EAST AFRICAN COMMUNITY

GUIDELINES ON PREPARATION OF SITE MASTER FILE FOR PHARMACEUTICAL MANUFACTURING FACILITIES

APPROVED BY THE EAC COUNCIL OF MINISTERS

SEPTEMBER 2014

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1. ABBREVIATIONS AND ACRONYMS

API	-	Active Pharmaceutical Ingredients
DUNS	-	Data Universal Numbering System
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
GMP	-	Good Manufacturing Practices
GPS	-	Global Positioning System
HVAC	-	Heating Ventilation and Air Condition
PAT	-	Process Analytical Technology
PIC/S	-	Pharmaceutical Inspection Cooperation Scheme
QC	-	Quality Control
SMF	-	Site Master File
WHO	-	World Health Organization

2. GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labeling.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

Site master File: is a document containing specific information about the activities undertaken in the pharmaceutical manufacturing site and is usually prepared by the manufacturer.

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

3. INTRODUCTION

3.1 The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

3.2 When submitted to a regulatory authority, the Site Master File should provide clear information on the manufacturer's GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

3.3 A Site Master File should contain adequate information but, as far as possible, not exceed 25 pages plus appendices on A4 paper sheets. Simple plans outline drawings or schematic layouts are preferred instead of narratives. The Site Master File, including appendices, should be readable when printed on A4 paper sheets.

3.4 The Site Master File should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The Site Master File should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each Appendix can have an individual effective date, allowing for independent updating.

4. SCOPE

These guidelines apply for all kinds of manufacturing operations such as production, packaging and labelling, testing, relabeling and repackaging of all types of medicinal products. The outlines of this guide could also be used in the preparation of a Site Master File or corresponding document by manufacturers of Active Pharmaceutical Ingredients.

5. LAY OUT OF THE SITE MASTER FILE:

5.1 Front Page:

Name and address of the applicant, Document number, Effective date, A bird view of the manufacturing site (photo), Date, Stamped

5.2 Table of contents

5.3 Approval page

Signed and dated by person(s) as prescribed by the Quality Management System

6. CONTENT OF SITE MASTER FILE

The Site Master File should include the following:

6.1 GENERAL INFORMATION

6.1.1 Contact information on the manufacturer

6.1.1.1 Brief information on the firm (including name and address), relation to other sites and, in particular any information relevant to understanding the manufacturing operations.

6.1.1.2 Name and physical address of the site, including GPS details, DUNS number (if available) telephone, fax, 24-hour telephone numbers

6.1.1.3 Name, phone number and e-mail for the contact person on the site

6.1.2 Authorized pharmaceutical manufacturing activities of the site

6.1.2.1 Copy of the valid manufacturing authorisation issued by the Local Drug Regulatory Authority should be provided *in annex 1*. If the local Drug Regulatory Authority does not issue manufacturing authorizations, the reason should be stated.

6.1.2.2 A copy of current GMP certificate issued by the local regulatory authority should be provided in *annex 2*

6.1.2.3 Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).

6.1.2.4 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site).

6.1.2.5 Number of employees engaged in production, quality control, storage, and distribution.

6.1.2.6 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.

6.1.2.7 List of GMP inspections of the site within the last 3 years; including dates and name/country of the Competent Authority having performed the inspection.

6.1.3 Any other manufacturing activities carried out on the site.

6.1.3.1 Description of non pharmaceutical activities on site, if any

6.2 QUALITY MANAGEMENT

6.2.1 The quality management system of the manufacturer

6.2.1.1 Brief description of the quality management systems run by the company and reference to the standards used.

6.2.1.2 Responsibilities related to the maintaining of the quality system including senior management

6.2.1.3 Information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies.

6.2.2 Release procedure of finished products

6.2.2.1 Detailed description of qualification (education and work experience) of the authorized person(s) responsible for batch certification and releasing procedures;

6.2.2.2 General description of batch certification and releasing procedure;

6.2.2.3 Role of authorized person in quarantine and release of finished products and in assessment of compliance with the marketing authorization;

6.2.2.4 The arrangements between authorized persons when several authorized persons are involved

6.2.2.5 Statement on the control strategies employed to release the different types of products e.g. process analytical technology (PAT) and/or real-time release or parametric release

6.3 MANAGEMENT OF SUPPLIERS AND CONTRACTORS

The Site Master File should provide information on management of suppliers and contractors as indicated below.

6.3.1 A brief summary of the establishment/knowledge of supply chain and the external audit programme;

6.3.2 A brief description of the qualification system of contractors,

6.3.3 Manufacturers of APIs and other critical materials suppliers;

6.3.4 Measures adopted where substandard/spurious/falsely-labelled/falsified/counterfeit medical products, bulk products, APIs or excipients are suspected or identified;

6.3.5 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;

6.3.6 List of contract manufacturers and laboratories including the addresses and contact information and flow-charts of supply chains for outsourced manufacturing and QC activities, e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw materials, etc., should be presented in annex 3

6.3.7 Description of the way in which the GMP compliance of the contract accepter is assessed.

6.4 PRODUCT QUALITY REVIEWS

6.4.2 Brief description of methodologies used.

6.5 PERSONNEL

6.5.1 Organization chart showing the arrangements for quality assurance, quality control and production should be provided in *Annex 4*

6.5.2 Qualifications, experience, and responsibilities of technical personnel should be included as *Annex 5*.

6.5.3 Outline of arrangements for basic and in-service training and how records are maintained.

6.5.4 Health requirements for personnel engaged in production**.**

6.5.5 Personnel hygiene requirements, including clothing.

6.6 PREMISES AND EQUIPMENT

6.6.1 Premises

6.6.1.1 Simple plan or description of manufacturing areas with indication of scale. Architectural or engineering drawings not required. Plant lay out should be attached in *annex 6*.

6.6.1.2 Nature of construction and finishes

6.6.1.3 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.

6.6.1.4 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned. Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%). Schematic diagrams should be added in *annex 7.*

6.6.1.5 Brief description of water systems with schematic drawings of the systems, including sanitation should be submitted. Quality references of water produced should be stated. Schematic diagrams should be added in *annex 8*.

6.6.1.6 Brief description of planned preventive maintenance programmes for premises and of the recording system.

6.6.1.7 Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc. Schematic diagrams should be added in *annex 9*.

6.6.1.8 Availability of written specifications and procedures for cleaning manufacturing areas

6.6.2 Equipment

6.6.2.1 Brief description of major equipment used in production and control laboratories together with the model, type and identification number. The list of equipment is should be provided in *annex 10*

6.6.2.2 Brief description of the procedures used for cleaning major equipment.

6.6.2.3 Brief description of planned preventive maintenance programmes for equipment and of the recording system.

6.6.2.4 Brief description of the company's Qualification and calibration policy, including the recording system. Reference should be made to the Validation master plan.

6.7 DOCUMENTATION

6.7.1 Arrangements for the preparation, revision, distribution and archiving of necessary documentation for manufacture should be stated.

6.7.2 Brief description of the validation master plan

6.7.3 Brief description of the change control procedure

9.7.4 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

6.8 PRODUCTION

6.8.1 Type of products

6.8.1.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters. Reference to *annex 11* should be made.

6.8.1.2 Policy for reprocessing or reworking should be stated.

6.8.1.3 Production capacities for the various dosage forms should be provided

6.8.2 Process validation

6.8.2.1 Brief description of general policy for process validation. Reference should be made to the Validation master plan.

6.8.2.2 Arrangements for computerized systems validation

6.8.3 Material management and warehousing

6.8.3.1 Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage.

6.8.3.2 Arrangements for the handling of rejected materials and products.

6.9 QUALITY CONTROL

6.9.1 Brief description of the quality control system: and the quality control department activities and procedures for the release of finished products should be stated.

6.9.2 Brief description of general Validation policy

6.10 DISTRIBUTION, COMPLAINTS, PRODUCTS DEFECT AND RECALL

6.10.1 Arrangements and recording system for distribution.

6.10.2 Arrangements for the handling of complaints and product recalls.

6.10.3 Arrangements for handling returned goods

6.11 SELF-INSPECTION

6.11.1 Short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

6.12 SHELF LIFE / STABILITY DETERMINATION PROGRAM

6.12.1 General policy for the determination of the shelf-life and stability of products manufactured at the site.

7. REFERENCES:

7.1. Annex 14-WHO guidelines for drafting a site master file (2011)
7.2. Explanatory Notes on the preparation of a Site Master File-Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, European Commission Enterprise Directorate-General
7.3. PIC/S Explanatory notes on the preparation of a Site Master File PE-008-4, (2011)

8. REVISION HISTORY

Revision No:	Date	Author(s)	Section(s) revised	Description of change	Approvals
00	September 2014	EAC TWG GMP Members	All	First approved version to be issued	REF: EAC/CM...../DECISION-----/26 SEPTEMBER 2014

9. LIST OF EXPERTS:

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13. ANNEXES TO THE SITE MASTER FILE

Annex 1	Copy of valid manufacturing authorizations/licenses
Annex 2	Copies of valid GMP certificate(s)
Annex 3	List of contract manufacturers and laboratories
Annex 4	Organizational chart
Annex 5	List of key personnel and qualifications
Annex 6	Plant lay out including flow of materials and personnel
Annex 7	schematic diagrams for the HVAC
Annex 8	schematic diagrams for water treatment system

Annex 9	schematic diagrams for the other utilities
Annex 10	List of major equipment used in production and quality control
Annex 11	List of products manufactured at the facility