SITE MASTER FILE

THIRD EDITION

KUALA LUMPUR, MALAYSIA

2014

SITE MASTER FILE
Guidance Notes

INTRODUCTION

These guidance notes are intended to assist manufacturers in their preparation of the Site Master File which will form part of the inspection report.

The Site Master File must be submitted as **loose, individually** numbered A4 sheets. Each sheet should have an **edition number** and an **effective date**. Each chapter (1 to 9) must start on a new sheet so that updates can be provided and the relevant sheets replaced. All updates must be submitted to the National Pharmaceutical Control Bureau (NPCB).

Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans, etc., should fit on A4 size paper. If more detailed information is required then this will be noted by the Inspector in his report.

SITE MASTER FILE

1. GENERAL INFORMATION ON THE MANUFACTURER

1.1 Brief information of the manufacturer:

a) Name and official address of the manufacturer;

b) Names and street address of the site, buildings and production units located on the site;

c) Contact information of the manufacturer including 24 hours telephone number of the contact personnel in the case of product defects or recalls;

d) Location plan or where relevant, identification number of the site e.g. GPS details or any other geoghrapic location system;

e) The location and immediate environment adjacent to manufacturer;

f) The size of the site, types of buildings and their ages;

g) Other manufacturing activities on the site.

1.2 Manufacturing activities as licensed by the Drug Control Authority (DCA):

a) State the relevant document as issued by the Drug Control Authority (DCA) including validity of licence document (Appendix 1 : Copy of valid Manufacturing Licence). Any conditions and/or restrictions should be stated;

b) Brief description of the manufacture, importation, exportation, distribution and other activities as authorised by the relevant Competent Authorities including foreign authorities for any dosage forms/activities;

c) List of GMP inspections of the site within the last 5 years including dates and name/country of the Competent Authority having performed the inspection.

1.3 Any other manufacturing activities carried out on the site:

a) This covers both pharmaceutical and non-pharmaceutical activities.

2. QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER

2.1 Short description of the quality management system of the manufacturer:

a) State the company's Quality Policy. Brief description of the quality management systems run by the company and reference to the standard used;

b) Responsibilities related to the maintaining of quality system including senior management;

c) Define the responsibility of the Quality Assurance (QA) function;

d) Describe the elements of the QA system e.g.;

   i. Organisational structure, responsibilities, procedures, processes;

   ii. Specifications, test methods, and other quality related data collection.

e) Information of activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies;\

f) Describe the audit programmes (self inspection or audits by external organisations undertaken);

g) Describe how the results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e. quality, efficacy and safety of the product;

2.2 Release procedure of finished products:

a) Describe the procedure for release of finished products for sale;

b) Detailed description of qualification requirements (education and work experience) of the Authorised Person(s) responsible for batch certification and releasing procedures;

c) General description of batch certification and releasing procedure;

d) Role of Authorised Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation;

e) The arrangements between Authorised Persons when several Authorised Persons involved;

f) Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release.

2.3 Management of suppliers and contractors:

a) Record if standards such as ISO 9001-9004 are used by the company to assess its suppliers;

b) When suppliers of critical starting materials and packing materials – active ingredients, excipients, containers and closures as well as printed materials are assessed, give details of how this is done;

c) Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical material suppliers;

d) Measure taken to ensure that products manufactured are compliant with TSE (Transmitting Animal Spongiform Encephalothy) guidelines (if relevant);

e) Measure adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified;

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

For each outside contractor, give:

i. Name and address of the company;
ii. Telephone No;
iii. Fax No;
iv. Brief outline of the activity being undertaken in not more than 100 words.

2.4 Quality Risk Management (QRM):

a) Brief description of QRM methodologies used by the manufacturer;

b) Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned;

2.5 Product Quality Reviews:

a) Brief description of methodologies used.

3. PERSONNEL

3.1 Organisation chart:

a) Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 2, including senior management and Authorised Person(s).

3.2 Qualifications, experiences and responsibilities of key personnel:

a) Brief details of academic qualifications and work related qualifications and years relevant experience since qualifying.

3.3 Number of employees engaged in the quality management production, quality control, technical and engineering support services, storage and distribution.

4. PREMISES AND EQUIPMENT

4.1 Premises:

a) Short description of plant; size of the site and list of buildings. If the production for different markets i.e. for local, EU, USA, etc. takes place in different buildings on the site, the building should be listed with destined markets identified including;

i. Provide a site plan highlighting manufacturing areas;

ii. Provide simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);

iii. Provide layouts and flow charts of the manufacturing areas showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms (Appendix 6);

iv. Provide layouts of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitive materials, indicated, if applicable;

v. Provide brief description of specific storage conditions if applicable, but not indicated on the layouts.

Note 1 : More details should be given for critical areas with potential risks of airborne contamination. This will include sterile product areas as well as areas for processing powders, granulation and tableting. For sterile product areas, a summary of the results of the most recent qualification/requalification should be given.

Note 2 : To reduce the narrative, schematic drawings should be used.

b) Nature of construction and finishes;

c) Brief description of heating, ventilation and air conditioning (HVAC) systems (Appendix 3);

d) Brief description of water systems including sanitation system. Schematic drawings of the systems are preferred (Appendix 3). The specification of the water produced must appear;

i. Chemical;
ii. Conductivity;
iii. Microbiological;

e) Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.;

f) Brief description of planned preventive maintenance programme carried out by the manufacturer and recording system and including services carried out by an outside contractor.

4.2 Equipment:

a) Listing and identification of major production equipment and quality control laboratory equipment (Appendix 7)**;**

b) Description of planned preventive maintenance programmes and recording systems;

c) Qualifications, Validation and Calibration;

i. Briefly describe the Company's general policy and protocols for qualification and validation (prospective and retrospective);

ii. Is there regular requalification of critical equipment?;

iii. Describe equipment calibration policy and records kept;

d) Description of GMP critical computerised systems (excluding equipment specific Programmable Logic Controllers)

4.3 Sanitation:

a) Availability of written specifications and procedures for cleaning of manufacturing areas and equipments;

b) Brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic Clean-in-Place, etc.).

5. DOCUMENTATION

5.1 Description of documentation system (i.e. electronic, manual). Informations includes:

a) Arrangements for the preparation, revision and distribution of necessary documentation for manufacture;

b) Who is responsible for the preparation, revision and distribution of documents;

c) Is there a standard format and instruction on how documents are to be prepared;

d) How is the documentation controlled?;

e) For how long are documents kept after the release of the batch?

5.2 When documents and records are stored or archived off site (including pharmacovigillance data, when applicable):

a) List of types of documents/records;

b) Name and address of storage and an estimated time required for retrieving the documents from the off-site.

6. PRODUCTION

6.1 Brief description of production operations using, wherever possible, appendices and flow charts specifying important parameters (see Appendix 4 of the Guide for the list of products manufactured):

a) Type of products manufactured on the site (see list at Appendix 4);

i. List of dosage forms of both human and veterinary products which are manufactured on the site;

ii. List of dosage forms of investigational medicinal products (IMP) manufactured for any clinical trials on the site and when different from the commercial manufacturing, information of production areas and personnel (if applicable);

iii. State any toxic or hazardous substances handled e.g. antibiotics, hormones, and cytostatics/cytotoxics. State whether the products are manufactured in a dedicated facility or on a campaign basis;

iv. Product types manufactured in a dedicated facility or on a campaign basis, if applicable;

b) *Describe the operations that are capable of being carried out at the site with the existing facilities and specify the types of pharmaceutical products. (see Appendix 4 for types of products manufactured);*

c) When packaging or repacking is undertaken, give a brief description of the activity only (e.g. labelling, filling etc.), and the nature of containers used (e.g. sachets, tamper evident glass containers);

d) If cytotoxic or radioactive substances are handled, give details of the products;

e) Briefly describe the production operations using flow charts, if possible;

f) Describe how products are identified during production and how in-process storage is organised;

g) Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology, and associated computerised systems.

6.2 Material management and warehousing.

6.3 Brief description of the general policy for process validation.

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

a) Labelling status e.g. by using labels or by computer;

b) Issuance of materials to manufacture and package;

c) The control of weighing;

d) How are materials used for manufacture identified and released?;

i. Control of Bulk Manufacture;

Checks on key parameters during manufacture e.g. blend times, filter integrity

tests;

Records of key parameters;

In-process checks;

Records of in-process checks;

ii. Packing;

Release of bulk, semi-finished products, packing materials;

Confirmation of identity and line clearance checks;

In-process checks;

iii. Quarantine and release of finished product.

6.5 Arrangements for handling of rejected materials and products:

a) Are reject materials and products clearly labelled? Are they stored separately in restricted areas?;

b) Describe arrangements for sentencing the materials and their disposal. Is destruction recorded?

6.6 Describe the policy for reprocessing or reworking.

7. QUALITY CONTROL

7.1 Description of the Quality Control system and of the activities of the Quality Control Department procedures for the release of finished products.

7.2 Activities of the Quality Control Department:

a) Briefly describe the activities of analytical testing, packaging, component testing, biological and microbiological testing;

b) If the review of batch documentation and release of final documentation takes place in this department, give details (see also para 2.2);

c) Outline the involvement in the arrangements for the preparation, revision and distribution of documents in particular those for specification test methods and release criteria if not mentioned elsewhere.

8. *DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALL*

8.1 Distribution (to the part under the responsibility of the manufacturer):

a) Types (wholesale licence holders, manufacturing licence holders, etc.) and locations (EU/EEA, USA, etc.) of the companies to which the products are shipped from the site;

b) Description of the system used to verify that each customer / recipient is legally entitled to receive medicinal products from the manufacturer;

c) Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring / control;

d) Arrangements for product distribution and methods by which product traceability is maintained;

e) Measures taken to prevent manufacturers' products to fall in the illegal supply chain;

f) A description of Storage and Distribution Practices:

i. Is the warehouse secure?;

ii. Is it environmentally controlled (air conditioning)?;

iii. Is there refrigerated or cool storage?;

iv. How are the materials stored e.g. pallet racking?;

v. How is the status of products controlled e.g. by computer, by label?;

vi. What are the methods of distribution to customers?;

vii. Does the despatch order ensure first in/first out (FIFO) and identify the lot number?;

viii. Records of Distribution.

Do the retained records permit full batch traceability from the factory to the customer, in terms of the date of sale, customer details and quantity despatched?

8.2 Arrangements for the handling of complaints and product recalls.

8.3 Complaints:

a) Is there a written complaints procedure?;

b) Who is responsible for;

i. Logging/recording;

ii. Classification;

iii. Investigating complaints.

c) Are written reports prepared?;

d) Who reviews these reports?;

e) For how long are complaints records kept?

8.4 Product Recalls:

a) Is there a written procedure which describes the sequence of actions to be followed including :

i. Retrieval of distribution data;

ii. Notification of customers;

iii. Receipt / segregation / inspection of returned product;

iv. Investigation / reporting of cause;

v. Reporting of corrective action.

b) Who is responsible for coordinating product recalls?;

c) Who notifies the National Pharmaceutical Control Bureau of complaints and recalls?;

d) Can recalls be effected below wholesaler level?

9. CONTRACT MANUFACTURE AND ANALYSIS

9.1 List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply chains for outsourced manufacturing and Quality Control activities; e.g. sterillisation of primary packaging material for aseptic processes, testing of raw materials etc, should be presented in Appendix 5.

9.2 Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorisation.

10. SELF INSPECTION

10.1 Short description of the self inspection system:

a) Describe how the self inspection system verifies that those activities which have a bearing on quality comply with the planned arrangement;

b) Are the quality systems effective?;

c) Are there documented procedures for the self inspection system and for the follow-up actions?;

d) Are the results of self inspection documented and brought to the attention of the personnel having responsibility for the area and the activities inspected?;

e) Does the system ensure that those responsible for the area or activity take timely corrective action on the deficiencies found?

LIST OF APPENDIX NEED TO BE ATTACHED

APPENDIX 1 Copy of valid manufacturing authorisation

APPENDIX 2 Organisational charts

APPENDIX 3 Schematic drawings of water and HVAC systems

APPENDIX 4 Type of product manufactured and dosage form

APPENDIX 5 List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply-chains for these outsourced activities

APPENDIX 6 Layouts of production areas including material and personnel flows, general flow charts of manufacturing processes of each product type (dosage forms)

APPENDIX 7 List of major production and laboratory equipment

APPENDIX 4

TYPE OF PRODUCTS MANUFACTURED

A. Sterile Products

A.1 Liquid dosage forms (large volume solutions, including LVP and rinsing solutions)

A.1.1 Aseptically prepared

A.1.2 Terminally sterilized

A.2 Liquid dosage forms (small volume solutions, including SVP and eye drops)

A.2.1 Aseptically prepared

A.2.2 Terminally sterilized

A.3 Semi-solid dosage forms

A.4 Solid dosage forms

A.4.1 Solid fill

A.4.2 Freeze-dried

B. Non-sterile Products

B.1 Liquid dosage forms

B.2 Semi-solid dosage forms

B.3 Solid dosage forms

B.3.1 Unit dose form (tablets, capsules, suppositories, pessaries)

B.3.2 Multi dose form (powders, granules)

C. Biological Products

C.1 Vaccines

C.2 Serum

C.3 Blood Products

C.4 Others (describe)

D. Specifically Toxic and Hazardous Substances

D.1 Penicillins

D.2 Cephalosporins

D.3 Hormones

D.4 Cytotoxics / Cytostatics

D.5 Others (describe)

E. Packaging only

E.1 Liquid dosage forms

E.2 Semi-solid dosage forms

E.3 Solid dosage forms

F. Contract Manufacturing

F.1 Type of Products

F.2 Name of Contract Giver

G. Contract Analysis

G.1 Name of Contract Giver

H. Others (e.g. veterinary products, cosmsetics, etc.)

REFERRENCES

1. PIC/S Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File; PE 008-4, 1st January 2011

2. Site Master File; Second Edition; 2000