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Explanatory notes for drug establishments on the preparation of a site master file

GUI-0005

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Canada

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This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

Table of contents

The following table shows the two types of icons used in this document, and the way they are intended to be used.

Information: Supplementary information like quotes and legal references.

Tip: Things you ideally want people to do or understand.

About this document

1. Purpose

The aim of this document is to guide the preparation of the site master file. This guide will help drug establishments comply with Part C, Division 2 of the Food and Drug Regulations (the Regulations).

2. Scope

These Explanatory Notes apply to the preparation of the site master file by any person who conducts any of the licensable activities listed below with respect to a drug:

- fabrication
- packaging
- labelling
- testing

3. Introduction

These guidelines interpret the requirements for good manufacturing practices (GMP) in Part C, Division 2 of the Food and Drug Regulations.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* (the Act) and associated regulations.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

This guide is based on the Pharmaceutical Inspection Cooperation Scheme (PIC/S) document *Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File (SMF) (PE 008-4*). This guide reflects changes necessary to adapt the text to meet Canadian requirements

The content of the site master file provides information about Canadian and foreign buildings in the planning and conducting of GMP inspections. The site master file supports pre-market authorizations and applications for drug establishment licenses.

A site master file should be prepared to contain specific information about the quality management policies and activities of the site, the production and/or quality control of drug manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of these operations is carried out on the site, a site master file need only describe those operations, e.g. analysis, packaging, etc.

When submitted to Health Canada, 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.

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 letter size 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.

Content of site master file

You are requested to prepare a site master file for each location where you fabricate, package/label or test drugs. A list of Appendices to include with the site master file is provided at the end of this document.

You may refer to other related documents such as *Site master file (SMF) for source plasma establishments PI 019-3* and *Site master file (SMF) for plasma warehouses PI 020-3* for alternate formats to use.

1. General information on the manufacturer

1.1 Contact information of 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 a 24 hour telephone number of the contact personnel in the case of product defects or recall.
- Geographic location of the site as e.g. GPS details or any other geographic location system.

1.2 Authorized drug manufacturing activities of the site

- Copy of the valid manufacturing authorization issued by the relevant Regulatory Authority in Appendix 1; or when applicable, reference to the appropriate Regulatory Authority's database (e.g., Drug and Health Products Inspection Database, EudraGMP database, FDA Inspection Classification Database). If the Regulatory 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 Regulatory 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 other Regulatory Authority's database.
- List of GMP inspections of the site within the last 5 years; including dates and name/country of the Regulatory Authority having performed the inspection. A copy of current GMP certificate (Appendix 3) or reference to the Regulatory Authority's database should be included, if available.

1.3 Any other manufacturing activities carried out on the site

- Description of non-drug related 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.
- 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 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 market authorization requirements.
- The arrangements between Authorized Persons / Qualified Persons when several Authorized 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 l ingredients and other critical materials suppliers.
- Measures taken to ensure that products manufactured are compliant with TSE (Transmissible spongiform encephalopathy) guidelines.
- Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active ingredients or excipients are suspected or identified.
- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

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

- 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).
- 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).
- 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.
- 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.
- 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 computerized systems

- Description of GMP critical computerized 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

For this section, you can reference Appendix 1 or 2.

- 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 drugs 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.
- 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 (QC) 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, Canada 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 drugs 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 complaints, 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.

The following list of appendices should be referenced and provided with the site master file:

Appendix 1	Copy of valid manufacturing authorisation
Appendix 2	List of dosage forms manufactured including the International Non-proprietary (NN)-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	Organizational 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

Appendices

Appendix A – Glossary

Acronyms

EU: European Union

EMA: European Medicines Agency

FDA: Food and Drugs Administration

GMP: Good manufacturing practices

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

PAT: Process Analytical Technology

PLC: Programmable Logic Controller

QRM: Quality Risk Management

QC: Quality Control

TSE: Transmissible animal spongiform encephalopathy

USA: United States of America

Terms

These definitions explain how terms are used in this document. If there is a conflict with a definition in the *Food and Drugs Act* or associated regulations, the definition in the Act or regulations prevails.

Site master file: also known as a site reference file is prepared by the pharmaceutical manufacturer or the holder of an establishment licence. It 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.

Appendix B – References

Justice Canada

Canadian Acts and regulations can be found on the Justice Canada website: www.justice.gc.ca.

Food and Drugs Act
http://laws-lois.justice.gc.ca/eng/acts/F-27/index.html

Food and Drug Regulations
http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html

Health Canada

Guidance documents about good manufacturing practices (GMP) are available on the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents.html

International references

PIC/S references:

PIC/S Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File (SMF) (PE 008-4)

PIC/S Site Master File (SMF) for Plasma Warehouses (PI 020-3)

PIC/S Site Master File (SMF) for Source Plasma Establishments (PI 019-3)