MANUFACTURING & QUALITY AUDIT DIVISION

CENTRE FOR DRUG ADMINISTRATION

Ref. No.: GUIDE-MQA-002-007

Effective Date : 06 SEP 2004

GUIDANCE NOTES ON
AUDIT AND LICENSING OF PHARMACEUTICAL MANUFACTURERS

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GUIDANCE NOTES

Subject: AUDIT AND LICENSING OF PHARMACEUTICAL MANUFACTURERS

1 INTRODUCTION

Under the Medicines Act of Singapore, manufacturers of medicinal 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 must be submitted in the prescribed form which is available without charge from the Cashier, Centre for Drug Administration, Health Sciences Authority located at 11 Biopolis Way #11-03, Helios, Singapore 138667. The application form may also be obtained from our website at: http://www.hsa.gov.sg/html/business/00000000000000001571.html

All pharmaceutical manufacturers are required to conform with 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 inspections 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 Manufacturing & Quality Audit Division of the Centre for Drug Administration, 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.

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
- Personnel
- Premises & Equipment
- Documentation

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- Production
- Quality Control
- Contract Manufacture & Analysis
- Distribution, Complaints & Recalls
- Self-Inspection

A set of "Guidance on the Preparation of a Site Master File" will be made available to all pharmaceutical manufacturers before a GMP audit is conducted.

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, there will be a review of the past non-conformities to GMP 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 are classified into critical, major or minor.

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 out of lapses in discipline e.g. failure to review an SOP at the due date, using correction fluids to amend records, etc.

2.3 Post-Audit

2.3.1 A post-audit letter 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 risk-assessment approach for determining the frequency of GMP audit is based on various risk factors which include the types of dosage forms manufactured, results of the GMP audit and products recalled since the last audit, 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.

Under this system, a "high risk" manufacturer with "Unacceptable" GMP compliance rating would be re-inspected within 2 months, whilst a "low risk" manufacturer with an "Acceptable" GMP compliance rating would only be re-inspected once every 2 years.

3 ENQUIRIES

Enquiries or clarification on the audit and licensing of pharmaceutical manufacturers shall be made to :

Manufacturing and Quality Audit Division
Centre for Drug Administration
Health Sciences Authority
11 Biopolis Way #11-03,
Helios, Singapore 138667

Tel : (65)-68663510
Fax : (65)-64789068

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REVISION HISTORY

Rev No.	DCC Ref No.	Author	Date of Revision	Remarks of Revision
001	-	-	01 Feb 1999	New.
002	-	-	05 May 1999	-
003	-	-	03 Aug 2001	Change of organisation name
004	-	-	01 Nov 2002	To replace "World Health Organsiation (WHO) Good Manufacturing Practices (GMP) for Pharmaceutical Products" with "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"
005	-	Terrance Ong	09 Dec 2002	Update document format.
006	206	Terrance Ong	01 Mar 2004	1) Change 3D HSA logo to 2D HSA logo. 2) Change Centre name to Centre for Drug Administration 3) Detached Revision History from Guidance Notes.
007	254	Terrance Ong	06 Sep 2004	1) Re-located Revision History to the main document. 2) Updated CDA address and website address. 3) Change the term “Inspection” to Audit.