The Drug Manufacturer's Guide to Site Master Files

From the Editors of

THE FOOD & DRUG LETTER

The Executive Briefing Series

FDANEWS

The Drug Manufacturer's Guide to Site Master Files

Table of Contents

About the Author

Cornelia Wawretschek is a pharmaceutical technical assistant with GxP Services in Germany and a freelance consultant for quality assurance. Prior to her consulting work, she worked for Schering AG Berlin in its department of pharmaceuticals as an analyst, chemical development and quality assurance, responsible for GMP optimization, SOP systems, manufacturing documentation, preparation and execution of audits and inspections by authorities, training programs, qualification and validation.

Introduction

Before competent regulatory authorities conduct an inspection, they will ask for a drug manufacturer's current Site Master File to become familiar with the company.

The Site Master File is a company description compiled by the drug manufacturer that contains all good manufacturing practice (GMP) aspects.

It is also a regulatory requirement. You can find the *Explanatory Notes for the Preparation of a Site Master File* (Appendix A) in Part III of the EU GMP Guideline, which was republished in December 2010. The format and structure of the document correspond to F.5 PIC/S PE 008-4: *Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File*, which can be found in Appendix B. The Site Master File document is also explicitly required in Part I of the EU GMP Guideline in Chapter 4: Documentation (revised version of January 2011).

The company description should meet all documentation requirements according to GMP standards. The authorities will examine the Site Master File and all references and appendices for accuracy (plausibility), completeness and actuality. So the Site Master Files becomes part of the quality assurance system of a company.

A Site Master File has two purposes. First, it is intended for submission to the authorities. Second, it is expected to be a part of the management of suppliers and service providers. The Site Master File plays a further important role in project and company audits in connection with purchase and sale of shareholdings (due diligence audits).

This management report will explain the purpose of the Site Master File, why it is needed, how it is structured, its scope, the associated chapters of the EU GMP Guideline that comprise the Site Master File and what information is expected in each chapter.

History

In April 1993 the *Pharmaceutical Inspection Convention* (PIC) published Guideline PH 4/93, a detailed guidance for preparing a Site Master File in the form of a recommendation.

In November 2002 *Pharmaceutical Inspection Co-Operation Scheme* (PIC/S) published a revision of this document under the new title PE 008-1. The paper was supplemented with two important points: First the chapter on production updated the section *Reprocessing and Reworking* to include a topic on reworking processes. Secondly, the tasks and responsibilities of quality assurance versus quality control were clarified. In addition to these two major changes, the editor's coordinates were updated in the PE 008-2, July 2004 and PE 008-03, September 2007 revisions.

Focus of Recent Update (PE 008-4)

The Annex shaping the format and structure of contents of the Site Master File was completely revised (Chapter F.5) in version PIC/S PE 008-4 of January 2011. In addition, the contents of individual chapters were restructured, adapted to the current requirements and supplemented by numerous innovations, including:

- Quality management system (QMS) of the manufacturer;
- Release procedures;
- Quality Risk Management (QRM);
- Product Quality Review (PQR);
- Dealing with suppliers and service providers;
- Compliance with Transmitting Animal Spongiform Encephalopathy (TSE) guidelines;
- Use of modern control strategies such as Process Analytical Technologies (PAT) or parametric release;
- Traceability of batches in the supply chain; and
- Protection against counterfeiting and falsification.

It more closely examines the pharmaceutical quality system based on GMP regulations. As a consequence the version is less detailed. In addition, some topics are no longer listed in chapters. For example, training, health and personnel hygiene are not explicitly listed in Chapter 2 *Personnel* and qualification, validation and calibration are no longer mentioned in Chapter 3 *Premises*. However, these omissions do not mean that drug manufacturers can neglect these topics.

Version PIC/S PE 008-4 was the first guideline to be included in the newly created Part III of the EU GMP Guideline. The document was published under the title *Explanatory Notes on the Preparation of a Site Master File.* The supplement *for Pharmaceutical Manufacturers* was omitted.

Regulatory Requirements

The Site Master File as a document describing the GMP-related activities of the manufacturer is mentioned in Chapter 4 of the EU GMP Guideline in the section *Required GMP Documentation*. A company's obligation to answer questions and provide information to regulatory authorities is fixed in national legislation, as for example in § 66 of the *German Act on Medicinal Products* (AMG).

As for the European Medicines Agency (EMA), the *Guideline on the Compilation of Community Procedures on Inspections and Exchange of Information* (February 2011) makes a number of references to the necessity of consulting a Site Master File. It is a document aimed at standardizing inspections by regulatory authorities within the EU (Chapter C.10)

The document structure of PIC/S PE 008-4 (Chapter F.5) is similar to the previous versions:

1. Introduction
2. Purpose
3. Scope
4. Content of Site Master File
5. Revision history
6. Annex

In the following sections, italicized text indicates changes, followed by author thoughts and analysis.

Introduction

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 needs only describe those operations, e.g., analysis, packaging, etc.

The pharmaceutical manufacturer is responsible for the preparation of the Site Master File. In practice it is left to the respective drug manufacturer to decide who actually prepares the document. The contents of the Site Master File should reflect actual processes and procedures and must not conflict with the corresponding documentation. Therefore it makes sense to entrust the process to an interdisciplinary team of all divisions concerned with the preparation of the Site Master File. In many cases the head of quality assurance will coordinate this process.

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.

PIC/S PE 008-4 guidelines are primarily intended for submission to the regulatory authority. If the document is used for other purposes, the manufacturer shall decide whether to shorten the document or include other information.

… 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 …

An inspector does not expect narrative but rather short texts with references to appendices, simple plans, drawings and schematic layouts in DIN A4 format instead of detailed text. If necessary, he or she will ask questions. However, the complete Site Master File including lists, appendices and references may– depending on the size of the site and particularities of the mode of operation–reach a considerable length.

… The Site Master File, including appendices, should be readable when printed on A4 paper sheets.

The Site Master File must not necessarily be available in printed form. A transmission in electronic form is also possible. However, inspectors should be able to read the Site Master File, particularly plans, schematic layouts or comprehensive tables, when printed on A4 (or 8 1/2" by 11") paper sheets.

… 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.

The manufacturer should prepare and administer the Site Master File according to GMP requirements and update it at defined intervals. I recommend an interval of two years. It's also helpful to establish a change history to ensure transparency of changes and amendments made.

In conclusion, it takes considerable effort to prepare and maintain a Site Master File. However, the document is so important for the authorities and other external interested parties that it justifies the effort In addition, if manfacturers use the Site Master File as a checklist, it allows them the possibility of reconsidering all operations and procedures. They can then close gaps and optimize quality management.

Purpose

The purpose of a Site Master File is to fulfill the European regulatory requirements. The document provides a good overview of the products, processes and organization of a drug manufacturing site. In addition, it is also helpful and valuable for internal transparency.

Scope

… 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.

Although there is no general obligation to prepare a Site Master File, the European Commission notes: "These Explanatory Notes are intended to provide guidance on the recommended contents of a Site Master File. The need for a Site Master File is mentioned in Chapter 4 of the EU GMP Guideline."

In Germany, the German Ordinance on the Production of Pharmaceuticals and Active Substances (AMWHV) points to the EU GMP Guideline in its Article 3 on the interpretation of the Principles of GMP, the latter thus becoming legally binding. PIC/S PE 008-4 goes on to say:

… These Explanatory Notes apply for all kind of manufacturing operations such as production, packaging and labeling, 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 Blood and Tissue Establishments and manufacturers of Active Pharmaceutical Ingredients.

With the inclusion into Part III of the EU GMP Guideline and reference being made to Chapter 4, Part I the Site Master File becomes binding for the fields of application mentioned. If an inspector asks a pharmaceutical ingredient manufacturer for its Site Master File, the firm should adjust the document correspondingly.

Content of Site Master File

See section on the Annex.

Revision history

Changes in Version PE 008-4 are justified as follows: "Simplification of the document and implementation of requirements related to quality risk assessment policy."

Annex

The Annex contains information on the format manufacturers should use and provides the content of individual sections based on this structure.

The structure is based on the content of the EU GMP Guideline:

1. General information on the manufacturer
2. Quality management system of the manufacturer
3. Personnel
4. Premises and equipment
5. Documentation
6. Production
7. Quality control (QC)
8. Distribution, complaints, product defects and recalls
9. Self inspections

The manufacturer provides further information on the Site Master File in references to Appendices. The advantage of putting the information into the Appendices is that the company can update them independently of each other and of the master document.

Each Chapter refers directly to the required Appendices:

- Appendix 1: Copy of valid manufacturing authorization;
- 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 flowcharts of the supply chains for these outsourced activities;
- Appendix 5: Organizational charts;
- Appendix 6: Layouts 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; and
- Appendix 8: List of major production and laboratory equipment. A sample document can be found in Appendix C of this report.

For a sample Site Master Plan, see Appendix D.

The following sections will describe each chapter of the Annex in more detail. Text in italics indicates the most important changes and innovations compared to version PIC/S PE 008-3 and will be followed by author thoughts and analysis at the end of the corresponding section. Text that shifted to other paragraphs or were completely omitted will be discussed at the end of the chapter.

1. General information on the manufacturer

This chapter contains general information on the company or the premises to be described.

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-hour telephone number of the contact personnel in the case of product defects or recalls; and
- Identification number of the site, such as 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.

Note on 1.1: It is not necessary to mention the corresponding Internet address(es), but I recommend it. The D&B D-U-N-S number) is a nine-digit figure code that clearly identifies companies worldwide. Companies may thus be assigned to their parent companies, branches, subsidiaries and head offices.[1]

1.2 Authorized pharmaceutical manufacturing activities of the site

- *Copy of the valid manufacturing authorization 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 authorizations, this should be stated;*
- *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; where not covered by the manufacturing authorization;*

[1] http://www.upik.de/upik_anfrage.cgi?new=1

- *Type of products currently manufactured on-site (list in Appendix 2) where not covered by Appendix 1 or the EudraGMP database; and*
- *List of GMP inspections of the site within the last five 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.*

Note on 1.2: The changes now make it mandatory for companies to submit a copy of the manufacturing authorization and mention the EudraGMP access codes. The EudraGMP database run by the EMA contains data on manufacturing and import authorizations, manufacturing and import permits, and GMP Certificates to indicate compliance with the principles of GMPs. Parts of the database are publicly available and provide information about the manufacturing practice of the manufacturer, import licenses and GMP certificates.

1.3 Any other manufacturing activities carried out on the site

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

Figure 1 shows where you can find the contents of former paragraph C.1 in the new structure of the Site Master File.

Figure 1: Notification of changes to former paragraph C.1

PE 008-3	Topic	PE 008-4
C.1.4	Contact information	Chapter 1.1
C.1.5	Current products	Chapter 1.2; 6.1
C.1.6	Description of the company	Chapter 1.1; 1.3; 4.1
C.1.7	Number of employees	Chapter 3, para 2
C.1.8	Use of external support	Chapter 2.3, para 5
C.1.9	Quality management	Chapter 2

2. Quality management system of the manufacturer

Quite a bit of information has been added to this chapter. A manufacturer should provide a detailed presentation of its quality policy and a description of the quality assurance system. The following list shows the individual aspects, which a manufacturer must describe in the Site Master File:

- The quality management system of the manufacturer;
- Release procedure of finished products;
- Management of suppliers and contractors;
- Quality risk management (QRM); and
- Product quality review (PQR).

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;*

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

Note on 2.1: If your company follows other standards (i.e., the DIN ISO standard series) in addition to GMP, you should mention it here. Explain the role of senior management in maintaining the quality system as well as the extent of management's involvement in quality assurance procedures.

2.2 Release procedure of finished products

- *Detailed description of qualification requirements (education and work experience) of the Authorized Person(s)/Qualified Person(s) responsible for batch certification and releasing procedures;*
- *General description of batch certification and releasing procedure;*
- *Role of Authorized Person/Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorization;*
- *The arrangements between Authorized Persons/Qualified Persons when several Authorized Persons/Qualified Persons are involved; and*
- *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 significant amount of information has been added to the former chapter C.7 *Contract Manufacture and Analysis* (PIC/S PE 008-3):

- *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 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., sterilization of primary packaging material for aseptic processes, testing of starting raw materials, etc., should be presented in Appendix 4; and*
- *Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorization (where not included under 2.2).*

Note on 2.3: The paragraph on the use of outside assistance (bullet point 5) was also contained in paragraph C1.8 of the preceding version of the document. The current version recognizes the fact that outsourcing has long since been the current practice in companies.

2.4 Quality risk management (QRM)

- *Brief description of QRM methodologies used by the manufacturer; and*
- *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.

The company should describe the implementation of regular product quality reviews (PQR) as required by the EU GMP Guideline, Part I, Chapter 1.4. A summary of the other changes concerning former paragraph C.2 can be found in Figure 2.

Figure 2: Notification of changes to former paragraph C.2

PE 008-3	Topic	PE 008-4
C.2.3	Training	has been omitted
C.2.4	Health of Personnel	has been omitted

3. Personnel

Compared to the former paragraph C.2, this version is much shorter. The new chapter no longer discusses the topics of training, health requirements and personnel hygiene requirements. Instead, the chapter is limited to:

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

Bullet point 2 corresponds to former paragraph C. 1.7 as noted in Figure 1.

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);

- *Layouts 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;*
- *Layouts of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitizing materials indicated, if applicable; and*
- *Brief description of specific storage conditions if applicable, but not indicated on the layouts.*

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; and*
- *Schematic drawings of the systems in Appendix 7.*

4.1.3 Brief description of other relevant utilities, such as steam, compressed air, N2, etc.

Note on 4.1: The new chapter omits the description of maintenance (formerly C.3.6). Previously, the focus was on manufacturing areas. Now there is a focus on storage areas as well. Appendix 6 requires classification of rooms and pressure differentials between adjoining areas for all production areas. The purpose of the required layouts is to allow the inspector a rapid and structured overview of the premises and related equipment.

Layouts and site plans should be in DIN A4 format and should only be larger in exceptional cases. Identify the author and the date of creation (version) of the plans. Choose names of buildings and rooms, as well as numberings, so that they correspond to the designations on site and in other documents (e.g., SOPs, documentation on cleaning and manufacturing documentation).

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 computerized systems

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

Note on 4.2: The list of equipment is new in Appendix 8. The description of qualification, validation and calibration is no longer required. The same applies to the validation of cleaning procedures. Further changes to former paragraph C.3 are shown in Figure 3.

Figure 3: Notification of changes to former paragraph C.3		
PE 008-3	**Topic**	**PE 008-4**
C.3.2	Construction and Finishes	has been omitted
C.3.4	Special areas	Paragraphs 4.1; 6.1
C.3.6	Maintenance	has been omitted
C.3.9	Qualification, validation	has been omitted

5. Documentation

- Description of documentation system (i.e., electronic, manual); and
- *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.*

Note on 5: The description of the documentation system should include the following topics:

- Classification of documents and approval procedures for instructions, records and reports;
- Responsibilities for the preparation, revision and distribution of documents;
- Access rights and storage;
- Control of documentation;
- Retention periods; and
- Arrangements for archiving and data backup.

6. Production

6.1 Type of products

References to Appendix 1 or 2 can be made here. This chapter calls for:

- 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 sensitizing properties);
- *Product types manufactured in a dedicated facility or on a campaign basis, if applicable; and*
- *Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology and associated computerized systems.*

Note on 6.1: In previous versions of the Site Master File, Chapter C.1.5 described the handling of toxic or hazardous substances. The use of modern technologies is considered in bullet points 3 and 4.

6.2 Process validation

Reprocessing and reworking may influence validated processes. For this reason former paragraphs C.5.3 and C.5.5 have been combined:

- Brief description of general policy for process validation; and
- Policy for reprocessing or reworking.

6.3 Materials management and warehousing

Former paragraphs C.5.2 and C.5.4 have been combined:

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

Further changes concerning former paragraph C.5 are shown in Figure 4.

Figure 4: Notification of changes to former paragraph C.5

PE 008-3	Topic	PE 008-4
C.5.2	Handling of starting materials	Chapter 6.3
C.5.3	Reprocessing and rework	Chapter 6.2, para 2
C.5.4	Rejected materials	Chapter 6.3, para 2
C.5.5	Process validation	Chapter 6.2, para 1

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.*

Note on 7: This chapter should contain a brief description of elements of the quality control system and activities carried out. Further changes concerning former paragraphs C.6 and C.7 are shown in Figure 5.

Figure 5: Notification of changes to former paragraphs C. 6 and C. 7

PE 008-3	Topic	PE 008-4
C.6.1	Procedures for the release of finished products	Chapter 2.2, para 2
C.7.1	Contract manufacture and analysis	Chapter 2.3

8. Distribution, complaints, product defects and recalls

8.1 Distribution to the part under the responsibility of the manufacturer

- *Types (wholesale license holders, manufacturing license 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; and*
- *Measures taken to prevent manufacturers' products to fall in the illegal supply chain.*

8.2 Complaints, product defects and recalls

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

Note on 8: This chapter focuses on how to ensure full batch traceability from the manufacturer to the customer. It deals with the topic areas complaints, product defects and recalls with respect to batch traceability.

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.*

Appendices

A. Explanatory Notes on the Preparation of a Site Master File

B. Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File

C. Sample Document: SMF Appendix 8 Equipment and Devices for Production and Quality Control

D. Sample Site Master File

Appendix A: Explanatory Notes on the Preparation of a Site Master File

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Pharmaceuticals

Brussels,
SANCO/C8/AM/sl/ares(2010)1064603

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Explanatory Notes on the preparation of a Site Master File

These notes are intended to provide guidance on the recommended content of the Site Master File. A requirement for a Site Master File is referred to in Chapter 4 of the GMP Guide.

Status of the document: New

Commission Européenne, B-1049 Bruxelles / Europese Commissie,
B-1049 Brussel - Belgium
Telephone: (32-2) 299 11 11

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 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.

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 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.

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, 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.

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 is 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. 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, 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 Blood and Tissue Establishments and manufacturers of Active Pharmaceutical Ingredients.

4. CONTENT OF SITE MASTER FILE

Refer to the Annex for the format to be used.

ANNEX: 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, or any other geographic location system, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the site[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 authorizations, this should be stated.
- 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; where not covered by the manufacturing authorization;
- Type of products currently manufactured on-site (list in Appendix 2) where not covered by Appendix 1 or EudraGMP entry;
- 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;
- Responsibilities related to the maintaining of quality system including senior management;

[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.

- 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. sterilization 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 Authorization (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 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 computerized 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 manufacturers' products 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

Appendix B: Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 008-4
1 Annex
1 January 2011

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

Editor: PIC/S Secretariat

e-mail: info@picscheme.org
web site: http://www.picscheme.org

TABLE OF CONTENTS

1. DOCUMENT HISTORY

Adoption by the PIC Committee of Officials of PH 4/93	22-23 April 1993
Entry into force of PH 4/93	April 1993
Entry into force of PE 008-1	1 November 2002

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 manufacturer's 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 Editor's co-ordinates
25 September 2007	PE 008-3	Change in the Editor's 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 manufacturers' products 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

****

Appendix C: Sample Document: SMF Appendix 8 Equipment and Devices for Production and Quality Control

The equipment used for production and quality control is listed in the following. Critical equipment parts are underlined. Further critical equipment parts have been identified in the context of equipment qualification and may be found in the risk analyses of the corresponding qualification documentation.

In 4.2.1 the Site Master File Guideline requires a list of key production and quality control equipment wherein critical elements have to be identified. Unfortunately there is no practical definition as to what 'critical' means in this context. By its very nature almost every device to be qualified during qualification comprises more or less critical device parts, which deserve particular attention during qualification and later on in the life cycle of said device.

A list of all these device components would by far exceed the framework of the present Annex to the Site Master File and would—compared to other aspects of Good Manufacturing Practice—give too great a significance to the criticality of single components.

Maas & Peither Pharma GmbH have therefore decided to only mark the CIP system as critical and to otherwise refer to the qualification documents.

Production equipment and devices

- Weighing instruments, partly with connected printers
- Laminar flow
- Dust extraction
- Lifting devices
- Drum blenders, intensive mixers and free-fall blenders
- Sieve machines
- Fluid bed dryers/coaters/granulators with CIP system
- Spray dryers with CIP system
- Moist granulators
- Granulate mixers
- Passing sieve
- Compactors
- Extruders/spheronizers
- Cabinet dryers
- Eccentric press
- Rotary tablet presses (pilot and high performance machines)
- Deburring machines/dedusters
- Metal detectors
- Colloid mill
- Air jet mill
- Suspension tanks

- Stirring vessel with integrated heating/cooling system
- Coating pan
- Coating and film coating systems
- Automatic screw dosing unit
- Capsule filling machines (manual, pilot and high performance machines)
- Capsule deduster
- Capsule polishing machine
- Capsule weighing system
- Blister mashines with control camera
- Cartoning machines with camera, weighing unit and bar code reader
- Stamping tool
- Sealing machine
- Label printer
- Blister labeling unit
- Blister emptying machine

Quality control equipment and devices*

- Weighing instruments with connected printers
- Breaking strength tester
- Decomposition tester
- Dissolution tester
- Abrasion tester for tablets (friability tester)
- Automatic volumetric analyzer
- Automatic sieve analyzer
- Particle size measuring instrument (laser diffractometer, dry dispersion)
- Chromatographic systems (HPLC, DC)
- Spectrophotometer (UV/VIS, IR, NIR)
- pH meter
- Conductivity meters
- Mikroscopes
- Melting point apparatus
- Polarimeter
- Refractometer
- Titrators for conventional/potentiometric/Karl-Fischer titration
- Infrared dryer for determination of water content
- Colorimeter
- Device for differential thermal analysis
- Tensiometer
- Semiautomatic testing system for tablet hardness, weight, thickness and diameter

* Devices partly in the IPC laboratory

Appendix D: Sample Site Master File

Next check by: 31.12.2012

Site Master File created	(Date/signature)
Site Master File checked	(Date/signature)
Site Master File approved	(Date/signature)

Contents

A word in advance...

In a joint project the European Commission and Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S) have thoroughly revised and supplemented the content of the recommendations on creating a Site Master File, which was last modified in 2002. After PIC/S published the new document PE 008-4 at the end of 2010/start of 2011 on its website, the corresponding, virtually identical Directive of the European Commission was published in February 2011 for information purposes as the first document in the new Part III of the EU-GMP Guidelines. This was followed in January 2011 by the publication of the revised Chapter 4 of the guidelines. The Site Master File is listed there as one of the compulsory quality documents for pharmaceutical manufacturers; all pharmaceutical manufacturers are now obliged to maintain a Site Master File.

Two major issues are covered by the Site Master File.

- **Modern quality management**
  Quality management has its own chapter with comprehensive tasks not only on the quality management system but also on batch approval, supplier management, quality risk management and product quality checks. As a result, the ICH guidelines ICH Q9 and ICH Q10, which were also published as the new Part III of the EU GMP Directive, are now also found in the Site Master File.
- **Globalized markets and the resulting increase in falsification and the illegal sale of medicinal products and active substances**
  Even if the focus of the SMF remains unchanged in terms of its purpose in the description of the operational issues and local processes, the networks between companies along the whole delivery chain are much more detailed and specific than they were before. The relevant information in Chapters 2 and 8 of the SMF range from references to raw materials via the participation of contract manufacturers and laboratories right up to the sale of bulk and finished products.

1 General information on the manufacturer

Maas & Peither Pharma GmbH and all of the processes described here are imaginary. Any agreement with or similarity to existing or former companies is therefore pure chance or due to the general nature of the applicable GMP rules. For this reason this sample Site

Master File also does not contain all of the necessary appendices, such as the manufacturing authorization, location, room and equipment plans, etc.

1.1 Manufacturer contact information

Maas & Peither Pharma GmbH,
Pharmastraße 123, 60000 Pharmahausen, Germany

Telephone: +49 (0)60 - 12 34 - 0
Fax: +49 (0)60 - 12 34 - 99
Email: welcome@maas-peither-pharma.de
Internet: www.maas-peither-pharma.de

24-hour hotline:
Poison Information Centre for the States of Rhineland Palatinate and Hesse, +49 (0)6131 – 19 24 0

GPS coordinates:
99° 9' 99.9" N
9° 99' 99.99" O

Information that allows the unique identification of the affected company may include the GPS coordinates and the so-called D-U-N-S number®. The D-U-N-S number (D-U-N-S = Data Universal Numbering System, introduced by Dun & Bradstreet in 1962) is a nine-digit numerical code that enables companies around the world to be uniquely identified. The D-U-N-S number is assigned centrally by Dun & Bradstreet.

1.2 Approved pharmaceutical manufacturing activities of the business

All information on the pharmaceutical activities carried out in line with the approval of the relevant authority and the type of products manufactured can be seen from the copy of the manufacturing authorization in Appendix 1.

Maas & Peither Pharma GmbH is subject to regular inspections by the Regional Board Darmstadt pursuant to Section 64 of the German Pharmaceuticals Act (AMG); the last inspection took place on 01.04.2011; the corresponding GMP certificate is located in Appendix 3.

1.3 Other manufacturing activities undertaken in the production site

Only the pharmaceutical manufacturing activities stated in the manufacturing authorization are carried out.

Any other pharmaceutical or non-pharmaceutical activities must be stated here. Non-pharmaceutical manufacturing activities include the manufacture of cosmetics, food supplements or cleaning agents. Quality risks *may* emanate from such manufacturing activities (e.g., cross-contamination, increased microbiological loads, increased vermin occurrence) for medicinal products produced at the same locations and these must be countered by suitable measures. The manufacture of certain substances (e.g., pesticides and herbicides) is completely prohibited in rooms used to manufacture medicinal products.

2 Manufacturer's quality management system

2.1 The manufacturer's quality management system

Maas & Peither Pharma GmbH has implemented a quality management system that is based the European GMP regulations. The aim of this quality management system is to manufacture medicinal products such that they are suitable for their planned use, comply with the approval requirements and have a guaranteed level of security, quality and effectiveness. The focus is on the safety and protection of the patient.

This aim is achieved using a comprehensive process-oriented quality concept that covers both the quality-related internal processes (especially the warehousing, production and quality control processes as well as documentation and training) and effective control and monitoring of the quality related external processes (in particular supplier management, contract manufacture and order analysis).

The basis for this quality concept is the adequate utilization of resources guaranteed by business and departmental management. This affects the premises and equipment and in particular the availability of expert, adequately experienced and appropriately qualified employees. Their tasks and responsibilities are defined in written job descriptions.

All processes are executed as per the written instructions for trained employees and documented in full. This data is used to assess the product quality during batch release and is also assessed periodically to assess the efficiency of the quality management system.

Any variances from approved processes must be documented, approved by authorised employees and studied with the appropriate involvement of the responsible employees (LdH, LdQ, expert) and quality assurance (potential adverse effect on product quality of the affected and other batches, necessary corrective and preventative measures).

The effectiveness of the quality management system is monitored continuously. To achieve this, regular self-inspections are carried out as are others when the need arises. The appropriateness of all of the preventive and corrective measures undertaken is also assessed on a regular basis. Maas & Peither Pharma GmbH is also subject to regular inspections by the Regional Board Darmstadt pursuant to Section 64 of the German Pharmaceuticals Act (AMG) and is audited regularly by its customers.

It is explicitly desired that various standards (e.g., EU/US GMP, DIN EN ISO 9001, DIN EN ISO/IEC 17025 etc.) are stated. This also applies to the list of any available accreditations or certifications associated with this matter.

2.2 Approval process for finished products

2.2.1 Qualification requirements for the expert

The qualification requirements for the expert match the requirements of Section 15 of the German Pharmaceuticals Act (AMG). Maas & Peither Pharma also has the following minimum requirements:

- Promotion
- Several years of experience in a company producing solid forms of medicinal products
- Good knowledge of the regulatory requirements and the current status of science
- Comprehensive knowledge relating to pharmaceutical product development and approaches for clinical studies
- In-depth technical knowledge
- High level of quality awareness

These and any other additional requirements as well as limiting the responsibility between the two experts at Maas & Peither Pharma GmbH form part of the relevant job description.

The expert must be stated with the qualification *requirements* demanded. Information on the role of the expert in connection with quarantines and releasing finished products and in assessing compliance of the manufacturing process with the relevant approval documentation is required. If there are several experts, describe their responsibility limits.

2.2.2 Batch certification and approval

After completing batch manufacture the production and packing reports are to be checked for completeness and correctness by an authorized person from the production department; the LdH then undertakes the final check and approval of the manufacturing documentation. The process of analytical approval or rejection of the products, including the approval of the test report by the LdQ, is described in Point 7, Quality control (QC).

The manufacturing documentation approved by the LdH and the test log approved by the LdQ is passed on for checking initially to quality assurance and then to the expert. The documented check of the batch documentation by quality assurance explicitly also covers the check on the agreement with the dossier in the relevant destination country.

The expert decides on the approval or rejection of the relevant batch on the basis of their final check on all of the documentation. On approval the expert signs the certificate of compliance and thus approves the batch and then also releases it for use in LOGIFIXX. The release or rejection is documented directly in the batch list.

If finished medicinal products or test preparations are produced or tested on the basis of contracts (with Maas & Peither Pharma GmbH as the client and/or contractor), the processes, documentation and responsibilities are laid down in the responsibility limitation agreements. This also applies to any participation of other experts. If the responsibility is with Maas & Peither Pharma GmbH the process follows information provided here while considering the documentation specific to the contract.

The process described here is regulated in an SOP.

Such processes as Process Analytical Technology (PAT), Real Time Release or parametric release are not used.

2.3 Management of suppliers and contractors

The company's networks across the whole supply chain must be shown.

The raw materials used are the focus of the supplier qualifications and the audit programme, supplemented by information on the measures to be taken if there is (the suspicion of) falsification. The now compulsory information for TSE compliance concerns the safety of the materials used.

The necessary information on any contract manufacturers and laboratories goes far beyond the usual list: Detailed flow diagrams

that specifically show the interactions between activities that are outsourced and carried out by the company itself are to be located in a separate appendix. The limitation of responsibility between the client and contractor in guaranteeing approval compliance must also be explained.

2.3.1 Supplier qualification

The manufacturers and suppliers of goods and services that are relevant to quality as well as contract manufacturers and laboratories are qualified under the responsibility of quality assurance in cooperation with the LdH or LdQ and with the involvement of the relevant affected departments with the aim of maintaining the quality stipulated in the specifications and contracts for products and services.

The qualification program covers the following steps:

- Setting the requirements for suppliers or service providers;
- Pre-selection of (new) suppliers or service providers;
- Assessment of the supplier or service provider;
- Contractual agreements;
- Approval of the supplier (“potential" supplier) or service provider; and
- Ongoing monitoring of the supplier or service provider and, if appropriate, further qualification to become a "qualified" or "certified" supplier.

The scope of the relevant qualification measures, including any audits to be carried out, is set using the risks and a grade concept. For this, suppliers of active substances, primary packaging, printed packaging or critical resources as well as contract manufacturers and laboratories are audited repeatedly as part of the initial assessment and during ongoing monitoring.

If the ongoing or specific monitoring gives rise to areas of concern for quality problems, these are investigated and assessed, and appropriate corrective measures are agreed with the suppliers or service providers as required. If the problem continues the supplier or service provider may be downgraded or blocked.

2.3.2 Conformity of the medicinal product with the TSE guidelines

All medicinal products are produced in agreement with the applicable TSE guidelines. In order to guarantee this the relevant EDQM certificates are requested for the raw materials used if possible. If there is no EDQM certificate, the necessary scientific information is put together for materials from

species that are relevant for TSE and these provide evidence for compliance with the TSE guidelines. These include:

- Stating the species and animals' country of origin;
- Health status and age of the animals;
- Tissues and organs used (including the assessment of potential cross-contamination from other organs during and after death);
- Description of the manufacturing process, including all data on a reduction in any TSE pathogens during manufacture and information on the batch size and cleaning the production equipment; and
- Documents on the ability to trace the materials

2.3.3 Measures for (suspicion about) falsification of raw materials and products

The approach if there is a justified suspicion of product falsification is described in 8.2.1 Complaints and product faults. The approach for suspicions about falsified raw materials is similar and also involves all participants in the legal sales chain of the affected material.

2.3.4 Use of external service partners in connection with manufacture and quality controls

The necessary information on using external scientific, analytical and technical assistance must be supplemented to include a list of contract manufacturers and laboratories (in Appendix 4). This list should contain all of the essential (contact) information for the appointed companies and flow diagrams on the logistics of the outsourced activities (see Appendix 4).

Maas & Peither Pharma GmbH works on the basis of contracts with the following stipulated service partners. Contract manufacturers and laboratories are to be indicated by underline; the necessary flow diagrams to show the logistical interactions for cooperation with these contractors are found in Appendix 4.

2.3.4.1 Contract manufacturer and external warehouse

Lohnhersteller GmbH: Packaging of clinical trial drugs
Packstraße 45, 70007 Packstadt,
Tel.: 0707 - 12 34 56 - 0, Fax: 0707 - 12 34 56 - 9

Lohnlager GmbH: External warehouse
Logistikstraße 11, 60001 Pharmahausen-Neuhausen,
Tel.: 060 - 90 12 34 - 0, Fax: 060 - 90 12 34 - 9

2.3.4.2 Contract laboratories and analytical-scientific services

Laboratory A GmbH: Clean room monitoring
Laborstraße 1, 12345 Laborhausen,
Tel.: 0100 - 12 34 56 - 0, Fax: 0100 - 12 34 56 - 9

Laboratory B AG: Stability storage
Laborstraße 2, 23456 Laborhausen,
Tel.: 0200 - 12 34 56 - 0, Fax: 0200 - 12 34 56 - 9

Laboratory C GmbH & Co. KG: GC, TLC (test must be notified under Section 67 AMG) and AAS, DSC, elementary analysis, ICP, MS, NMR, x-ray diffractometry
Laborstraße 3, 34567 Laboranger,
Tel.: 0300 - 12 34 56 - 0, Fax: 0300 - 12 34 56 - 9

Laboratory D GmbH: Microbiological analysis
(Test with manufacturing authorization pursuant to Section 13 AMG)
Laborstraße 4, 45678 Labordorf,
Tel.: 0400 - 12 34 56 - 0, Fax: 0400 - 12 34 56 - 9

2.3.4.3 Technical services

Technical service A: Workplace medical service
Technikstraße 5, 60000 Pharmahausen,
Tel.: 060 - 23 45 67 - 0, Fax: 060 - 23 45 67 - 9

Technical service B GmbH: Laundry
Technikweg 6, 60000 Pharmahausen,
Tel.: 060 - 34 56 78 - 0, Fax: 060 - 34 56 78 - 9

Technical service C GmbH & Co. KG: Maintenance and calibration of the clean room
Technikstraße 7, 78901 Technikberg,
Tel.: 0500 - 12 34 56 - 0, Fax: 0500 - 12 34 56 - 9

Technical service D GmbH: Cleaning service for warehouse, manufacturing areas and laboratories
Technikpfad 8, 60000 Pharmahausen,
Tel.: 060 - 56 78 90 - 0, Fax: 060 - 56 78 90 - 9

Technical service E GbR: Advice on workplace safety/fire protection/environmental protection
An der Technik 9, 60000 Pharmahausen,
Tel.: 060 - 78 90 12 - 0, Fax: 060 - 78 90 12 - 9

Technical service F GmbH: Pest control
An der Wiese 10, 60000 Pharmahausen,
Tel.: 060 - 22 33 44 - 0, Fax: 060 - 22 33 44 - 9

Technik G GmbH: Auditing suppliers and GMP service providers
Auf der Wacht 11, 60606 Pharmastadt,
Tel.: 061 - 11 33 55 - 0, Fax: 061 - 11 33 55 - 9

In addition to the service providers stated here, some of the manufacturers of the production and laboratory devices are used to maintain and calibrate these devices.

2.4 Quality risk management (QRM)

Maas & Peither Pharma GmbH uses the quality risk management (QRM) process systematically in all GMP-relevant areas with the aim of detecting and assessing risks relating to the safety, effectiveness and quality of the medicinal products over their complete lifecycle. The QRM process is therefore also applied to the supply chain processes in order to guarantee the appropriate and continuous provision of approved medicinal products from Maas & Peither Pharma GmbH as defined by Section 52b AMG.

The QRM process covers the following process steps and sub-steps (the specific approach is defined in an SOP):

- QRM 1 Risk Assessment
  Risk Identification
  Risk Analysis
  Risk Evaluation
- QRM 2 Risk Control
  Risk Reduction
  Risk Acceptance
- QRM 3 Risk Communication
- QRM 4 Risk Review

During the risk assessment (QRM 1), potential risks are identified (*risk identification*) and graded according to the likelihood of their occurrence and effects, as well as the likelihood of their discovery *(risk analysis*). As part of the risk evaluation, the previously identified and analyzed risks are graded (semi-)quantitatively for the need of further analysis during the next process stage (*risk control*). As part of this risk control (QRM 2) the options for reducing the risk are checked and if necessary appropriate measures are defined and a decision is taking on accepting the remaining (residual) risk.

The work in QRM steps 1 and 2 is documented and provided to the relevant functions identified during the QRM process as part of *Risk Communication*

(QRM 3). The fourth step of the QRM process, *risk review* (QRM 4) ensures if necessary that the requirements for the risk assessment undertaken apply on a continuous basis or that new assessments are made if there are changes.

2.5 Product quality reviews

For each approved product a product quality review (PQR) is conducted at least once a year as per the requirements of the EU-GMP guidelines. All product batches produced since the previous assessment are included in this; an SOP regulates the specific approach. If the collection and assessment of data on the individual points stated above is undertaken by contract manufacturers or laboratories, the details must be laid down in a contract. The final assessment of all data on a product is made by the responsible expert at Maas & Peither Pharma GmbH; the PQR report is approved by the expert and management.

If corrective and preventive measures are derived from the PQR, checks are always made on whether these are also relevant for clinical test preparations. The preventive or corrective measures stipulated under the PQR are tracked using the CAPA system.

3 Personnel

The Maas & Peither Pharma GmbH organizational chart is found in Appendix 5.

Maas & Peither Pharma GmbH employs 293 people as of 01.06.2011. Of these 246 employees work in the departments stated above, as classified below:

- Quality assurance: 8.5 FTE (of which three are academics);
- Production: 119 FTE (of which 12 are academics; 18 FTE on a temporary basis);
- Quality control: 23.5 FTE (of which five are academics);
- Warehousing 15 FTE (of which one is an academic);
- Sales: 74 FTE (of which 28 are academics); and
- Technical service: 6 FTE (of which one is academic)

4 Rooms and equipment

4.1 Rooms

Maas & Peither Pharma GmbH is located at the Pharmahausen-Süd Industrial Area; the company's premises are protected from unauthorized access. The premises cover 16,500 m^2 with the buildings described below, which are owned by the company:

- Administration (built in 1965, last renovation 2004);
- Warehouse (built in 1965, 2,150 m^2, last renovation 1995);
- Production (built in 1965, last renovation 2006, 2,400 m^2); and
- Quality control (built in 1965, last renovation 1986, 1,100 m^2)

The warehouse and production are connected to each other.

The following plans of the production areas and warehouses are found in Appendix 6:

- 6/1 – Operations plan
- 6/2 – Building plan production ground floor
- 6/3 – Building plan production 1st floor
- 6/4 – Building plan production 2nd floor
- 6/5 – Building plan warehouse

If applicable, the production building plans include information on room classification and the pressure differences between neighbouring areas and the warehouse plans contain information on special storage conditions. Very poisonous, hazardous or sensitive materials are not used in the production.

Information on personnel and material flows as well as on the manufacturing activities carried out in the individual rooms is found in the following overview plans in Appendix 6:

- 6/6 – Production – Personnel/material flows
- 6/7 – Production – Assignment of manufacturing activities – rooms

4.1.1 Brief description of the air conditioning system

All areas for openly handling raw materials and/or products are qualified with reference to clean room class D (RKD) The secondary packaging takes place in clean room class E (RKE).

No room classes are defined in the EU-GMP guidelines for manufacturing non-sterile solid forms; so it is an individual decision by Maas & Peither Pharma GmbH to carry out production in rooms of a similar class to clean room D. Here "similar" means that the ventilation system is designed to comply with the particle limit values stated

for this clean room class in Annex 1 of the EU-GMP guidelines but other limit values and intervals have been established for microbiological and particle monitoring.

The air conditioning system's design is purely for external air (two-channel system with variable control of the air volume flows). The air feed is a turbulent air flow via twisting inlets—the air suction uses non-short circuiting covers and floor air suction devices. The details are summarized in the following table:

AC design parameters

Range	Temperature	Humidity	Filter combination	Overpressure	Air change rate
E range	21 °C ± 2 °C*	40–65% r. F.	F7 → F9	Refer to plans (Appendices 6, 7)	8 times
D range			F7 → F9 → H14		20 times

* Summer compensation 3 °C

Temperature, humidity and pressure are monitored and recorded continuously; the relevant optical and acoustic alarm systems have been installed.

4.1.2 Brief description of the water system

The water preparation system is used to create purified water, which is used in production as well as to clean the devices. The quality of the purified water is specified as per Ph. Eur.

The quality of the feed water (Pharmahausen town drinking water) meets the requirements of the drinking water regulations. Purified water is produced from this drinking water using ion exchangers, reverse osmosis, membrane degasification and electrodionisation (EDI). Cold storage is used and the distribution is via a ring pipe system. The storage container and ring pipe system are made of stainless steel. The storage container is permanently ozonized; a UV lamp is installed ahead of the ring pipe system. The regular sanitisation is hot (water heating device) or cold ozone sanitization (distribution system).

Continuous monitoring and control of the water system is provided using the following parameters:

- Fill level measurement storage container (capacitive limit level measurement);
- Flow speed (volume flow measurement for return);
- Temperature measurement on storage container;
- Ozone measurement (before UV, after UV, in return); and
- Measurement of pressure, conductivity, temperature and TOC

Detailed information on the design and execution of the system (including system capacity and material specifications for the container, ring pipe, valves, filters etc.) and the location of all measurement and sampling points and the limit values specified for the measuring and testing parameters can be seen in the overview plans in Appendix 7:

- 7/3 – Overview plan water system;
- 7/4 – Overview plan material specifications;
- 7/5 - Overview measuring and sampling locations, measuring and testing parameters, specifications; and
- 7/6 – Overview sampling points

4.1.3 Brief description of other supply systems

Details about media supply are found in the summary plan in Appendix 6 stated below:

- 6/8 – Production – Media supply

4.2 Equipment

4.2.1 Key production and quality control equipment

A list of the key equipment for production and quality control, including lists of critical elements, is found in Appendix 8.

4.2.2 Cleaning and disinfection

The cleaning of all devices, equipment and machines is exclusively conducted by Maas & Peither Pharma GmbH employees and takes place in line with the regulations verified in the cleaning validation process. This covers the proper disassembly, cleaning, drying and re-assembly and also defines the permitted resting periods after use until cleaning starts and after cleaning up to repeat use.

Cleaning is undertaken with drinking water using acid and alkaline detergents by hand or using a dishwasher if a CIP system is not listed in the device list in Appendix 8. The final rinse always takes place using purified water.

4.2.3 GMP-critical computerised systems

The GMP-relevant, computerised systems stated below are used at Maas & Peither Pharma GmbH:

- ERP software LOGIFIXX
- LIMS FloDaSys
- Chromatography data system

5 Documentation

If external archiving is used, the following information must be provided:

- **List of externally archived documents and records (including any externally archived pharmacovigilance documentation);**
- **Name and address of the external archive; and**
- **Time required for obtaining documents from the archive.**

The documentation system is a key element of quality management at Maas & Peither Pharma GmbH. It covers on the one hand requirement documents for controlling quality-relevant processes and on the other records that provide all quality-related processes and each batch to be tracked seamlessly and uniquely.

The creation/revision, checking, approval and distribution of all GMP instruction documentation is controlled by quality assurance as per the relevant SOP regulations. The GMP-compliant creation, checking, analysis and approval of records are also regulated in SOPs. The original instruction documents and all records are stored securely. Access rights, archiving locations and storage periods are regulated in an SOP.

Product-related instruction documentation, such as master manufacturing regulations, specifications and test instructions are created, checked and approved in agreement with the release and in the case of test preparations in agreement with the SOP requirements that match IMPD. Changes to these documents are subject to the Maas & Peither Pharma GmbH change control process.

Batch-specific manufacturing and packaging instructions as well as test instructions and specifications are checked and issued in documented form as authorized copies of these master documents by quality assurance; this process is regulated in an SOP.

Paper-based quality documentation is managed manually.

All documents are archived internally at Maas & Peither Pharma GmbH.

6 Production

6.1 Type of products

Maas & Peither Pharma GmbH specializes in creating solid forms and the following processes are mainly used for this:

- Powder mixture
- Granulation
- Pelletizing
- Tableting
- Coating
- Dragee manufacture
- Hard gelatine capsule filling
- Primary packaging (glass, plastic, aluminium, composite films)
- Secondary packaging

Sample flow diagrams of the key production processes are found in Appendix 6:

- 6/9 – Production – General flow diagrams of the manufacturing processes for each prescription type

The product types manufactured can be viewed from the copy of the manufacturing authorization in Appendix 1. Poisonous, hazardous or sensitizing substances are not used in production. Such processes as Process Analytical Technology (PAT), Real Time Release or parametric release are not used.

The production of small batches of clinical test preparations takes place under the responsibility of the LdH by employees from the "provision of clinical test preparations" group.

6.2 Process validation

Process validation aims to check production processes and their critical process parameters to see whether they effectively and reproducibly result in the expected specified results under routine production conditions. The requirements for process validation are qualified and calibrated equipment, validated computer systems, validated analysis methods, approved manufacturing instructions and test requirements and the appropriate training of the participating employees.

Process validation follows a lifecycle model as a homogeneous concept, starting with the analysis of development data as a requirement for planning the scale-up and conformity batches and ending in an ongoing verification of the process suitability up to the end of a product's routine produc-

tion. The validation scope in the various validation phases is based on written risk analyses.

The details on implementing process validations are regulated in the validation master plan and in SOPs.

6.2.1 Reworking and reconditioning

Reconditioning (product processing using a production process that varies from the release) does not take place.

Any reworking is carried out and documented on a risk basis using approved manufacturing and test instructions. The reworking is assessed as part of the product quality review; a decision is taken on including the reworked batch in the ongoing stability program based on the risk. The details are described in an SOP.

6.3 Materials management and storage

6.3.1 Handling raw materials and packaging materials

On delivery, the items delivered and the accompanying documentation are checked for completeness and correctness; all containers are also checked to ensure the packaging and closures are in perfect condition and they are cleaned externally if necessary. After entry into the ERP system (LOGIFXX) each container is marked.

The sampling of all batches to remove analysis and reference samples is undertaken by authorized and specially trained employees as per the SOP regulations and approved sampling plans. Only single-use tools and containers are used for this; sampled containers are marked accordingly.

The material is then stored in the quarantine area of the warehouse for raw materials and packaging materials, which is where they remain until a decision on quality (approval or rejection, for details refer to Point 7.2, Checking materials and products) is made. Only released material may be used for production.

Raw materials are weighed and picked using the relevant production order by trained employees while complying with the necessary regulations for cleaning, line clearance and labeling; printed packaging materials are issued exclusively by specially authorized people.

6.3.2 Handling intermediate, bulk and finished products

The production and packaging are undertaken by trained employees as per the approved production and packaging instructions and while complying with the regulations that must be applied relating to line clearance, cleaning, labeling and invoicing.

The sampling of all batches to remove analysis and reference samples is undertaken by authorized and specially trained employees as per the SOP regulations and approved sampling plans.

The storage of intermediate products and bulk goods (containers and labeling as per production/packaging instruction) until further processing takes place in the buffer warehouse within the production area (D-area). Only approved products may be processed. Packaged products are stored until approved in the warehouse's quarantine area for primary packaged bulk goods and finished products. Only products with approval for use (for details refer to Point 2.2.2, Batch certification and approval) may be dispatched. Picking for dispatch takes place as per the requirements of the shipping order.

6.3.3 Handling rejected materials, products and market returns

Rejected materials or products are to be marked as blocked and stored securely in the blocked warehouse. Rejected materials are then either sent back to the supplier or—like rejected products—destroyed after documentation. The details are described in an SOP.

Goods rejected by the marketplace are never re-used. Such goods are to be marked as blocked and stored securely in the blocked warehouse until destruction has been documented.

7 Quality control (QC)

The current guidelines on the Site Master File require the following information in this chapter: "Description of the Quality Control activities carried out on the site in terms of physical, chemical, microbiological and biological testing."

This information is part of the manufacturing authorization so in principle reference to Appendix 1 of the Site Master File would be adequate. But such a reference on its own provides little information in terms of work correctly carried out by quality control. Vice versa, a detailed list of this work would go beyond all reasonable limits and may be very detailed in terms of the necessary, regular updates.

With this background Maas & Peither Pharma GmbH has chosen the following compromise: The reference to the manufacturing authorization related to analytical activities was supplemented by the description of additional key quality control tasks.

Information on the type of quality control work carried out can be taken from the manufacturing authorization in Appendix 1. Additional details on the activities and responsibilities of quality control are described below.

7.1 Sampling and reference samples

Raw materials and packaging materials, intermediate products, bulk goods and finished products are sampled as per the approved sampling plans by authorized and specially trained personnel. The details are regulated in SOPs. The sample quantities specifically required for a particular product are determined within the framework of the analytical method validation/establishment and process validation and laid out jointly with the details on representative sampling in the approved sampling plan.

The required quantities of reference samples (reference and other samples) are stored for the statutorily stipulated periods of time in an air-conditioned, separate, locked area of the warehouse as per the SOP.

7.2 Checking materials and products

Analysis samples of materials and products are checked as per the approved test regulations, the raw data collected is documented in full and checked for completeness and correctness by a second employee. If analysis results are collected by external laboratories their analysis certificates are checked carefully as per the SOP regulations. At each time during processing the results received are checked by the relevant employee to ensure they match the specification and if the results do not comply with the specifications an OOS process is started.

The LdQ decides on the basis of the available (internal and if appropriate external) analysis data (test protocol) on the approval or rejection of the relevant material or product and approves the test report. The process of approval for use by the expert is described in Point 2.2.2, Batch certification and approval.

7.3 Reagents and reference standards, chemicals and solutions

Reagents and—if not from an official source—reference standards are characterized carefully according to their purpose. The characterization, handling and marking of these substances is described in the relevant SOPs. The characterization of the company's own primary standards and the derivation of secondary work standards takes place in collaboration with a qualified contract laboratory (refer to Point 2.3.4.2, Contract laboratories and analytical-scientific services).

Reagents, reference standards, chemicals and solutions are marked clearly. Solutions are created and documented in line with the approved regulations.

7.4 OOS results

The investigation of OOS results follows a staged concept; the details are described in an SOP. An OOS test covers checks for

- Obvious laboratory errors;
- Laboratory errors that are not obvious;
- Sampling errors; and
- Manufacturing errors.

(In the case of a proven, obvious laboratory error no other checks are carried out.)

Batches with confirmed OOS results are blocked. Corrective and preventive measures derived from OOS checks are tracked via the CAPA system.

7.5 Validation of analytical methods

Analytical methods are validated as per the regulations of the ICH Q2(R1) guidelines. The detailed approach is described in an SOP.

The maintenance of the validated status of all methods is ensured with the aid of the change control system and a regular check of the validation status (including as part of the PQR).

7.6 Stability tests

Stability tests are undertaken on the basis of the ICH guidelines (ICH Q1) and the EU-GMP guidelines. The specific approach is described in an SOP by which the product-specific stability plans and reports are also created. As per the SOP regulations bracketing and matrixing designs can be applied based on the risk pursuant to ICH Q1D.

The air-conditioned storage of stability samples in their commercial packaging is undertaken by a qualified service provider as per the requirements for air conditioning zones I and II. Stability samples are checked by Maas & Peither Pharma GmbH quality control as per the requirements of the test methods and specifications stated in the approved stability plan.

The requirements for labeling, storing and transporting all products are set based on the approved stability reports for the initial and follow-up stability storage. The approved stability reports from the ongoing stability program flow into the PQR.

8 Sales, complaints, product faults and returns

As was the case for Chapter 2.3, Chapter 8 is also heavily characterized by the protective measures required in the age of global markets to prevent the falsification of medicinal products and illegal sales. The focus here is on the following aspects:

- **Where are the shipments going?**
  - **Who are the recipients (wholesalers, manufacturers etc.)?**
  - **Where are the recipients (EU/EEC, USA, other countries etc.)?**
- **Security measures in terms of**
  - **ensuring that the recipients of the products are legally authorized to receive them and—if necessary—have the relevant authorization;**
  - **appropriate transport conditions (e.g., controlling and monitoring the temperature);**
  - **Ability to track the products; and**
  - **Preventing illegal sales**

This content matches the changes to medicinal product legislation as a result of modifying the Directive 2001/83/EC on preventing the falsification of medicinal products and protection from illegal sales. This means that in future most prescribed medicinal products (and also some OTC preparations yet to be defined) must in future have appropriate security features—and other such measures. To date the details on this have not been defined but without doubt all pharmaceutical companies will be confronted with comprehensive changes in terms of packaging, labeling, transport and sales.

8.1 Sales (if the responsibility of the manufacturer)

The Maas & Peither Pharma GmbH products are sold in Germany, the European Union and Switzerland via wholesalers. All supplied wholesalers have the necessary authorization; a copy of this authorization must be presented

to Maas & Peither Pharma GmbH before the first delivery. Qualified pharmaceutical advisors prepare the technical information for doctors including any samples. Each shipment of products is documented in full so that it is possible to track the batch if necessary. The transportation of products from Maas & Peither Pharma GmbH is undertaken exclusively using qualified freight forwarders who have a quality management system and appropriate track and trace systems in place. The uniquely labeled transport containers are also protected from unauthorized access during transportation by a seal. The intact seal and the delivery papers are checked as part of the incoming goods inspection by the wholesaler.

The transport conditions and measures for checking and monitoring them are laid down in writing while considering the following parameters:

- Available stability data;
- Planned transport route; and
- Planned transport time.

If critical parameters are identified here these are checked and recorded. Quality-critical transport processes are validated.

Decisions will be taken in good time by establishing additional security elements to protect against illegal sales (verification of the genuine nature of a product, identification of the individual packaging) on the basis of new, future statutory requirements from the revision of Directive 2001/83/EU.

8.2 Complaints, product faults and recalls

8.2.1 Complaints and product faults

Each complaint received is documented and passed on immediately to quality assurance no matter how it is received. Quality assurance records all incoming complaints and undertakes initial grouping—pharmaceutical-technical or medical complaint—and a risk assessment. Medical complaints are then processed further by the qualified person for pharmacovigilance; pharmaceutical-technical complaints are coordinated with quality assurance.

As part of the ongoing process, on the basis of the initial risk assessment, checks are always made on whether other batches may be affected and whether the complaint may have been caused by falsification. All of the measures laid down during processing are tracked using the CAPA system. The management and the expert are informed regularly about all justified complaints and annually about all complaints received.

If there is justified suspicion of falsification the management, qualified person for pharmacovigilance and expert are informed immediately; the quali-

fied person for pharmacovigilance informs the relevant authority (also without delay). The complaint is then processed in close cooperation with the relevant authority.

An SOP regulates the detailed process, tracking and documentation of complaints.

8.2.2 Recalls

If there is justified suspicion of the need for a recall, the management, qualified person for pharmacovigilance and expert are informed immediately; the qualified person for pharmacovigilance informs the relevant authority (also without delay). This is then processed in close cooperation with the relevant authority as per the regulations in the alarm and action plan.

SOPs regulate the implementation of recalls including the return, accounting and destruction of recalled products; all potentially affected batches and their sales routes are determined. All of the measures laid down during a recall are tracked using the CAPA system. Each recall is documented in full and the associated final reports are approved by quality assurance, the expert, the qualified person for pharmacovigilance and the management as well as any other responsible people as required by the alarm plan.

9 Self-inspections

All quality-related areas of the company are subject to regular self-inspection; the details are described in an SOP. The self-inspection program is produced annually by quality assurance in cooperation with the specialist departments and approved by the responsible people; modifications to the self-inspection program during the year to meet current requirements are desirable.

Within this framework all GMP-relevant departments are generally inspected at least once a year; shorter or longer intervals may be set on the basis of the risks, e.g., depending on compliance with previous self-inspections or as a result of important changes to rooms, equipment, processes or numerous variances etc.

The results of each inspection are documented in self-inspection reports that are available to the inspected department and the responsible person. With the aid of the CAPA system, appropriate follow-up measures are defined and their implementation is tracked. The results of the self-inspections flow into the PQR.

10 Appendices

Maas & Peither Pharma GmbH is a virtual company; so Appendices 1, 3, 6 and 7 have not been created.

Appendix 1: Copy of the valid manufacturing authorization (not included in the available sample SMF).

Appendix 2: Not applicable. The list of prescription forms can be taken from Appendix 1.

Appendix 3: Copy of the valid GMP certificate (not included in the available sample SMF).

Appendix 4: Contract manufacturers and laboratories—logistics.

Appendix 5: Organizational chart.

Appendix 6: Overview plans of the production and warehouse departments, media supplies and general flow diagrams from the manufacturing processes (not included in the available sample SMF).

Appendix 7: Overview plans of the ventilation systems and the water system (not included in the available sample SMF).

Appendix 8: List of key devices and equipment in production and quality control.