

# A Competent Regulatory Document: Site Master File

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**Abstract:** A Site Master File (SMF), also referred to as plant master file or site reference file, is prepared by the manufacturer and contains specific information about the quality management system in place, 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. Guidance on the preparation and set up is provided in the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Explanatory Notes for Industry on the Preparation of a Site Master File in the current version as of July 2004 (PE 008-2). PIC/S is a cooperative arrangement between health authorities whose purpose includes leading the international development, implementation, and maintenance of harmonised GMP standards and quality systems of world-wide pharmaceutical inspectorates.

**Key Words:** Site Master File (SMF), Quality Management System, Pharmaceutical Inspection Co-Operation Scheme (PIC/S), GMP

## I. INTRODUCTION

Dealing with GMP in the 21<sup>st</sup> century is still extremely cumbersome. GMP regulations and quality system expectations still differ between regions and countries. Although there is a need for pharmaceuticals companies to establish global supply chains and to work globally regulatory authorities still seems to work locally with respect to GMP. Good Manufacturing Practices are in effect in several countries either implemented through national codes or drug laws, regulations (as in USA and Japan) or directives as in the European Union. Even if the national implementation differs the intent of authorities is the GMP to be strictly followed to consistently assure pharmaceutical product quality. That means for the regulatory authorities to approve efficacious and safe drugs of good pharmaceutical

product quality as fast as possible, and to protect patients from unsafe or inefficacious drugs.

That means for the pharmaceutical companies that they can only be economically successful, when they produce products which are fit for their intended use, comply with the requirements of the marketing authorization and GMP and do not place patients at risks due to inadequate safety, quality or efficacy.

GMP-Inspections are on-site assessments of the compliance of manufacturers with the principles of GMP performed by officials (inspectors) of competent authorities. According to the definition of the WHO [72]: “Inspections are part of the overall drug quality assurance system. The objective of inspecting pharmaceutical manufacturing facilities is either to enforce Good Manufacturing Practice (GMP) compliance or to provide authorization for the manufacture of specific pharmaceutical products, usually in relation to an application for marketing authorization.” A Site Master File is a tool to facilitate the inspection procedure when submitted to a regulatory authority prior to an inspection. The aim of a SMF is to demonstrate the company’s compliance with GMP and giving a general overview about the facility and its operations.

Although it is not mandatory in the most countries to provide a SMF some pharmaceutical companies would prefer providing them to their competent authority on a voluntary base. Some countries will always request for a SMF some countries will not, this only depends on the national legal requirements. However, a SMF, if available, can assist and will be useful to the regulatory authority in planning and conducting of GMP inspections.

## II. RESEARCH METHODOLOGY

EU: United Kingdom

Authority and Inspections

The licensing Authority in the UK is the Medicines

and Healthcare products Regulatory Agency (MHRA). The primary aim of the MHRA is to safeguard public health by ensuring that all medicines and devices on the UK market meet appropriate standards of quality, safety and efficacy. The MHRA was formerly known as the Medicines Control Agency (MCA), which was established in 1989 as an Executive Agency of the Department of Health. On 1 April 2003 the Medicines Control Agency (MCA) and the Medicinal Devices Agency (MDA) merged into a single executive agency, the MHRA [36]. The responsible department at the MHRA for inspections is the “Inspection and Standards Division”. The MHRA GMP Inspectorate carries out regular and repeated inspections of manufacturing sites both in the United Kingdom and in those non-EU countries with which the EU does not have a Mutual Recognition Agreement. All sites named on a manufacturer’s licence are subject to regular inspections. Each site is inspected every 2-3 years depending on the nature and scale of operation. Inspection enables the Licensing Authority to confirm that licence holders are complying with the conditions of their licence, with the provisions of the Medicines Act and with GMP. The ability to demonstrate compliance with the principles of GMP will result in the issuing of a GMP certificate. Section 111 to 114 of the Medicines Act empowers the MHRA to:

The enforcement powers under the Medicines Act is the basis for inspections relating all types of licenses. It is a requirement of UK legislation that licence holders shall make their premises available for inspections by the Licensing Authority at any reasonable time.

Following an inspection, the Inspector prepares a summary of his findings. This inspection report is sent to the licence applicant asking for proposals to remedy them. In the most serious cases the report is referred to the Licensing Authority for more formal action which can include the refusal, variation, suspension or revocation of a licence, or part of a licence [18]. Under the Freedom of Information Act 2000 the MHRA is required to release certain information upon request. Commercial sensitive information will not be disclosed. Request for information can be made when using the Freedom of Information Request Form. The Agency is obliged to respond to requests within 20 working days.

#### GMP:

The UK complies with the European legislation. The primary legislation in the UK is laid down in the “Medicines Act 1968 as amended”, which regulates in part the manufacture, distribution and importation of medicinal products. The principles and the guidelines of EU GMP applies and are even set out in the MHRA publication the Rules and Guidance for Pharmaceutical Manufacturers and Distributors usually known as “The Orange Guide”. From its first publication in 1971 the 'Orange Guide', has been an essential reference for all involved in the manufacture and distribution of medicines in Europe. The Orange Guide collates European and UK guidance documents and information on legislation relating to the manufacture and distribution of medicines for human use. The Orange Guide is available from TSO (The Stationary Office: [www.tso.co.uk/bookshop](http://www.tso.co.uk/bookshop)).

A manufacturer’ license or a manufacturer’s special licence must be held before a medicinal product is manufactured, whether the product is for use within the UK or for export. The Manufacturing and Wholesale Dealing Regulations (SI 2005 No 2789) detail the obligations and standard provisions relating to manufacturer’s licenses. In the UK a manufacturer’ license is the same as a manufacturing authorisation. A manufacturer’s special licences is a license which permits the manufacture and supply of “exempt relevant medicinal products” i.e. unlicensed relevant medicinal products exempt from the requirement to hold a marketing authorisation. This exemption permits supply to meet the specific needs of an individual patient The facilities in third countries (non EU/EEA countries) must either be approved by a PIC member state or the UK Medicines Inspectorate. Inspections may be conducted. Non-EEA manufacturers will be required to sign undertakings in accordance with the SI 1977 No. 1038 (as amended by SI 1992 No. 2845 and SI 1994 No. 3144) to:

- permit premises where the product is or is to be manufactured and the operation carried on or to be carried on in the course of manufacturing it to be inspected by or on behalf of the United Kingdom licensing authority;
- comply with the conditions described by SI 1977 No. 1038, conditions of which are set out in the Schedule to this instrument;
- comply with any conditions attached to the

marketing authorisation in relation to the manufacture of the product;  
and declare that, in relation to the manufacture of the product, any requirements imposed by or under the law of the country in which it is or is to be manufactured have been or will be complied with [30].

#### Site Master File

The MHRA is the regulatory authority which provides the most information about a SMF and is extensively using modifications of the PIC/S Site Master File guideline for UK specific purposes. The preparation of a SMF facilitates the inspection process.

An application for a manufacturer's licence (in the UK the manufacturing authorisation is a manufacturer's licence) or a manufacturer's special licence should be accompanied by a Site Master File. A SMF should be submitted either as a hard copy or as a CD Rom to the MHRA.

The following guidance notes regarding the preparation of a SMF are available on the MHRA homepage:

- MHRA Guidance Note 27 [15]: Guidance notes for industry on the preparation of a Site Master File.
- MHRA Guidance Note 28 [16]: Guidance notes for industry on the preparation of a Site Master File for an overseas site subject to inspection by the UK regulatory authority.
- MHRA Guidance Note 30 [17]: Site Master File Model. For Manufacturing "Specials" Licence holders or applicants for Manufacturing Authorisations relating to small-scale activities, including investigational medicinal products.

A SMF for an overseas site subject to inspection by the MHRA is UK specific and contains minor UK specific modifications of the PIC/S guide. For example under a new section 1.5.4 names, dosage forms and UK Product License number of all medicinal products are manufactured on site for the export to the UK should be provided. A template for a Site Master File can be found on the Thai FDA homepage [17]. The Site Master File Model is a SMF for small-scale activities, including investigational medicinal products. The structure of the sections is completely different to the PIC/S guideline and is specific for the MHRA only.

A very interesting example for usage of a Site Master File in the UK is the company G&G Food Supplies

Ltd. G&G made available their Site Master File on their homepage as a word document [65].

In the UK the SMF is an important tool to support inspections and inspection procedures.

### III.SUMMARY AND CONCLUSION

The GMP implementation and regulations (and quality system expectations) still differ between regions and countries. ROW or so called emerging countries became more and more important for global working pharmaceutical companies. As a consequence the number of inspections of manufacturing sites has increased continuously. In this context it is necessary that PIC/S will go ahead to expand their membership and will go ahead working on global GMP harmonisation. From industry perspective it is hoped that any inspectorate will accept PIC/S and ICH inspections as the standard in the future [67].

A possible tool for manufacturing sites to facilitate the inspection process is to provide a Site Master File prior to the inspection to the competent regulatory authority. A Site Master File is a brief and comprehensive company description demonstrating the sites GMP compliance. Depending on national requirements a SMF is not required, can be either voluntary submitted or must be submitted to the national regulatory authority. As a general rule manufacturers are advised to refer to national regulations whether it is required to provide a SMF or not.

Information about a Site Master File is hard to find. A SMF is not mentioned in an ICH guideline [4, 5] or in a GMP guideline. The current version of explanatory notes on the preparation of a Site Master File of the Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme (PIC/S) is the only available international guideline on a SMF. Many health authorities have implemented the PIC/S guideline, or a slight modification of the PIC/S guideline, as national guidelines.

Preparation and maintenance of a SMF is a complex task, which requires co-ordination and resources. A decision analysis with a fictive grid analysis was performed in order to clarify the question if there is a benefit for manufacturing sites to invest time and resources in order to prepare a SMF or not. For global working companies it is concluded that there are more arguments to set up a SMF than against a SMF.

There are great differences in the usage of a SMF in different regions. As examples the United Kingdom, Germany, the United States and Taiwan were selected. The EMEA considered a Site Master File as “helpful” for preparing and carrying out the inspection. The same applies for competent regulatory authorities in Germany, the MHRA in the United Kingdom and the regulatory authority of Taiwan. The UK has in addition UK specific modifications in place. The US FDA recognised among other things that the content a Drug Master File Type 1 (which had similar content to a Site Master File) was often outdated. As a consequence the FDA considered a Type 1 Drug Master File as an “inadequate vehicle” for information and has no longer accepted Type 1 Drug Master Files since July 2000.

It remains open if the ICH guideline Q10 on pharmaceutical quality systems, once adopted, will have impact on set up and usage of a SMF.

However, a SMF can serve as a competent regulatory document for manufacturing sites to answer to questions from regulatory authorities regarding production, quality control, quality policy and quality assurance system etc.

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