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The Rules Governing Medicinal Products in the European Union
Volume 4

EU Guidelines to

Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

Part III

Explanatory notes for pharmaceutical manufacturers on the preparation of a Site Master File and content of a Site Master File

Draft agreed by GMP/GDP Inspectors Working Groups	September 2009
Release for public consultation	15 December 2009
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Final text agreed by GMP/GDP Inspectors Working Groups	
Adopted by European Commission	
Deadline for coming into operation	

The Site Master File concept has been developed by PIC/S and has become a standard expectation of EU authorities. Following a recent revision of the explanatory notes by PIC/S, it has been proposed that the status of the Site Master File is more formally linked to the EU regulatory framework.
It is proposed that a new informational Part III of the EU GMP Guide is created for documents which are not themselves GMP guidelines and have no statutory force but which complement the GMP guidelines and related regulatory procedures such as, in this case, inspections.
It is expected that in the future, further documents will be added to the new Part III and that such documents would be included following public consultation.
The document is identical to the content of the Site Master File by PIC/S and is published in parallel.

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1. INTRODUCTION

1.1 The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the company, 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.

1.2 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.

1.3 A Site Master File should be detailed enough but, as far as possible, not exceed approximately twenty-five to thirty A4 pages plus appendixes.

1.4 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 and effective and expiry dates. It should be subject to regular review to ensure that it is up to date and representative of current activities. The format and headings should follow these guidance notes.

1.5 Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans etc should fit on A4 sheets of paper and copies should be readable.

2. PURPOSE

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that can be useful to the regulatory authority in planning and conducting GMP inspections.

3. SCOPE

These Explanatory Notes apply to the preparation and content of the Site Master File. Refer to national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File and supply it and version updates to the Supervisory Authority.

These Explanatory Notes apply for all kind of manufacturing operations such as production, packaging and labelling, testing, relabelling and repackaging of all types of medicinal products as well as active pharmaceutical ingredients. This guide could also be used in the preparation of a Site Master File or corresponding document by Blood and Tissue Establishments.

4. CONTENT OF A SITE MASTER FILE

Refer to Annex for the format to be used.

Annex

CONTENT OF A SITE MASTER FILE

1. GENERAL INFORMATION ON THE COMPANY

1.1 Contact information on the firm

- Name and official address of the company;
- Names and street addresses of the site, buildings and production units;
- Contact information of the company including 24 hrs telephone number of the contact personnel in the case of product defects or recalls.
- Identification number of the site such as e.g. DUNS, if available
- GPS details

1.2 Pharmaceutical manufacturing activities as licensed by the Competent Authorities.

- Brief description of manufacture, import, export, distribution and other activities as authorized by the relevant Competent Authorities including foreign authorities with authorized dosage forms/activities, respectively;
- Copy of the valid manufacturing authorisation issued by the relevant Competent Authority and, if available, also for API manufacturers in Appendix 1; or when applicable, reference to EudraGMP.
- Type of products currently manufactured on-site (list in Appendix 2);
- General information if toxic or hazardous (i.e. with high pharmacological activity and/or with sensitising properties) substances are handled on the site;
- Key parameters (e.g. toxicological, pharmacological) considered for the identification of toxic or hazardous substances handled on the site.
- Information of supervision of competent authorities, dates and outcome of latest GMP-inspections. A copy of current GMP certificate (Appendix 3) or reference to EudraGMP, should be included, if available.

1.3 Any other manufacturing activities carried out on the site

- Description of non-pharmaceutical activities on-site, if any.

2. QUALITY MANAGEMENT SYSTEM OF THE COMPANY

2.1 Description of the quality management system of the company

- Information of the quality management systems run by the company and reference to the relevant standards (as ISO, ICH…);
- Responsibilities related to the maintaining of quality system including senior management;
- Information of accredited and certified activities carried out by the company, including dates and contents of accreditations, names of accrediting bodies.

2.2 Quality policy of the company

- Brief description of elements of the quality management system e.g. organisational structure, quality manual (or equivalent documentation), responsibilities, procedures, processes;

- Description of system of product quality reviews and management review programme;
- Brief description of validation and change control policies of the company.

2.3. Release procedure of finished products

- Name(s) of responsible person(s) / Qualified Person(s) responsible for batch certification and releasing procedures;
- General description of batch certification and releasing procedure;.
- Details of products for which the control strategy employs PAT and/or Real Time Release or Parametric Release and a brief description of the procedures employed;
- Brief description of Quality Control Department's activities in the release of finished products e.g. if the review of batch documentation and release of final documentation takes place in this department;
- Role of Authorised Person/ Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation. QP activities should be specified, including arrangements when several QPs are involved;
- Arrangements for the handling of rejected materials and products.

2.4 Qualification policy for contractors and starting materials manufacturers and other parties involved in the supply chain

- When applicable, brief summary of the QRM approach for the external audit program;
- General policy for the control strategy of starting materials;
- Brief description of the quality systems used to qualify contractors, API manufacturers and suppliers, and other critical materials suppliers, including details of any associated audit and vendor qualification programmes, and the application of any Quality Risk Management principles;
- Measures taken to ensure that products manufactured are compliant with TSE (Transmitting animal spongiform encephalopathy) guidelines.

2.5 Quality Risk Management Policy of the company

- Brief description of QRM policy of the company;
- Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Details should be provided as to whether the system operates across site or limited in scope. Any application of the QRM system to assess continuity of supply should be discussed;
- Responsibilities within QRM system and integration of QRM system in the overall quality system;
- Description how the identification, assessment, control, communication and review of risks is carried out under the QRM system.

2.6 Documents and records stored or archived off-site (including pharmacovigilance data)

- List of documents/records;
- Name and address of storage site;
- Time required retrieving documents.

3. PERSONNEL

- Organisation chart showing the arrangements for quality management, production and quality control in Appendix 4 [including senior management and Qualified Person(s)];
- Number of employees engaged in the quality management, production, quality control, storage and distribution respectively;
- Key personnel; qualifications and experience requirements and responsibilities;
- Short description of training policy of the company; initial and in-service training programmes, qualification procedure of personnel;
- Health requirements for personnel engaged in production and in special activities;
- Gowning and laundry policy of the company.

4. PREMISES AND EQUIPMENT

4.1 Premises

- Short description of plant; size of the site, type and age of buildings;
- Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);
- Lay out and flow charts of the production area should be provided in Appendix 5. They should show the room classification and pressure differentials between adjoining areas and indicate the production activities of the rooms. The production operations for each product type/ dosage forms and department/ process line types, including the steps for sampling and information related the open/closed phased or isolators used, should be presented in the Appendix;
- Description of special areas for the storage and handling of highly toxic, hazardous and sensitising materials, if applicable;
- Brief description of warehouses, storage areas and specific storage conditions if needed;
- If different buildings are used for domestic and export products, list the buildings.

4.1.1 Brief description of ventilation systems

- Design criteria of the system e.g. Specification of the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%);
- Filter designs and efficiency; alarm system, limits for testing and changing;
- Policy of requalification and maintenance of the system.

4.1.2 Brief description of water systems (schematic drawings of the systems in Appendix 6) including sanitation

- Specifications of the water produced;
- Monitoring system, sampling policy and frequency of testing;
- Method and frequency for sanitation.

4.2 Equipment

- Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Appendix 7.

4.2.1 **Preventive maintenance and calibrations**

- Description of preventative maintenance and calibration system, responsibilities and recording system.
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4.2.2 **Qualification and validation**

- Brief description of the company's general policy for qualification and validation.

4.2.3 **Cleaning and sanitation**

- Cleaning validation policy of the company and method of evaluation the effectiveness of cleaning; principles for establishing allowable residue limits;
- Cleaning agents and quality of water used for cleaning;
- Brief description of cleaning methods and frequency for the, air handling system, dust extraction system, production areas and critical equipment.
- Arrangements for the handling of spillages of potent/toxic substances where applicable.

4.2.4 **GMP critical computerised systems**

- Description of GMP critical computerised systems;
- Validation policy of the computerized systems.

5. DOCUMENTATION

- Description of documentation system of the company;
- Brief description of preparing, revision, releasing, distribution, controlling and archiving systems of documents.

6. PRODUCTION

6.1. Type of products

- Type of products manufactured including
  - description of both human and veterinary products which are manufactured on the site
  - description of investigational medicinal products which are manufactured including the detailed information of production areas and personnel responsible and stage of development of IMP if different than commercial manufacturing processes
- Note any toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitising properties);
- Note which products are manufactured in a dedicated facility or on a campaign basis;
- Note any process using Quality by Design, Process Analytical Technology and/or Design Space and/or Real Time Release. For PAT application, brief description of the relevant technology, and associated computerized systems;
- Details of products manufactured for which a Design Space in accordance with ICH Q8 is employed;
- Description on the storage/warehousing of products manufactured and measures for ensuring GMP compliance.

6.2 Process validation

- Brief description of general policy for process validation. When applicable, continuous validation approach;
- Policy for reprocessing or reworking;

6.3 Material management and warehousing

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

7. QUALITY CONTROL

- Description of the Quality Control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing. The elements of the QC system e.g. specifications, test methods, validation policy (CA) and other quality related data collection should be described.

8. CONTRACT MANUFACTURING

- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- List of contractors including the addresses and contact information in Appendix 8;
- Comprehensive flow charts of supply-chains for both incoming and out-going materials and activities, including but not limited to APIs, excipients, packaging materials, bulk products, finished products, samples for QC testing – if outsourced;
- Brief description of the details of the technical contract between the contract giver and acceptor and the way in which the GMP compliance is assessed to ensure product compliance with the Marketing Authorization.

9. DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

9.1 Distribution

- 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;
- Description of a system for verification of each customer (in principle wholesaler, pharmacy, hospital, physician, veterinarian) proving that the customer is entitled to receive medicinal products and a system for regular verification of this justification
- Brief description of the controls exercised during transit, e.g. temperature monitoring/ control;
- Arrangements for product distribution and methods by which product traceability is maintained;
- Measures taken to prevent product diversion and measures to be adopted where counterfeit products are suspected and identified.

9.2 Complaints, product defects and recalls

- Brief description of the system for handling complains, product defects and recalls

10. SELF INSPECTIONS

- 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

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Appendix 1	Copy of valid manufacturing authorisation
Appendix 2	List of products (dosage forms and/or APIs) manufactured including for dosage forms the INN-names of APIs used
Appendix 3	Copy of valid GMP Certificate
Appendix 4	Organisational charts
Appendix 5	Lay outs of production areas including process, equipment, waste and personnel flows
Appendix 6	Schematic drawings of water systems
Appendix 7	List of major production and laboratory equipment used indicating the frequency for requalification
Appendix 8	List of contractors including the addresses and contact information

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