HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

DECEMBER 2017

AUDIT AND LICENSING OF PHARMACEUTICAL MANUFACTURERS

HSA
Health Sciences Authority

1 INTRODUCTION

Under the Medicines Act and Health Products Act's Health Products (Therapeutic Products) Regulations of Singapore, manufacturers of medicinal and therapeutic products for human use are required to be licensed before they can manufacture the products for sale or supply. An application for a Manufacturer's Licence can be submitted online via PRISM or in the prescribed manual form which is available without charge from the Audit & Licensing Division, Health Products Regulation Group, Health Sciences Authority located at:

11 Biopolis Way #11-01 Helios Singapore 138667.

All pharmaceutical (including therapeutic products and Chinese Proprietary Medicines) manufacturers are required to conform to the current Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products, which encompasses all the recommendations of the World health Organisation (WHO) in relation to GMP before a Manufacturer's Licence is granted or renewed. Pre-approval and routine GMP audits are conducted to assess the conformance of pharmaceutical manufacturers to GMP standards. The PIC/S Guide to GMP for Medicinal Products may be downloaded from http://www.picscheme.org.

2 GMP AUDIT

2.1 Pre-Audit

2.1.1 Before the audit of your manufacturing premises, GMP Auditors from the Audit & Licensing Division of the Health Products Regulation Group, Health Sciences Authority would request from you an updated Site Master File for pre-audit assessment and would inform you of the Audit Agenda and date of audit via a pre-audit letter.

2.1.2 A Site Master File is a description of your manufacturing site or plant, and its level of GMP compliance. As a guide, it should contain not more than 25 to 30 pages. The 9 topics required to be addressed in a Site Master File are :

- General Information
- Pharmaceutical Quality System
- Personnel
- Premises & Equipment
- Documentation

- Production
- Quality Control
- Outsourced Activities
- Complaints and Product Recall
- Self-Inspection

The Site Master File should be prepared in accordance to the "Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File (PE 008)" which is available on under the “Documents for Industry” section as part of PIC/S Publications.

http://www.picscheme.org/en/publications#selCategory_Documents%20for%20Industry

2.2 Site Audit

2.2.1 On the day of the site audit, the audit team will meet the manufacturer's representatives, introduce themselves, and give a brief description of the purpose of the visit and scope of activities. Then the manufacturer will be requested to give an update of the plant and any recent changes (e.g. changes to key personnel, major equipment and facilities, etc.), if any.

2.2.2 Following the update, for routine audit there will be a review of the non-conformities to GMP in the previous audits and the corrective actions taken to rectify them, and product recalls, if any. After this, the audit team will proceed with the audit of the plant, including the warehouse, production areas, filling and packaging areas, and the quality control (QC) laboratories. During the tour of the plant, observations will be made and recorded by the GMP auditors; this would include the recording of details of status labels for verification.

2.2.3 Upon completion of the site audit, the team will adjourn to the meeting room to review documentation such as batch records, analytical records, GMP training records, validation documents, records of self-inspection, product complaints, etc.

2.2.4 After the documentation review, the lead auditor would request for some time to prepare the list of non-conformities observed, if any. Then a wrap-up meeting will be convened where, the audit team will present the findings to the manufacturer, including the handing over of the list of non-conformities to the manufacturer. The audit ends after the wrap-up or exit meeting.

2.2.5 Non-conformities observed would be classified into critical, major or minor in the correspondences following the on-site audit.

A critical non-conformity is one that can affect the quality and safety of the product, and may cause harm to the patients if administered. Such non-conformities would include mix-ups, mislabeling, release of products where the potency is grossly above or below the labelled amounts. A critical non-conformity will lead to the manufacturer being given an "Unacceptable" GMP compliance rating.

A major non-conformity is one that may affect the quality and safety of the product, and includes unauthorised process changes, unvalidated manufacturing processes that have a major impact on quality.

A minor non-conformity is not likely to affect the quality and safety of the product. These include deficiencies arising from lapses in discipline e.g. failure to review an SOP at the due date, etc.

2.3 Post-Audit

2.3.1 A report will be sent to the manufacturer to obtain his response to the non-conformities observed and the time frames required for correcting the non-conformities. If the audit team is satisfied with the corrective actions and time frames for rectification, the audit will be "closed out". The due date for the next audit will be determined using a risk assessment system.

2.3.2 Establishment of Audit Frequency

The frequency of GMP audit is based on a risk-assessment approach, which include various risk factors such as risk classification of the manufacturers, degree of compliance to GMP and other quality and regulatory concerns, if any.

In general, manufacturers of sterile products are classified as "high risk", whilst manufacturers of non-sterile oral preparations and external preparations are classified as "medium risk" and "low risk" respectively.

"High risk" manufacturers or those with lower GMP compliance rating would be subject to more frequent audits.

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:

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

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