restrictive approval, shall file an application with the PMDA for GMP compliance Inspection of foreign manufacturing sites.

Following the application for GMP Compliance Inspection, the applicant shall submit “Documents pertaining to manufacturing control and quality control of product(s) concerning the compliance inspection” and “Documents pertaining to manufacturing control and quality control of manufacturing sites concerning the compliance inspection”, at request of the PMDA. For details of required documents, see “5. Attached documents for the application of inspection prepared by foreign manufacturers”.

Even applications and attached documents are concerning foreign manufacturing sites, it should be prepared in the Japanese language. If the attachment includes a large volume of documents written in a foreign language, it is acceptable to prepare only an overview of such documents in Japanese.

## **2. Scope of Drugs subject to GMP Compliance Inspection**

Drugs and APIs (the products shows below a. ~ g. and APIs for over-the-counter drugs do not require GMP compliance Inspection.)

- a. Drugs that are intended to be used for the extermination or prevention of rats, flies, mosquitoes, fleas and other similar creatures, which are not used directly on human bodies.
- b. Drugs that are intended to be used mainly for disinfection and sanitization, which are not used directly on human bodies.
- c. Drugs that are, APIs, intended to be mainly used for the manufacturing of drugs indicated in a. or b.
- d. Drugs that are manufactured at manufacturing sites that only conduct processes of powdering and/or cutting crude drugs.
- e. Drugs that are manufactured and/or marketed by pharmacies.
- f. Of gases used for medical purposes, 1) nitrous oxide, 2) oxygen, 3) nitrogen, 4) carbon dioxide, 5) compound of nitrous oxide and oxygen.
- g. In addition to a. through f., drugs included in the Japanese Pharmacopoeia, which are designated by the Minister of Health, Labour and Welfare as causing mild action to human bodies (107 items including gum arabic).

## **3. Facilities subject to the Inspection**

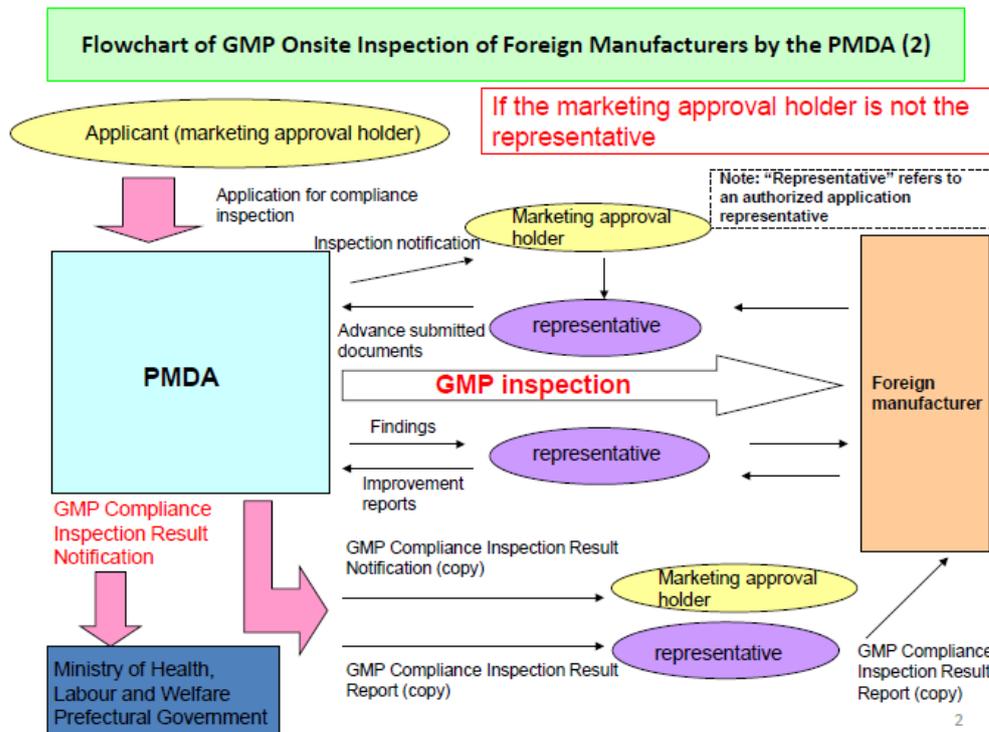
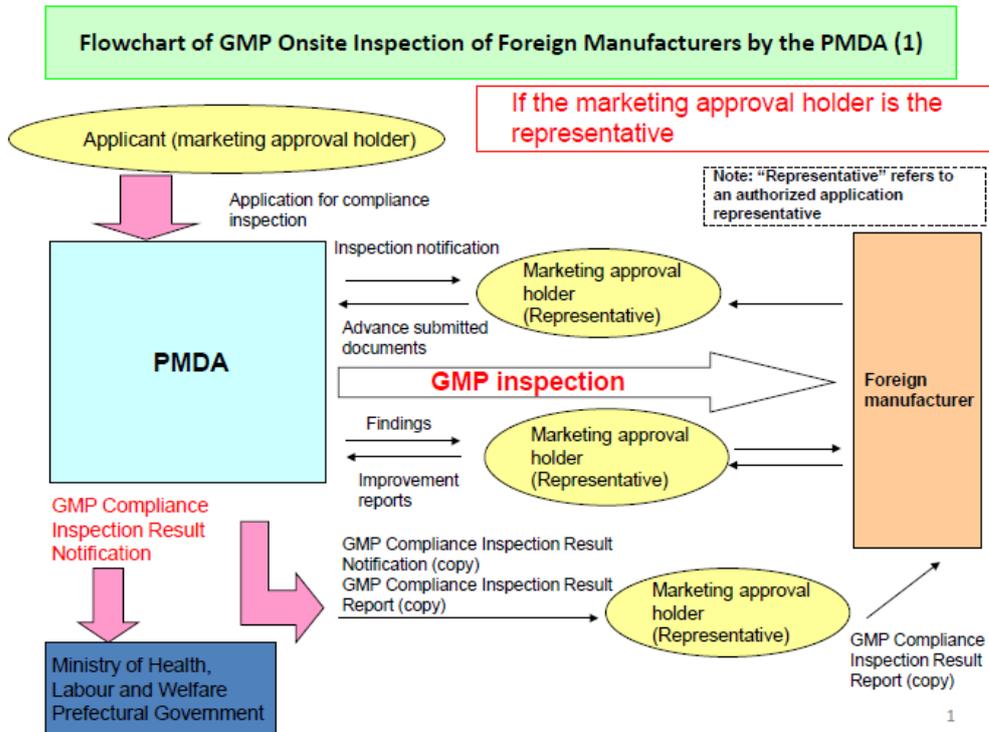
All manufacturing sites (including external testing laboratories) listed in the marketing approval application or authorization.

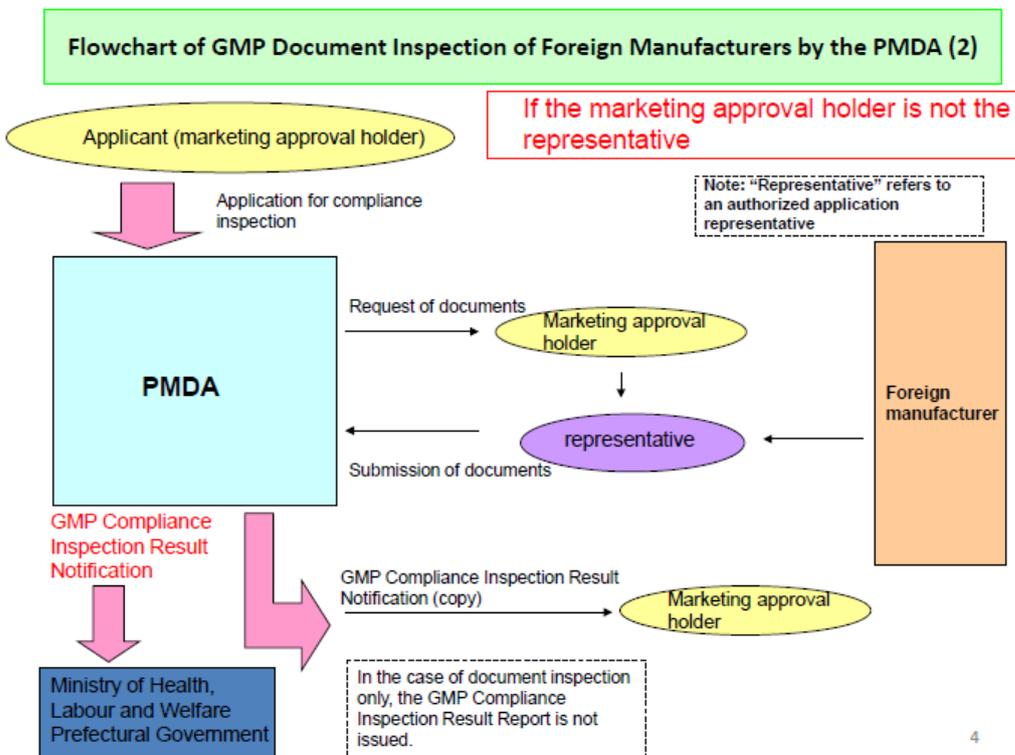
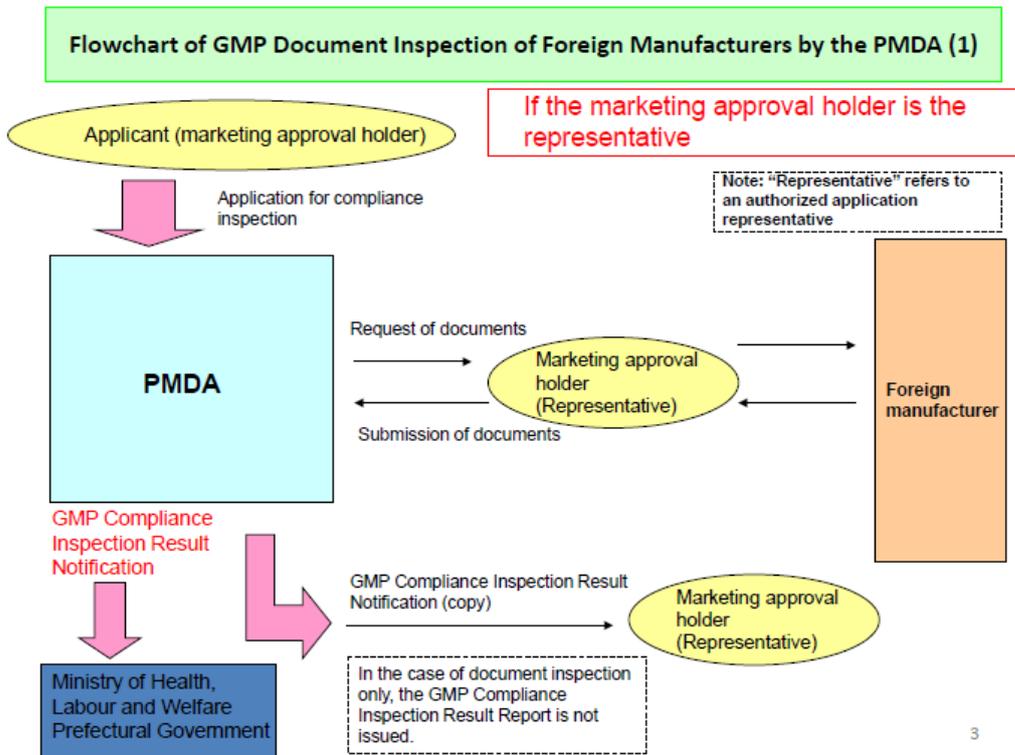
## **4. Flow of GMP Compliance Inspection**

- a. A marketing authorization holder that is applying for the marketing approval, or a marketing authorization holder that has obtained marketing approval, shall file an application with the PMDA for GMP compliance Inspection of foreign manufacturing sites. The PMDA shall conduct the inspection.
- b. In principle, GMP compliance Inspection shall be onsite inspection by the PMDA. However, inspection may be conducted on documents only (hereinafter “document inspection” ), by the PMDA’ s judgment on GMP compliance etc. based on the product’ s risk, the country’ s GMP standards and their operation, and documents submitted for the inspection.
- c. The PMDA shall report the inspection results to the Ministry of Health, Labour and Welfare, using the form of “GMP Compliance Inspection Result Notification” . The PMDA shall issue a copy of the GMP Compliance Inspection Result Notification to the marketing approval holder that applied for the inspection, and a copy of the “GMP Compliance Inspection Result Report” to the foreign manufacturer on which the onsite inspection

was conducted. In the case of document inspection only, a copy of the GMP Compliance Inspection Result Report is not issued.

[Flowcharts]





## 5. Documents to be attached to the Application of Inspection

- (1) For compliance inspections conducted for marketing approval or approval of partial changes
  - a. Copies of Compliance Inspection Result Notifications and/or Inspection Report of GMP inspections conducted within two years from the date of the application for the compliance inspection (including those conducted by other authorized compliance inspectorates etc.)
  - b. In the case of foreign manufacturing sites, as for manufacturing sites in countries with which MRA is concluded, a copy of Compliance Certificate or GMP Inspection Report of that country based on the MRA, as for manufacturing sites in countries with which MOU is exchanged, a copy of Certificate or GMP Inspection Report of that country based on the MOU, and as for manufacturing sites in other countries, WHO Certificate, or Compliance Certificate issued by the country's relevant authority.
  - c. Copy of marketing approval application for the applied product(s)
  - d. Other documents required by the authorized compliance inspectorates (based on separate Office Memorandum "Documents required by PMDA for the Application of GMP Compliance Inspection" by Office of Compliance and Standards, July 29, 2008)
- (2) Compliance inspection conducted every five years following marketing approval
  - a. Copies of Compliance Inspection Result Notifications and/or Inspection Report of GMP inspections conducted within two years from the date of application for the compliance inspection (including those conducted by other authorized compliance inspectorates etc.)
  - b. In the case of foreign manufacturing sites, as for manufacturing sites in countries with which MRA is concluded, a copy of Compliance Certificate or GMP Inspection Report of that country based on the MRA, as for manufacturing sites in countries with which MOU is exchanged, a copy of Certificate or GMP Inspection Report of that country based on the MOU, and as for manufacturing sites in other countries, WHO Certificate, or Compliance Certificate issued by the country's relevant authority.
  - c. Copy of marketing approval
  - d. Copies of partial change approvals over the past five years
  - e. Copies of notification of minor changes over the past five years
  - f. If applications for two or more products are made simultaneously, the applicant shall categorize applications by worksite, workroom, area, equipment etc., select representative products for each category, and submit documents that show reasons for these categorization and selection. (If representative products are selected in

line with these rules, documents indicated in a., b. and c. may be limited to those concerning the representative products.)

- g. Whether there was product recall concerning the applied product(s) over the past five years (If there was, overview of the recall)
- h. Statement (prepared by the applicant)
- i. Other documents required by the authorized compliance inspectorates (based on separate Office Memorandum “Documents required by PMDA for the Application of GMP Compliance Inspection” by Office of Compliance and Standards, July 29, 2008)

As for documents required by the PMDA after the submission of GMP Compliance Inspection application which is indicated under “Other documents required by the authorized compliance inspectorates” , please refer to the attached “Documents to be submitted for GMP Compliance Inspection (Documents required by the PMDA)” .

## **6. Inspection Fee**

Inspection fee shall be covered by the marketing authorization holder that applies for or obtains marketing approval.

If GMP Compliance Inspection has been conducted on the same product at the same manufacturing site, based on GMP compliance applied by another marketing authorization holder, and if a copy of the Compliance Inspection Result Notification (no older than two years, in principle) can be provided to the second marketing authorization holder, the second marketing authorization holder does not need to receive the GMP Compliance Inspection concerning the manufacturing site.

### **(Reference regulatory provisions (excerpts))**

- \* Article 14, Paragraph 1 of the Pharmaceuticals Affairs Law (Approval of marketing of drugs)

A person intending to market a drug shall, for each product, obtain marketing approval of the Minister of Health, Labour and Welfare.

- \* Article 14, Paragraph 6 of the Pharmaceuticals Affairs Law

A person who wishes to obtain the approval or who has been granted the approval specified in Paragraph 1 for a drug shall be subjected to a document inspection or an onsite inspection by the Minister to determine whether the method of manufacturing control or quality control in the manufacturing plant complies with the specifications specified by MHLW ordinance before approval and during a period specified by cabinet order not exceeding 3 years after the approval was granted.

- \* Article 14-2, Paragraph 1 of the Pharmaceuticals Affairs Law (Inspections by the PMDA)

The Minister of Health, Labour and Welfare may have the PMDA conduct the inspection of drugs as specified in Paragraph 1 and Paragraph 6 of the previous Article.

- \* Article 21 of the Pharmaceutical Affairs Law Enforcement Ordinance (Period of Inspection for Standards for Methods of Manufacturing Control or Quality Control)

The period specified by the government ordinance pursuant to the provisions of Article 14, Paragraph 6 of the Law shall be five (5) years.

- \* Article 50, Paragraph 1 of the Pharmaceutical Affairs Law Enforcement Regulations (Application for GMP Compliance Inspection)

Application for the inspection specified in Article 14, Paragraph 6 of the Law shall be made by submitting an application using Form No. 25 to the Minister of Health, Labour and Welfare.

- \* Article 50, Paragraph 2 of the Pharmaceutical Affairs Law Enforcement Regulations

The following documents shall be attached to the application specified in the preceding paragraph.

- 1 Documents on the manufacturing control and quality control of the product subject to the GMP Compliance Inspection
- 2 Documents on the manufacturing control and quality control of the manufacturing site subject to the GMP Compliance Inspection

- \* Article 50, Paragraph 3 of the Pharmaceutical Affairs Law Enforcement Regulations

In the application of the provisions of Paragraph 1 to cases where the Minister has decided to have the PMDA conduct the GMP Compliance Inspection pursuant to the provisions of Article 14-2, Paragraph 1 of the Law, in the same paragraph “to the Minister” shall read “to the PMDA” .

- \* Article 51 of the Pharmaceutical Affairs Law Enforcement Regulations (Notification of GMP Compliance Inspection Results)

Notification of the results of the GMP Compliance Inspection from authorized compliance to the marketing approval holder licensing authorities or to the approval authorities shall be made by submitting a notification using Form No. 26.

様式第二十五 (一) (第五十条関係)  
Form No. 25 (1) (in relation to Article 50)

医 薬 品 適 合 性 調 査 申 請 書  
医薬部外品  
Application for GMP Compliance Inspection of Drugs/Quasi Drugs

主たる機能を有する事務所の名称 Name of Main Office		
主たる機能を有する事務所の所在地 Address of Main Office		
製造販売業の許可番号及び年月日 Number and Date of License for Marketing Approval		
調査を受けようとする製造所の名称 Name of Manufacturing Site Applied for Inspection		
調査を受けようとする製造所の所在地 Address of Manufacturing Site Applied for Inspection		
製造業者の氏名 (法人にあっては、名称及び代表者の氏名) Name of Manufacturer (In the case of corporation, names of the corporation and its representative)		
製造業者の住所 (法人にあっては、主たる事務所の所在地) Address of manufacturer (In the case of corporation, location of the main office)		
製造業の許可区分又は外国製造業者の認定区分 Category of License for Manufacturing Operation or Accreditation of Foreign Manufacturer		
製造業の許可番号又は外国製造業者の認定番号及び年月日 Number of License for Manufacturing Operation or Number and Date of Accreditation of Foreign Manufacturer		
申請品目 Applied Product(s)	一般的名称 Nonproprietary Name	
	販売名 Brand Name	
	承認申請受付番号又は承認番号 Approval Application Acceptance Number or Approval Number	
	承認申請年月日又は承認年月日 Date of Approval Application or Approval	
調査手数料金額 Amount of Inspection Fee		
備 考 Remarks		

上記により、医薬品の適合性調査を申請します。  
 医薬部外品

I hereby apply for GMP Compliance Inspection of Drugs  
 of Quasi-drugs

年 月 日  
 year Month Day

住所 (法人にあつては、主たる事務所の所在地)  
 Address (Address of head office if the undersigned is a corporate )

氏名 (法人にあつては、名称及び代表者の氏名) ㊞  
 Name (Name of corporation and its representative if the Seal  
 undersigned is a corporate body)

独立行政法人医薬品医療機器総合機構理事長  
 都道府県知事 殿  
 To the Chief Executive of the Pharmaceuticals and Medical Devices Agency  
 To the Prefectural Governor

(注意)

(Instruction for filling out the form)

- 1 用紙の大きさは、日本工業規格 A4 とすること。  
 1 Print the form on A4 (Japanese Industrial Standards-JIS) paper.
- 2 字は、墨、インク等を用い、楷書ではっきりと書くこと。  
 2 Use ink for writing, and write Japanese letters clearly in standard (square) style.
- 3 製造業の許可区分又は外国製造業者の認定区分欄については、第 26 条第 1 項、第 2 項若しくは第 3 項又は第 36 条第 1 項、第 2 項若しくは第 3 項の各号いずれかに該当するかを記載すること。  
 3 As for the "Classification of License for Manufacturing Operation or Accreditation of Foreign Manufacturer" column, indicate the category of the license or the accreditation; Article 26, Paragraph 1, 2, or 3 and/or Article 36, Paragraph 1, 2, or 3.
- 4 備考欄には製造所に係る製造業者の氏名又は名称及び住所又は所在地を記載すること。  
 4 As for the "Remarks" column, indicate the name and address of the manufacturer who owns the applied manufacturing site.
- 5 独立行政法人医薬品医療機器総合機構理事長に申請する場合にあつては、薬事法関係手数料令において定める適合性調査手数料を機構の口座に払い込んだことを証する書類の写しを裏面に貼付すること。  
 5 If the application is sent to the Chief Executive of the Pharmaceuticals and Medical Devices Agency, attach to its back a copy of evidence proving the payment of the GMP Compliance Review fee to the PMDA's bank account, as stipulated in the Ordinance on Fees concerning the Pharmaceuticals Affairs Law.

様式第二十六 (一) (第五十一条、第五十五条、第二百六十三条関係)  
Form No. 26 (1) (in relation to Article 51, Article 55 and Article 263)

医 薬 品 適 合 性 調 査 結 果 通 知 書  
医 薬 部 外 品  
Drugs  
Quasi Drugs  
GMP Compliance Inspection Result Notification

名称 Name	一般的名称 Nonproprietary Name	
	販売名 Brand Name	
申請者名 Name of Applicant		
承認申請年月日又は承認年月日 Date of Approval Application or Approval		
適合性調査申請年月日 Date of Application for GMP Compliance Inspection		
調査を行った製造所の名称 Name of Inspected Manufacturing Site		
調査を行った製造所の所在地 Address of Inspected Manufacturing Site		
製造業者の氏名 (法人にあつては、名称及び 代表者の氏名) Name of Manufacturer (In the case of corporation, names of the corporation and its representative)		
製造業者の住所 (法人にあつては、主たる事 務所の所在地) Address of manufacturer (In the case of corporation, location of the main office)		
製造業の許可区分又は 外国製造業者の認定区分 Category of License for Manufacturing Operation or Accreditation of Foreign Manufacturer		
製造業の許可番号又は 外国製造業者の認定番号及び年月日 Number of License for Manufacturing Operation or Number and Date of Accreditation of Foreign Manufacturer		
調査結果 Inspection Results		
備 考 Remarks		

上記により、  
医薬品  
医薬部外品  
の適合性調査の結果を通知します。

I hereby notify GMP Compliance Inspection result of  
Drugs  
Quasi-drugs

年 月 日  
year Month Day

適合性調査権者  
Authorized GMP Compliance Inspectorates

Ⓢ  
Seal

厚生労働省労働大臣  
To: Minister of Health,  
Labour and Welfare 殿  
都道府県知事  
To: Prefectural Governor

(注意)

(Instruction for filling out the form)

- 1 用紙の大きさは、日本工業規格 A4 とすること。  
1 Print the form on A4 (Japanese Industrial Standards-JIS) paper.
- 2 字は、墨、インク等を用い、楷書ではっきりと書くこと。  
2 Use ink for writing, and write Japanese letters clearly in standard (square) style.

(ひな形)  
(Form- )

報告年月日： 年 月 日  
Date of Report: yyyy, mm, dd

GMP 調査結果報告書  
GMP Compliance Inspection Result Report

(独) 医薬品医療機器総合機構理事長 殿  
To the Chief Executive of the Pharmaceuticals and Medical Devices Agency

調査実施責任者：  
Responsible Inspector:  
調査実施者：  
Inspector:

1. 参照番号  
1. Reference No.
2. 一般的事項  
2. General
  - (1) 調査実施日  
(1) Date of Inspection
  - (2) 申請者（製造販売業者）の氏名  
(2) Name of Applicant (Marketing Approval Holder)
  - (3) 申請者（製造販売業者）の住所  
(3) Address of Applicant (Marketing Approval Holder)
  - (4) 調査対象製造業者等の氏名  
(4) Name of Inspected Manufacturers, etc.
  - (5) 調査対象製造業者等の住所  
(5) Address of Inspected Manufacturers, etc.
  - (6) 調査対象施設の名称  
(6) Name of Inspected Facilities
  - (7) 調査対象施設の所在地  
(7) Address of Inspected Facilities
  - (8) 調査対象製造所に係る製造業者等の【許可・認定】の区分、番号及び年月日  
(8) Category, Number and Date of License/Accreditation of Manufacturer, etc. who owns the Inspected Manufacturing Site

- (9) 調査の範囲
- (9) Scope of Inspection
  
- (10) 調査対象製造業者等の責任者の氏名、所属及び連絡先
- (10) Name, Division and Contact of Responsible Person of Inspected Manufacturer, etc.
  
- (11) 前回調査結果等
- (11) Results of the Previous Inspection

3. 調査内容

3. Description of Inspection

- (1) 調査目的
- (1) Purpose of Inspection
  
- (2) 【適合性調査【実地・書面】・立入検査等】
- (2) [GMP Compliance Inspection (Onsite/Document)/ On-spot Inspections etc.]
  
- (3) 調査事項
- (3) Inspection Item(s)
  - ① 製造所概要
  - (i) Outline of Manufacturing Site
  
  - ② 構造設備面
  - (ii) Structures and Facilities
  
  - ③ 管理運用面
  - (iii) Control and Operation
    - (製造工程)
    - (Manufacturing Process)
  
    - (製品原料資材保管)
    - (Storage of Raw Materials/Packaging Materials for Products)
  
    - (包装表示等)
    - (Packaging, Labeling, etc.)
  
    - (試験検査)
    - (Testing)
  
    - (管理監督)
    - (Control and Supervision)
  
- ④ 承認申請書記載内容との整合性
- (iv) Consistency with the Description Specified in the Application for Approval

4. 参考情報

4. Reference Data

5. 指摘内容

5. Deficiency

- ① 重度の不備事項
- (i) Critical Deficiency
  
- ② 中程度の不備事項
- (ii) Major Deficiency
  
- ③ 軽度の不備事項
- (iii) Minor Deficiency

6. 措置及び改善結果確認

6. Corrective Action and Verification of Improvements Made

7. 総合判定

7. Total Judgment

(了)  
(Completion)

## Sources

- “Enforcement of Laws etc. for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Law”, PFSB Notification No. 0709004 by the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, July 9, 2004
- “Enactment, Revision or Repeal of Ministerial Ordinances and Notices related to Standards for Manufacturing Control (GMP/QMS) of Drugs, Medical Devices etc., following the Enforcement of Laws etc. for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Law”, PFSB/CND Notification No. 0330001 by the Manager of the Compliance and Narcotic Division, PFSB, MHLW, March 30, 2005
- “Handling of Applications for GMP Compliance Inspection”, PFSB/ELD Notification No. 0330006 and PFSB/CND Notification No. 0330005 from the Managers of the Evaluation and Licensing Division and the Compliance and Narcotic Division, PFSB, MHLW, March 30, 2005