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

GMP Compliance Inspection concerning Pharmaceuticals of Foreign Manufacturers is an 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 show 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 (110 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.
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, June 18, 2015)

(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, June 18, 2015)

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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter "the Act") (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 Act

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 Act (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 Act 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 Act Enforcement Regulations (Application for GMP Compliance Inspection)

Application for the inspection specified in Article 14, Paragraph 6 of the Act 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 Act 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 Act 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 Act, in the same paragraph “to the Minister” shall read “to the PMDA”.

* Article 51 of the Act 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)

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

Year Month Day

Address
Address of head office if the undersigned is a corporate body

Name
Name of corporation and its representative if the undersigned is a corporate body

To the Chief Executive of the Pharmaceuticals and Medical Devices Agency
To the Prefectural Governor

(Note)

1. Print the form on A4 (Japanese Industrial Standards-JIS) paper.
2. Use ink for writing, and write Japanese letters clearly in standard (square) style.
3. Unless otherwise specified, 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. For the “Remarks” column, indicate the name and address of the manufacturer who owns the applied manufacturing site.
5. If the application is sent to the Chief Executive of the Pharmaceuticals and Medical Devices Agency, attach a copy of evidence proving the payment of the GMP Compliance Inspect fee to the PMDA’s bank account, as stipulated in the Ordinance on Fees concerning the Pharmaceuticals Affairs Law.
<table>
<thead>
<tr>
<th>Name</th>
<th>Nonproprietary Name</th>
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<tbody>
<tr>
<td></td>
<td>Brand Name</td>
</tr>
</tbody>
</table>

| Name of Applicant |
| Date of Application for GMP Compliance Inspection |
| Name of Inspected Manufacturing Site |
| Address of Inspected Manufacturing Site |

| Name of Manufacturer (in the case of corporation, names of the corporation and its representative) |
| Address of manufacturer (in the case of corporation, location of the main office) |
| Category of License for Manufacturing Operation or Accreditation of Foreign Manufacturer |
| Number of License for Manufacturing Operation or Number and Date of Accreditation of Foreign Manufacturer |

| Inspection Results |
| Remarks |
Tentative translation (as of March 1, 2016)

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

Year Month Day

Authorized GMP Compliance Inspectors

Seal

To: Minister of Health, Labour and Welfare

To: Prefectural Governor

(Note)

1. Print the form on A4 (Japanese Industrial Standards-JIS) paper.
2. Use ink for writing, and write Japanese letters clearly in standard (square) style.
報告年月日：年 月 日
Report date: yyyy,mm,dd

GMP調査結果報告書
GMP Inspection Report

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

調査実施責任者：
Principal Inspector:

その他の調査実施者：
Co-Inspector:

1. 参照番号
1. Reference Number

2. 一般的事項
2. Brief report of the inspection activities undertaken

（1）調査実施日（調査に要した時間を含む。）
（1）Inspection dates

（2）調査対象製造業者等の氏名（法人にあっては、名称）
（2）Name of the manufacturer inspected

（3）調査対象製造業者等の住所（法人にあっては、主たる事務所の所在地）
（3）Address of the manufacturer inspected

（4）調査対象製造所の名称
（4）Name of the site inspected

（5）調査対象製造所の所在地
（5）Address of the site inspected

（6）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
（6）Category, number and date of Manufacturing License of the site inspected
### (7) 調査対象製造所で実施している活動（該当するもの全てに印）

<table>
<thead>
<tr>
<th>□原薬製造</th>
<th>□最終製品製造</th>
<th>□中間製品（バルク製剤）製造</th>
<th>□小分け、包装、表示工程</th>
<th>□外部試験検査機関</th>
<th>□市場への出荷判定</th>
<th>□その他（ ）</th>
</tr>
</thead>
</table>

### (8) 調査の範囲

### (9) 調査対象製造業者等の責任者の氏名、所属及び連絡先

| (9) Name, title and contact information of the authorized person in the inspected site |

### (10) 前回調査結果等（年 月 日実施）

| (10) Results of previous inspection |

3. 調査内容

3. Content of Inspection

(1) 調査目的

(1) Purpose of inspection

(2) 調査の分類【適合性調査【実地・書面】・立入検査等】

(2) Kind of inspection【Compliance inspection【On-site·Desktop·Exploratory Inspection 】

(3) 調査事項

(3) Details on inspection

① 製造所及び品目の概要

① Description of the site and the products inspected

② 品質管理監督システム
② Quality System

③ Equipment and facilities system

④ Products and Materials Holding System

⑤ Manufacturing System

⑥ Packaging and Labeling System

⑦ Laboratory Control System

⑧ Conformity with the Standard for Biological Ingredients

⑨ Discrepancy between NDA file and MF for API

4. reference information

5. Observations

(1) Contents

① Critical deficiency

② Medium deficiency
② Major deficiency

③ 軽度の不備事項
③ Minor deficiency

（2）措置及び改善結果確認
（2）Corrective action and review of report

指摘事項書交付日：
Issue date of observation:
改善計画／報告書受理日：
Receipt date of corrective action plan/report:

① 重度の不備事項に対する改善計画／報告の内容
① Corrective action plan/report against critical deficiency

② 中程度の不備事項に対する改善計画／報告の内容
② Corrective action plan/report against major deficiency

③ 軽度の不備事項に対する改善計画／報告の内容
③ Corrective action plan/report against minor deficiency

6. 総合判定 ：平成＊＊年＊＊月＊＊日
6. Synthetic judgment ：yyyy,mm,dd

（了）

End
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 (revision PFSB Notification No. 0619002 June 19, 2007)

“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 (revision PFSB/CND Notification No. 0830-1, August 30, 2013)

“Handling of Application for GMP Compliance Inspection”, PFSB/ELD Notification No 0702-1 and PFSB/CND Notification No, 0702-1 from the Managers of the Evaluation and Licensing Division and the Compliance and Narcotic Division, PFSB, MHLW, July 2, 2015

“Documents required by PMDA for the Application of GMP Compliance Inspection” by Office of Compliance and Standards, PMDA, June 18, 2015