IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
December 2015 Vol.:5, Issue:1

Comparative Study of Site Master File Requirements of Various Regulatory Agencies in Pharmaceutical Manufacturing Facilities

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Chagi Venkatesh[1] and S.B.Puranik[2]

[1]Research scholar Prist University, Thanjavur, Tamilnadu, India

[2]Research Guide Prist University, Thanjavur, Tamilnadu, India

Submission: 4 December 2015
Accepted: 10 December 2015
Published: 25 December 2015

Keywords: SMF, GMP, Regulatory requirements

ABSTRACT

The current article aims at consolidation of seven major Regulatory requirements of different countries into one Site Master File. This is being done to get all the information in this article for use in Pharmaceutical Manufacturing Industry as a ready reference. Similar sections of selected regulatory guidelines have to be under one general requirement. Sections which are special to certain Regulatory Authorities have to available in additional information. This study helps in avoiding repetition of similar guidelines that are common to major regulatory authorities. The site Master file consists of General information of Manufacturing practices of Pharmaceutical industry, Additional information with respect to different Regulatory Guidelines.

INTRODUCTION

Good Manufacturing Practices (GMP) guidelines are not prescriptive instructions on how to manufacture products. They are the sequence of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfil GMP requirements. It is the company's responsibility to determine the most effective quality standards. Regulations for manufacturing pharmaceutical products is very stringent, so it is necessary to understand the similarities and differences among GMP requirements for the manufacturing of pharmaceutical products & general requirement which are used in manufacturing by the Regulated countries which will be beneficial to the pharmaceutical companies of both ROW countries & Regulated countries [1].

"GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization".

GMP guidelines represent minimal standards that are necessary condition for marketing authorization. Drugs are considered to be adulterated if GMPs are not met. GMP standards are, however, only guidelines and alternative processes and control mechanisms can be used under the condition that equivalent assurance is attained.

GMP guidelines typically comprise strong recommendations on quality management, personnel, production facilities and equipment, documentation and records, production and in-process controls, packaging and identification labelling, storage and distribution, laboratory controls, validation, complaints and recalls, and contract manufacturers.

Compliance with GMP is necessary condition for marketing authorization. In other words, domestic and foreign producers of pharmaceutical companies cannot sell or market their drugs without it. While GMP compliance has not been universally adopted in the developing world, governments in less developed countries are under pressure to comply with GMP requirements when granting marketing authorizations to domestic companies and the west has developed a variety of strategies to ensure that developing countries adopt the rules. GMP requirements require major investment in upgrading manufacturing facilities and this has implications for local

producers. An interesting empirical question is the impact of these changes on local markets and access to and affordability of medicines in developing countries.

The Site Master File (SMF) is prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site. If only part of a pharmaceutical operation is carried out on the site, a SMF need only describe those operations eg. Analysis, packaging etc. These guidance notes have been prepared for the manufacturers to prepare the SMF which can suffice the requirement of planning and auditing the facilities by the regulatory bodies.

Objective:

1. Objective of this article is to outline the notes on preparation of site master file by comparing the guide given in Schedule M, WHO GMP, USFDA, MHRA, PICS and TGA.
2. Based on the above comparative notes, model of site master file shall be prepared with basic details of any pharmaceutical industry.

All the above mentioned guidance documents shall be reviewed for the guidelines to prepare SMF, Comparative study shall be conducted for guidelines. In the comparative study of guides to prepare SMF for different sections required in the SMF shall be outlined.

1) As per Schedule M Drugs and Cosmetics ACT India.
2) European Commission: Health and Consumers Directorate general.
3) US-FDA: Unites States, Food and Drug Administration.
4) The Drug Manufacturer's Guide to Site Master Files.
5) Medicines and Healthcare products regulatory Agency (MHRA).
6) Pharmaceutical inspection convention (PIC)/Pharmaceutical inspection co-operation scheme.
7) Therapeutic goods and Administration.
8) World Health Organisation.

Comparative study of GMP guideline of regulated countries:

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
1	General information	General information on the manufacturer	General information on the manufacturer	General information	General information on the manufacturer	General information
1.1	Brief information of the firm	Contact information on the manufacturer	Contact information on the manufacturer	Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understanding the manufacturing operations	Contact information on the manufacturer	Brief information on the firm (including name and address), relation to other sites, and, in particular, any information relevant to understanding the manufacturing operations
1.2	Pharmaceutical manufacturing activities as permitted by the licensing Authority	Authorised pharmaceutical manufacturing activities of the site	Authorized pharmaceutical manufacturing activities of the site	Pharmaceutical manufacturing activities as licensed by the national authority	Authorised pharmaceutical manufacturing activities of the site.	Pharmaceutical manufacturing activities as licensed by the national authority
1.3	Other manufacturing activities, if any, carried out on the premises	Any other manufacturing activities carried out on the site	Any other manufacturing activities carried out on the site	Any other manufacturing activities carried out on the site	Any other manufacturing activities carried out on the site	Any other manufacturing activities carried out on the site
1.4	Type of product			Name and Exact		Name and exact

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	licensed for manufacture with flow charts mentioning procedure and process flow.	----	----	Address of the Site, Including Telephone, Fax and 24 Hrs Telephone Numbers.	----	address of the site, including telephone, fax, and 24-hour telephone numbers
1.5	Number of employees engaged in the production, quality control, storage and distribution.	----	----	Type of Products Manufactured	----	----
1.6	Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis	----	----	A Short description of the site	----	Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
						a campaign basis)
1.7	Short description of the Quality Management System of the firm	----	----	Number of employees engaged in production, quality control, storage and distribution	----	Short description of the site (size, location, and immediate environment and other manufacturing activities on the site)
1.8	Products details registered with foreign countries	----	----	Use of outside scientific, analytical or other technical assistance in relation to Manufacture and analysis (if so, see chapter 7 for technical details required).	----	Number of employees and workers engaged in:
1.9	----	----	----	Short description of the quality management system of the firm responsible for Manufacture.	----	Use of outside scientific, analytical, or other technical assistance in relation to manufacture and

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
						analysis
1.10	----	----	----	----	----	Short description of the quality management (QM) system of the firm responsible for manufacture
2	Personnel	Personnel	Personnel	Personnel	Personnel	Personnel
2.1	Organisational chart showing the arrangement for quality assurance including production and quality control	Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Appendix 5, including senior management and Qualified Person(s);	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)	Organisation chart showing the arrangements for quality assurance, including Production and quality control.	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);	Organization chart showing the arrangements for quality assurance, including production and quality control
2.2	Qualification, experience and responsibilities of key personnel	Number of employees engaged in the quality management, production, quality control, storage and distribution respectively	Number of employees engaged in the quality management, production, quality control, storage and distribution	Qualifications, experience and responsibilities of key personnel	Number of employees engaged in the quality management, production, Quality control, storage and distribution respectively.	Qualifications, experience, and responsibilities of key personnel

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
			respectively.			
2.3	Outline for arrangements for basic and in-service training and how the records are maintained	----	----	Outline of arrangements for basic and in-service training and how records are Maintained.	----	Outline of arrangements for basic and in-service training and how records are maintained
2.4	Health requirements for personnel engaged in production.	----	----	Health requirements for personnel engaged in production	----	Health requirements for personnel engaged in production
2.5	Personal hygiene requirements, including clothing.	----	----	Personnel hygiene requirements, including clothing	----	Personnel hygiene requirements, including clothing.
3	Premises	Premises and equipment	Premises and Equipment	Premises and equipment	Premises and Equipment	Premises and equipment premises
3.1	Simple plan or description of manufacturing areas drawn to scale	Premises	Premises	Simple plan or description of manufacturing areas with indication of scale (Architectural or engineering	Brief description of heating, ventilation and air conditioning (HVAC) systems	Simple plan or description of manufacturing areas with indication of scale (architectural or engineering

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
				drawings not required).		drawings not required) Attach layout of the plant.
3.2	Nature of construction and fixtures/fittings	Equipment	Brief description of heating, ventilation and air conditioning (HVAC) systems)	Nature of construction and finishes.	Brief description of water systems	Nature of construction and finishes.
3.3	Brief description of ventilation systems. More details should be given for Critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of sterile products	Cleaning and sanitation	Brief description of water systems	Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the Systems are desirable). Classification of the rooms used for the manufacture of sterile Products should be mentioned.	Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.	Brief description of ventilation systems. More details should be given for critical areas with Potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	should be mentioned			Room classification should be given in accordance With the grading system outlined in the EC/PIC Guide to GMP.		
3.4	Special areas for the handling of the highly toxic, hazardous and sensitizing materials	GMP critical computerised systems	Brief description of other relevant utilities, such as steam, compressed air, N2, etc.	Special areas for the handling of highly toxic, hazardous and sensitizing materials	Equipment Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Appendix- 8.	Special areas for the handling of highly toxic, hazardous, and sensitizing materials
3.5	Brief description of water system (schematic drawings of systems), including sanitation	----	Equipment	Brief description of water systems (schematic drawings of the systems are desirable), Including sanitation.	Cleaning and sanitation	Brief description of water systems (schematic drawings of the systems are desirable), including Sanitation.
3.6	Description of planned preventive maintenance	----	Cleaning and sanitation	Maintenance (description of planned preventative maintenanc	GMP critical computerised systems	Description of planned preventive maintenance program for premises

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	programs for premises and Of the recording system.			e programme s and Recording system).		and of the recording system.
3.7	Equipmen t	----	GMP critical computerized systems	Brief description of major production and control laboratories equipment (a list of Equipment is not required).	----	Equipment 3.7 Brief description of major equipment used in production and control laboratories (a list of Equipment is not required).
3.8	Brief descriptio n of major equipmen t used in productio n and Quality Control Laborator ies (a list of equipmen t required)	----	----	Maintenanc e (description of planned preventativ e maintenanc e programme s and Recording system).	----	Description of planned preventive maintenanc e programs for equipment and of the recording System.
3.9	Descripti on of planned preventiv e maintena nce programs	----	----	Qualificatio n and calibration, including recording system. Arrangeme nts for	----	Qualificatio n and calibration, including the recording system. Arrangeme

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	for equipment and of the recording system			Computerised systems validation.		nts for computerized Systems validation.
3.10	Qualification and calibration including the recording systems and Arrangements for computerized systems validation.	----	----	Sanitation Availability of written specifications and procedures for cleaning manufacturing areas and equipment	----	----
4	Documentation	Documentation	Documentation	Documentation	Documentation	Documentation
4.1	Arrangements for the preparation, revision and distribution of;	Description of documentation system (i.e. electronic, manual)	Description of documentation system (i.e., electronic, manual);	Arrangements for the preparation, revision and distribution of necessary documentation for manufacture	Description of documentation system (i.e. electronic, manual);	Arrangements for the preparation, revision, and distribution of necessary documentation for manufacture
4.2	Necessary documentation for the manufacture;	When documents and records are stored or archived off-site (including pharmacovigilance data,	When documents and records are stored or archived off-site (including pharmacovigilance	Any other documentation related to product quality which is not mentioned	When documents and records are stored or archived off-site (including pharmacovigilance data,	Any other documentation related to product quality that is not mentioned elsewhere

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
		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	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	elsewhere (eg. microbiological controls on air and water).	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.	(e.g., microbiological controls on air and water)
4.3	Any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water)	----	----	Additional Documentation	----	----
5	Production	Production	Production	Production	Production	Production
5.1	Brief description of production operations using, wherever possible,	Type of products	Type of products	Brief description of production operations using, wherever possible, flow sheets	Type of products	Brief description of production operations using, wherever possible, flow sheets

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	flow sheets and charts specifying important parameters			and Charts specifying important parameters.		and charts Specifying important parameters.
5.2	Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage	Process validation	Process validation	Arrangements for the handling of starting materials, packaging materials, bulk and Finished products, including sampling, quarantine, release and storage.	Process validation	Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage
5.3	Arrangements for the handling of rejected materials and products	Material management and warehousing	Materials management and warehousing	Arrangements for the handling of rejected materials and products.	Material management and warehousing	Arrangements for the handling of rejected materials and products.
5.4	Brief description of general policy for process validation	----	----	Brief description of general policy for process validation	----	Brief description of general policy for process validation.
6	----	Quality management system of the	Quality management system of the	----	Quality management system of the	----

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
		manufacturer	manufacturer		manufacturer	
6.1	----	The quality management system of the manufacturer	The quality management system of the manufacturer	----	The quality management system of the manufacturer	----
6.2	----	Release procedure of finished products	Release procedure of finished products	----	Release procedure of finished products	----
6.3	----	Management of suppliers and contractors	Management of suppliers and contractors	----	Management of suppliers and contractors	----
6.4	----	Quality Risk Management (QRM)	Quality risk management (QRM)	----	Quality Risk Management (QRM)	----
	----	Product Quality Reviews	Product quality reviews	----	Product Quality Reviews	----
7	Quality Control	Quality control	Quality control	Quality control	Quality Control	Quality Control
7.1	Description of the quality control system and of the activities of the Quality Control Department. Procedures for the release of the finished products	Description of the Quality Control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing	Description of the Quality Control activities carried out on the site in terms of physical, Chemical, and microbiological and biological testing.	Description of the Quality Control system and of the activities of the Quality Control Department. Procedures for the release of finished products	Description of the Quality Control activities carried out on the site in terms of physical, chemical, and microbiological and biological testing	Description of the quality control system and the activities of the quality control department. Procedures for the release of finished products
8	Distribution, complaints and product	Distribution, complaints, product defects and recalls	Distribution, Complaints, Product defects and recalls	Distribution complaints and products	Distribution, Complaints, Product defects and recall	Distribution, Complaints and product recall

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	recall			recall		
8.1	Arrangements and recording system for distribution	Distribution (to the part under the responsibility of the manufacturer)	Distribution to the part under the responsibility of the manufacturer	Arrangements and recording system for distribution	Distribution	Arrangements and recording system for distribution
8.2	Arrangements for handling of complaints and product recalls	Complaints, product defects and recalls	Complaints, product defects and recalls	Arrangements for the handling of complaints and product recalls.	Complaints, product defects and recalls	Arrangements for the handling of complaints and product recalls
8.3	------	------	------	Complaints	------	------
8.4	------	------	------	Product Recalls	------	------
9	Self-inspection	Self-inspections	Self-inspection	Self-inspection	Self-inspections	Self-inspection
9.1	Short description of the self-inspection system indicating whether an outside, independent and experienced external export was involved in evaluating the manufacturer's	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	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	Short description of the self-inspection programme	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.	Short description of the self-inspection system

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
	compliance with Good manufacturing Practices in all aspects of production					
10	Loan licence manufacture and licensee	----	----	Contract manufacture and analysis	----	Contract manufacture and analysis
10.1	Description of the way in which compliance of Good Manufacturing Practices by the loan licensee shall be assessed	----	----	Description of the way in which the GMP compliance of the contract acceptor is Assessed.	----	Description of the way in which the GMP compliance of the contract acceptor is Assessed
11	Sanitation	----	----	----	----	Sanitation
11.1	Availability of written specifications and procedures for cleaning manufacturing areas and equipment	----	----	----	----	Availability of written specifications and procedures for cleaning manufacturing areas and equipment

Sl .No.	Schedule M[2]	European Commission[3]	US FDA[4]	MHRA[5]	PICS [6]/ TGA[7]	WHO[8]
12	Export of drugs	----	----	----	----	----
12.1	Products exported to different countries	----	----	----	----	----
12.2	Complaints and product recall, if any	----	----	----	----	----

SUMMARY

From the above comparative analysis of selected GMP Guidelines, we infer that the following points have to be considered for preparation of one site master file as a common platform.

All the selected guidelines briefed about the preparation of site master file with required sections and the sections given slightly varies from one guideline to another guideline. Similar sections of all the selected guidelines are General information on the manufacturer, personnel, premises and equipment, documentation, Production, Quality control, Complaints and products recall, self-inspection. European commission, USFDA and PICS/ TGA details about Quality management system of the manufacturer are under different heading. However, schedule M, MHRA and WHO guidelines give the detail of quality management system of the manufacturer under general information section. Therapeutic goods and Administration- Australia follows the procedure of PIC/PICS (Pharmaceutical inspection convention (PIC)/Pharmaceutical inspection co-operation scheme) Guideline. Details about contract manufacture and analysis are explained by MHRA and WHO whereas same is given under loan license manufacture and license in schedule M. Sanitation is given under separate headings in schedule M and WHO, remaining selected guidelines give the information of sanitation under premises and equipment section. Schedule M is given to mention the details about export of drugs.

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