HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

DECEMBER 2024

GMP CONFORMITY ASSESSMENT OF AN OVERSEAS MANUFACTURER

HSA
Health Sciences Authority

1. Introduction

Based on the Health Products (Therapeutics Products) Regulations 2016 and Health products (Cell, Tissue and Gene Therapy Products) Regulations 2021 under the Health Products Act of Singapore, the standard of manufacture and quality control of the therapeutic products and cell, tissue or gene therapy products (CTGTP) 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 inspections by HSA, overseas manufacturers of therapeutic products and cell, tissue and gene therapy products who intend to register these products in Singapore may be subjected to assessment under the **Overseas Audit Programme (OAP)** or otherwise known as **GMP Conformity Assessment.**

Under this Overseas Audit Programme (OAP), HSA has the prerogative to perform on-site GMP inspection(s) of the overseas manufacturers to assess their GMP compliance based on PIC/S Guide to GMP for Medicinal Products for therapeutic products and HSA Guidelines on Good Manufacturing Practice for CTGTP.

Overseas manufacturers which have been previously inspected 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 complies with the required GMP standards, an on-site GMP inspection may not be performed.

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

2. Definitions/Abbreviations

ATPB	Advanced Therapy Products Branch
CTGTP	Cell, Tissue or Gene Therapy Products
DEVA	Documentary Evidence Verification Application
GMP	Good Manufacturing Practice
HSA	Health Sciences Authority
OAP	Overseas Audit Programme
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QSD	Quality System Dossier
SMF	Site Master File
TPB	Therapeutic Products Branch
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 and CTGTP.

4. Scope

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

GMP Conformity Assessment is in support of product registration. All new overseas manufacturers of therapeutic products and CTGTP, who intend to register their products in Singapore will be subjected to GMP Conformity Assessment with effect from 1 April 2004 and 1 March 2021 respectively. Product registration for therapeutic products or CTGTP for human use is a **pre-requisite** to initiate the GMP Conformity Assessment of overseas manufacturers.

5. Overseas On-Site Inspection Application

5.1 The application form to request for overseas GMP on-site inspection is available at:

Product Category	Reference
Therapeutic Products	https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment
Cell, Tissue and Gene Therapy Products	https://www.hsa.gov.sg/ctgtp/registration/gmp-comformity-assessment

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

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

5.3 General requirements on overseas on-site inspection application:

- The application should be made by a Responsible Person (e.g. Managing Director, Head of Quality) from a Singapore registered firm/company with a valid Account and Corporate Regulatory Authority of Singapore (ACRA) account.

- The Applicant/Authorised Person (e.g. Regulatory Affairs personnel) should hold either the 'Submitter' role for 'Overseas Audit Programme' or a 'CRIS Admin' role in PRISM.

  Note: this is only applicable for therapeutic products.

- 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.

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

  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 the respective branch depending on the product category:

Product Category	Address
Therapeutic Products	**Therapeutic Products Branch (TPB)** **Pre-marketing Division** Health Products Regulation Group Health Sciences Authority 11 Biopolis Way #11-03 Helios Singapore 138667
Cell, Tissue and Gene Therapy Products	**Advanced Therapy Products Branch (ATPB)** **Medicinal Products Pre-Market Cluster** Health Products Regulation Group Health Sciences Authority 11 Biopolis Way #11-01 Helios Singapore 138667

- For subsequent applications, where manufacturers have been previously inspected 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 with: *PIC/S PE 008: Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File*.

  The completed application form and SMF should be scanned and attached in the associated product registration application(s) and submitted to TPB or ATPB accordingly.

6. GMP Documentary Evidence Verification Application (DEVA)

6.1 The application form to request for GMP DEVA is available at:

Product Category	Reference
Therapeutic Products	https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment
Cell, Tissue and Gene Therapy Products	https://www.hsa.gov.sg/ctgtp/registration/gmp-comformity-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 General requirements for GMP DEVA application:

- The application should be made by a Responsible Person (e.g. Managing Director, Head of Quality) from a Singapore registered firm/company with an Account and Corporate Regulatory Authority of Singapore (ACRA) account.
- The Applicant/Authorised Person (e.g. Regulatory Affairs personnel) should hold either the 'Submitter' role for 'Assessment of GMP Evidence from Overseas Manufacturer' or a 'CRIS Admin' role in PRISM. *Note: this is only applicable for therapeutic products.*
- 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.
- 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 documentary evidence and all supporting documents.
- Applicants should ensure that the GMP documentary evidence submitted is representative of the latest GMP compliance status of the overseas manufacturing site.
- Applicants should ensure that the scope of the submitted GMP documentary evidence covers the required authorised manufacturing activities and the dosage form(s) of the product to be registered.
- HSA shall consider the GMP documentary 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 documentary evidence shall be considered to remain valid for 3 years from the last date

of inspection. Expired certificates will not be accepted. If the submitted evidence is expiring or has expired, HSA reserves the right to request for an updated GMP documentary evidence before proceeding with the evaluation.

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

- GMP Certificate (Certificate of GMP Compliance), or
- Establishment Inspection Report (EIR) and close out letter issued by US/FDA
  Note: The close out letter (which may be in the form of an email correspondence) should indicate the inspection classification of the facility, conclusion that the inspection was closed out and that the manufacturer was in an acceptable state of compliance with regard to cGMP.

6.5 Other GMP documentary evidence that may be requested for submission as supporting documents:

- 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)
- Exit Notice
- Unredacted inspection report
- List of regulatory inspections
- Site Master File
- Contract/Quality agreements

These supporting documents should be accompanied with valid GMP documentary evidence listed in Section 6.4, that reflects the latest compliance status of the overseas manufacturer.

HSA reserves the right to request for additional information/GMP documentary evidence if these supporting documents are submitted in the absence of a valid GMP Certificate or EIR and close out letter.

6.6 The following information should be provided in the GMP documentary 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 documentary evidence
- Dates of inspection
- Name of 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

6.7 HSA **DOES NOT** consider the following documents as acceptable GMP documentary 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)
- Letter of commitment

7. Fees for Overseas On-Site Inspection and GMP DEVA Application

The details of the fees are available at the HSA website:

Product Category	Reference
Therapeutic Products	https://www.hsa.gov.sg/therapeutic-products/register/gmp-conformity-assessment
Cell, Tissue and Gene Therapy Products	https://www.hsa.gov.sg/ctgtp/registration/gmp-comformity-assessment

Payment can be made either via GIRO (preferred) or eNETS.

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

7.1 Overseas On-Site Inspection Application

The fees payable are inclusive of the associated travel and accommodation costs for each on-site inspection 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 inspection if English is not the language used during the inspection. The one-time fee for QSD evaluation shall be payable upfront at the point of submission of the application and fee for overseas on-site GMP inspection shall be payable upon receiving notification from HSA.

7.2 GMP DEVA Application

The relevant fee shall be payable upfront upon submission of request for the GMP DEVA application.

8. Other Information

HSA reserves the rights to request for further information to facilitate the evaluation of the GMP DEVA and to rescind 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 GMP compliance 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
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Health Products Regulation Group
Health Sciences Authority

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HSA
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