HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

JULY 2020

GMP CONFORMITY ASSESSMENT OF AN OVERSEAS MANUFACTURER

HSA
Health Sciences Authority

1. Introduction

Based on the Therapeutics Products Regulations under the Health Products Act of Singapore, the standard of manufacture and quality control of the therapeutic products for human use shall be taken into consideration by the Health Sciences Authority. While manufacturers located within Singapore are subjected to licensing and periodic GMP audits by HSA, overseas manufacturers of therapeutic products who intend to register therapeutic products in Singapore may be subjected to **Overseas Audit Programme (OAP) Assessment** or otherwise known as **GMP Conformity Assessment.**

Under this Overseas Audit Programme (OAP), HSA has the prerogative to perform on-site GMP audit(s) of the overseas manufacturers to assess their GMP compliance based on PIC/S Guide for Medicinal Products.

Overseas manufacturers which have been previously audited and found to conform to GMP standards by at least one Pharmaceutical Inspection Co-operation Scheme (PIC/S) member authority may submit GMP evidence such as valid GMP certificate for evaluation via GMP Documentary Evidence Verification Application (DEVA). If the submitted evidence is found to be acceptable to demonstrate that the overseas manufacturer compiles with the required GMP standards, an on-site GMP audit may not be performed.

However, HSA reserves the right to conduct an on-site audit of an overseas manufacturing site, where deemed necessary. For example, audits may be conducted in cases where HSA has regulatory information or concerns regarding the GMP compliance of the overseas manufacturing site.

2. Definitions/Abbreviations

DEVA	-	Documentary Evidence Verification Application
GMP	-	Good Manufacturing Practice
HSA	-	Health Sciences Authority, Singapore
OAP	-	Overseas Audit Programme
PIC/S	-	Pharmaceutical Inspection Co-operation Scheme
QSD	-	Quality System Dossier
SMF	-	Site Master File
US/FDA	-	Food and Drug Administration, United States
WHO	-	World Health Organization

3. Purpose

This guidance document is intended to provide information on the requirements for applications submitted to HSA to support the registration of therapeutic products.

4. Scope

This guidance document applies to all manufacturers of therapeutic products located outside of Singapore whose products are registered or subjected to registration in Singapore.

GMP Conformity Assessment is in support of product registration. With effect from 1st April 2004, all new overseas manufacturers who intend to register their products in Singapore will be subjected to GMP Conformity Assessment by HSA.

Overseas manufacturers will need to be audited by HSA. For application for overseas on-site audit, please refer to Section 5 for details. For overseas manufacturers which have been previously audited and found to conform to GMP standards by at least one Pharmaceutical Inspection Co-operation Scheme (PIC/S) member authority, GMP evidence such as valid GMP certificate may be submitted for evaluation. For GMP Documentary Evidence Verification Application (DEVA), please refer to Section 6 for details.

5. Overseas On-Site Audit Application

5.1 The application form to request for overseas GMP on-site audit is available at: https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment

5.2 Overseas manufacturers will be subjected to an on-site audit due to, but not limited to, the following situations:

- Unavailability of acceptable GMP evidence for the manufacturer
- Inadequate/insufficient GMP evidence to demonstrate GMP compliance
- Regulatory information or concerns regarding GMP compliance of manufacturer
- Product alerts related to product defects and/or product recalls

5.3 General requirements on overseas an on-site audit application:

- The application should be made by a Singapore registered firm/company and the firm/company should authorize a responsible person (e.g. Managing Director, Regulatory Personnel) to request for the application. This person must have an Account and Corporate Regulatory Authority of Singapore (ACRA) account.

- All entries shall be made in English. All the information required in the form should be provided wherever applicable. Incomplete information may cause unnecessary delay in the processing of the application.

- If the space provided in the application form is insufficient, a separate sheet (A4 size) may be used. Attachment numbers should be made at the top right hand corner on these additional attached sheets used.

- All attachments should be listed in the "List of Attachment" section in the application form.

- For first time application, QSD (in English) is required to be submitted together with the completed application form, with the intention to demonstrate that the manufacturer has a quality system in place that can potentially meet the PIC/S GMP standards.

  Refer to *Preparation of a Quality System Dossier (GUIDE-MQA-019)*: https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment

  The completed application form and QSD must be sent to:

  Therapeutic Products Branch (TPB)
  Pre-marketing Division
  Health Products Regulation Group
  Health Sciences Authority
  11 Biopolis Way #11-03 Helios
  Singapore 138667

- For subsequent applications, where manufacturers have been previously audited by HSA, only the updated SMF (in English) is required to be submitted with the completed application form.

  The SMF should be prepared in accordance to *PIC/S PE 008: Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File* which is available at: https://www.picscheme.org/en/publications

  The completed application form and SMF must be sent to:

  Audit & Licensing Division
  Health Products Regulation Group
  Health Sciences Authority
  11 Biopolis Way, #11-01, Helios,
  Singapore 138667

6. GMP Documentary Evidence Verification Application (DEVA)

6.1 The application form to request for GMP DEVA is available at: https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment

6.2 HSA will only accept documentary evidence of GMP conformance from overseas PIC/S member authorities who are deemed to have equivalent GMP standards adopted by Singapore.

List of PIC/S member authorities is available via: http://www.picscheme.org

6.3 The acceptable GMP evidence issued by a competent authority listed under Section 6.2 may be in the form of:

- GMP Certificate (Certificate of GMP Compliance), or
- Certificate of a Pharmaceutical Product issued in WHO Format; or
- Manufacturer's License or Manufacturing Authorization incorporating the specific therapeutic product(s)/dosage form(s)

For overseas manufacturers that has been audited by US/FDA, acceptable GMP evidence may be in the form of Establishment Inspection Report (EIR) and covering letter issued by US/FDA stating the inspection classification of the facility, conclusion that the inspection is closed and the manufacturer is considered to be in an acceptable state of compliance with regards to cGMP

6.4 General requirements for GMP DEVA application:

- The application should be made by a Singapore registered firm/company and the firm/company should authorize a responsible person (e.g. Managing Director, Regulatory Personnel) to request for the application. This person must have an Account and Corporate Regulatory Authority of Singapore (ACRA) account.
- All certificates/documents shall be in the English language. Where certificates/documents are not in the English language, an accurate certified translation shall be provided.
- Original or certified true copy of the certificate/documents shall be submitted, whenever possible.
- Applicants should ensure that the manufacturer's name and complete site address (including the postal code) stated in the application form and all supporting documents should be consistent with the information stated in the submitted GMP evidence and all supporting documents.
- Applicants should ensure that the scope of the submitted GMP documentary evidence covers the required authorised activities and the applicable dosage form(s) stated in the application form.
- HSA shall consider the GMP evidence to remain current until the date of expiry of the GMP evidence. In cases where no expiry date is stated or established by the issuing authority, the GMP evidence shall be considered to remain valid for 3 years from the date of inspection. Expired certificates shall not be accepted. If the submitted evidence is expiring or has expired, HSA reserves the right to request for an updated GMP evidence before proceeding with the evaluation.

6.5 The following information should be provided in the GMP evidence and/or additional supporting documents issued by the relevant authority:

- Name of the manufacturer
- Address of the manufacturing site
- Date of issue and/or expiry of the GMP evidence
- Name of therapeutic product(s) (if applicable) and/or corresponding dosage form(s)
- Authorised activity (for example: manufacture, primary packaging and secondary packaging) of the authorised dosage forms
- Approved steps of manufacture at the site (if applicable)
- GMP standards which the manufacturer complies with

6.6 HSA **DOES NOT** consider the following documents as an acceptable GMP evidence although they may be requested as additional supporting documents:

- Annual product registration certificate from US/FDA
- Annual Registration of Drug Establishment Certificate from US/FDA
- Information from Drug Establishment Current Registration Site (DECRS)
- US/FDA Form 482 and 483
- Letter from US/FDA stating that no Form 483 was issued
- Other quality system certificate (for example: ISO Certificate)

7. Service Charges for Overseas On-Site Audit and GMP DEVA Application

The details of the service charges are available at the HSA website:
https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment

Please note that there will be no refund of any payment made for submitted application(s)

The available modes of payment are:
- Non-GIRO: eNETS (Credit/Debit Card)
- GIRO (Preferred)

Payment by GIRO requires pre-registration. The GIRO application form is required to be submitted by post to the HSA Finance Department. The correspondence address can be found in the application form. The registration process will take around 3 to 4 weeks after the submission of the application form.

The GIRO application form can be downloaded via HSA website under Fees:
https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment

7.1 Overseas On-Site Audit Application

The firm/company must provide an undertaking that it is agreeable to the service charges payable which are inclusive of the associated travel and accommodation costs for each on-site audit performed. In addition, the company is also required to bear the additional cost to arrange for translator(s) to be available during the on-site audit if English is not the language used during the audit. The one-time service charge for QSD evaluation shall be payable upfront at the point of submission of the application and the service charges for overseas GMP audit shall be payable upon receiving notification from HSA.

7.2 GMP DEVA Application

A service charge shall be payable upfront upon submission of request for the GMP DEVA application

8 Other Information

HSA reserves the rights to remove the endorsement of GMP compliance given to any overseas manufacturer where evidence exists or there are reasons to believe that the manufacturer does not meet an acceptable standard.

9 End of Document

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

Contact Information:

For further information, please contact:

Overseas Audit Unit
Audit Branch
Audits and Licensing Division
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way #11-01 Helios
Singapore 138667
Website: www.hsa.gov.sg

For feedback please go to:
https://crm.hsa.gov.sg/event/feedback.aspx

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