PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE

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1. DOCUMENT HISTORY

Adoption by the PIC Committee of Officials of PH 4/93	22-23 April 1993
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2. INTRODUCTION

2.1 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.

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

2.3 A Site Master File should contain adequate information but, as far as possible, not exceed 25-30 pages plus appendices. 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.

2.4 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.

3. PURPOSE

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

4. SCOPE

These Explanatory Notes apply to the preparation and content of the Site Master File. Manufacturers should refer to regional / national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File.

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. The outlines of this guide could also be used in the preparation of a Site Master File or corresponding document by Blood and Tissue Establishments and manufacturers of Active Pharmaceutical Ingredients.

5. CONTENT OF SITE MASTER FILE

Refer to Annex for the format to be used.

6. REVISION HISTORY

Date	Version Number	
1 November 2002	PE 008-1	Revision of format (in line with SOP on SOPs) and introduction; delete reference to the Site Master File as being Part B of the PIC/S inspection report; new point C.5.3 on reprocessing/rework; better distinction between Quality Assurance and Quality Control; explanation of abbreviations; minor editorial changes. All changes adopted at PIC/S Committee meeting on 8 October 2002.
1 July 2004	PE 008-2	Change in the Editorôs co-ordinates
25 September 2007	PE 008-3	Change in the Editorôs co-ordinates
1 January 2011	PE 008-4	Simplification of the document and implementation of requirements related to quality risk assessment policy

CONTENT OF SITE MASTER FILE

1. GENERAL INFORMATION ON THE MANUFACTURER

1.1 Contact information on the manufacturer

- Name and official address of the manufacturer;
- Names and street addresses of the site, buildings and production units located on the site;
- Contact information of the manufacturer including 24 hrs telephone number of the contact personnel in the case of product defects or recalls;
- Identification number of the site as e.g. GPS details, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the site or any other geographic location system[1].

1.2 Authorised pharmaceutical manufacturing activities of the site.

- Copy of the valid manufacturing authorisation issued by the relevant Competent Authority in Appendix 1; or when applicable, reference to the EudraGMP database. If the Competent Authority does not issue manufacturing authorisations, this should be stated;
- Brief description of manufacture, import, export, distribution and other activities as authorised by the relevant Competent Authorities including foreign authorities with authorised dosage forms/activities, respectively; where not covered by the manufacturing authorisation;
- Type of products currently manufactured on-site (list in Appendix 2) where not covered by Appendix 1 or the EudraGMP database;
- 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. A copy of current GMP certificate (Appendix 3) or reference to the EudraGMP database 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 MANUFACTURER

2.1 The quality management system of the manufacturer

- Brief description of the quality management systems run by the company and reference to the standards used;

[1] A D-U-N-S reference is required for Site Master Files submitted to EU/EEA authorities for manufacturing sites located outside of the EU/EEA.

- Responsibilities related to the maintaining of quality system including senior management;
- Information of activities for which the site is accredited and certified, including dates and contents of accreditations, names of accrediting bodies.

2.2. Release procedure of finished products

- Detailed description of qualification requirements (education and work experience) of the Authorised Person(s) / Qualified Person(s) responsible for batch certification and releasing procedures;
- General description of batch certification and releasing procedure;
- Role of Authorised Person / Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation;
- The arrangements between Authorised Persons / Qualified Persons when several Authorised Persons / Qualified Persons are involved;
- 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 brief summary of the establishment/knowledge of supply chain and the external audit program;
- Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical materials suppliers;
- Measures taken to ensure that products manufactured are compliant with TSE (Transmitting animal spongiform encephalopathy) guidelines.
- Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified;
- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- 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. sterilisation of primary packaging material for aseptic processes, testing of starting raw-materials etc, should be presented in Appendix 4;
- Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorisation (where not included under 2.2).

2.4 Quality Risk Management (QRM)

- Brief description of QRM methodologies used by the manufacturer;
- 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

- Brief description of methodologies used

3. PERSONNEL

- Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 5, including senior management and Authorised Person(s) / Qualified Person(s);
- Number of employees engaged in the quality management, production, quality control, storage and distribution respectively.

4. PREMISES AND EQUIPMENT

4.1 Premises

- 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 buildings should be listed with destined markets identified (if not identified under 1.1);
- Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);
- Lay outs and flow charts of the production areas (in Appendix 6) 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;
- Lay-outs of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitising materials indicated, if applicable;
- Brief description of specific storage conditions if applicable, but not indicated on the lay-outs.

4.1.1 Brief description of heating, ventilation and air conditioning (HVAC) systems

- Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%).

4.1.2 Brief description of water systems

- Quality references of water produced;
- Schematic drawings of the systems in Appendix 7.

4.1.3. Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.

4.2 Equipment

4.2.1 Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Appendix 8.

4.2.2 Cleaning and sanitation

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

4.2.3 GMP critical computerised systems

- Description of GMP critical computerised systems (excluding equipment specific Programmable Logic Controllers (PLCs)).

5. DOCUMENTATION

- Description of documentation system (i.e. electronic, manual);
- When documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): List of types of documents/records; Name and address of storage site and an estimate of time required retrieving documents from the off-site archive.

6. PRODUCTION

6.1. Type of products

(references to Appendix 1 or 2 can be made):

- Type of products manufactured including
  - list of dosage forms of both human and veterinary products which are manufactured on the site
  - 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
- Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitising properties);
- Product types manufactured in a dedicated facility or on a campaign basis, if applicable;
- Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology, and associated computerised systems.

6.2 Process validation

- Brief description of general policy for process validation;
- 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 (QC)

- Description of the Quality Control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing.

8. DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

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

- 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 the system used to verify that each customer / recipient is legally entitled to receive medicinal products from the manufacturer;
- Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/ control;
- Arrangements for product distribution and methods by which product traceability is maintained;
- Measures taken to prevent manufacturersôproducts to fall in the illegal supply chain.

8.2 Complaints, product defects and recalls

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

9. 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.

Appendix 1	Copy of valid manufacturing authorisation
Appendix 2	List of dosage forms manufactured including the INN-names or common name (as available) of active pharmaceutical ingredients (API) used
Appendix 3	Copy of valid GMP Certificate
Appendix 4	List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply-chains for these outsourced activities
Appendix 5	Organisational charts
Appendix 6	Lay outs of production areas including material and personnel flows, general flow charts of manufacturing processes of each product type (dosage form)
Appendix 7	Schematic drawings of water systems
Appendix 8	List of major production and laboratory equipment

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