Health Canada
Health Products and Food Branch

OUR MANDATE:

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Guidance Document

Site Reference File Guideline

Supersedes:

Date issued:
June 15, 2000

Date of implementation:
July 1st, 2000

*Revisions were made to this document on 2002-02-27 to reflect changes to the Health Products and Food Branch organizational structure. There were no other changes made to the content of the document.

Ce document est aussi disponible en français.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Definition

"Site Reference File" (SRF) contains factual, specific and concise information about the establishment, and other information which is relevant to the GMP requirements of Division 2 of the ***Food and Drugs Act and Regulations***. The Site Reference File should only describe those manufacturing operations taking place at the named site and any closely integrated operations at adjacent and nearby buildings. It is prepared, maintained and updated by the holder of the Licence.

1.2 Purpose

The purpose of the Site Reference File is to provide an establishment profile containing the facts about the firm, (eg. structure, tombstone data), the activities of the firm, (eg. names of drugs produced, dosage forms, packaging), the personnel, the premises (eg.layout plans), the equipment, (eg. function, specifications) as per this guideline.

1.3 Expected Benefits

- Once the Site Reference File is set up by the establishment and verified by the inspector, subsequent inspections should take less time since the establishment is expected to keep the SRF updated and the inspector will only need to verify that information.

- The inspection report will be more focused making it easier to understand. Of course the inspector will note, in his report, any deviations found in the SRF.

1.4 Format

A Site Reference File should be succinct, not more than thirty 8½" x 11" pages. The style, format and headings adopted for the SRF and outlined in this guideline is consistent with international convention.

The Site Reference File must be submitted as loose individually numbered pages. Each page should have a date issued, a date revised and an effective date. There are 14 sections in the SRF and each must start on a new sheet so that updates can be provided and the relevant sheets replaced.

Wherever possible simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans etc, should fit on 8½" x 11" paper. Deliberate limits have been set on the length of the narrative. If more detailed information is required then the inspector can attend to this during the inspection.

Site Reference Files submitted in an electronic format are acceptable provided they are in WordPerfect or Microsoft Word format.

1.5 Guidance

- Revision of the Site Reference File need only be made when these are major changes which may affect the quality of the product. Only replacement pages need to be resubmitted.
- The SRF can be submitted directly to Ottawa instead of to the importer, if the importer is so advised.
- If there are several importers, only one copy of the SRF need be submitted to Ottawa as long as the SRF is properly cross referenced and the importer is advised.
- The PIC "Site Master File" format is acceptable in place of the SRF format.
- The Canadian agent is responsible for arranging for the foreign SRF.
- The SRF applies for both human and veterinary drugs.
- The SRF will have to be translated if in a foreign language.
- The SRF, on its own, does not consitute evidence of GMP.

2. GENERAL INFORMATION

- Brief information on the establishment including name and address, relation to other sites and, particularly, any information relevant to understand the manufacturing operations. (not to exceed 250 words, 1 page)

- Name and exact location of the site including telephone, fax, internet address and 24 hour telephone number with the name of a contact person.

- Establishment License Number

- Type of actual drug products (human or veterinarian) fabricated, imported, packaged, tested and/or stored including dosage form, DIN /export only.

- Antibiotic, antineoplastics, steroids, hormones or other toxic or hazardous substances handled, mentioning the way they are handled in dedicated or on a campaign basis. If a containment facility is used, describe it.

- Products other than drugs (cosmetics, food etc.) that are manufactured, imported, packaged, tested and /or stored on the site.

- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis. State their names, addresses, phone and fax numbers and a brief outline of the activity being undertaken by each one in not more than 100 words (half a page).

- A short description of the site (not more than 250 words 1 page) which includes the location and immediate environment.

Requirement, Division 2, C.02.004 and C.02.015

3. PREMISES

- Size of site
- Type and age of buildings and simple floor plans indicating production/activity areas. Where feasible use 8½" x 11" sheets.
- Simple plan or description of laboratory areas and manufacturing areas with indication of scale (architectural or engineering drawings are not required). Label areas and annotate plan with names.
- Construction and finishes. (500 words or less) For large plant limit to critical areas eg. processing, packaging and critical storage areas.
- Brief description of ventilation systems. (500 words or less) More details should be given for critical areas with potential risks of airborne contamination. (schematic drawings of the systems are desirable)
  The following should be covered:
  - the design criteria including
  - specification of the air supply
  - temperature,
  - humidity,
  - pressure differentials and air change rate,
  - simple pass or recirculation rate (%)
  - filter design and efficiency e.g.
  - Bag 99% eff.
  - Hepa 99.997% eff.
  - details of any alarms on the ventilation system should be given.
  - the limits for changing the filters should be given.
  - If DOP is introduced, the point must be shown.
- Classification of the rooms used for the manufacture of sterile products should be mentioned.
- Special areas for the handling of highly toxic, hazardous and sensitizing material
- Water Systems (Please see under Section 4 Equipment)
- Maintenance (description of planned preventative maintenance programmes and recording system). (250 words)
- Sanitation (Please see Sanitation under 4 Equipment and also under 6 Sanitation.)
- Validation of air systems, utilities and support systems: submit a brief summary of all validation studies conducted including protocols, sub-contracters, results, etc.

Requirement, Division 2, C.02.005

4. EQUIPMENT

- Brief description of major production and control laboratories equipment (a list of equipment is not required). Note: that makes and model numbers are not required.

- A description of planned preventative maintenance programmes and recording system. This should indicate if there are written procedures and reporting forms, who is responsible and how the system works.

- Is the machinery constructed of appropriate material (e.g. AISI grade 316 stainless steel for product contact equipment?)

- Have other materials been suitably validated e.g. polypropylene, chrome plated brass, PVC, non reactive plastic materials?

- Is the equipment designed with ease of cleaning in mind?

- Only a general description is required e.g. a rotary tablet press etc. If the equipment has additional devices, these should be recorded e.g. automatic weighing machines with printer; a labeller incorporating a bar code reader for the label; a lot number and expiry date over printer; a freeze drier equipped with a steam sterilisation facility.

- Brief description of water systems (schematic drawings of the systems are desirable and capacity ie. max. quantity per hour). The following should be included:

    - construction materials of the vessels and pipework
    - specification of any filters in the system must be given
    - if water is stored and circulated, what is the temperature at the point of return
    - the specification of the water produced a) chemical b) conductivity c) microbiological
    - the sampling points and frequency of testing
    - the procedure and frequency for sanitation

- In the quality control laboratory only general descriptions such as ph meters, chromatographic equipment GLC, HPLC with computer systems, particle size analyzers.

- In microbiology use general descriptions such as incubators (temperature ranges) facilities for LAL testing, membrane filtration sterility testing, antibiotic assay, etc.

- In particular give brief information on the use of computers, microprocessors etc. in the factory.

- Maintenance (250 words/one page)

    - Who is responsible for maintenance and servicing?
    - Are there written procedures and contractual details for outside work?
    - Are maintenance routines which could affect product quality clearly identified?
    - Are records kept of:
        1. type and frequency of service/check;
        2. details of service repairs and modifications?

- Are reports made known to the users?

- Qualification validation and Calibration (750 words/3 pages)

    - Briefly describe the company's general policy and protocols for qualification and validation (prospective and retrospective).
    - Is there regular post validation monitoring of critical equipment?
    - An outline of process validation may be given here or cross-referenced.
    - Describe the system for the disposition of development and validation batches.
    - What are the arrangements for computer validation, including software validation?
    - Describe equipment calibration policy and records kept.

Requirement, Division 2, C.02.006

5. PERSONNEL

- Number of employees employed in production, quality control, storage and distribution, and engineering

- Organization/relationship chart indicating reporting scheme for quality assurance, including production and quality control.

- Qualifications, experience and responsibilities of key personnel and their replacement in their absence

- Outline of arrangements for basic and in-service training, methods used, assessment, retraining and record maintenance

Requirement, Division 2, C.02.007, C.02.008

6. SANITATION

- Person responsible for the Sanitation Programme
- Programme including validation, monitoring and names of cleaning agents
- Water, air and dust extraction systems
- Handling of waste
- Pest control
- Health hygienic behavior and plant clothing (description, use, handling, laundering)
- Health of personnel including person(s) responsible for checking health of employees, medical examinations, illness reporting.
- Sanitation for Premises and Equipment
    - Cleaning procedures for manufacturing areas and equipment (250 words/one page)
    - Are there written specifications and procedures for cleaning, cleaning agents and their concentration for the method of cleaning and the frequency?
    - Are cleaning agents changed from time to time?
    - Have the cleaning procedures been validated and what was the method of evaluating the effectiveness of cleaning?
    - Are cleaning methods monitored routinely by chemical and/or microbiological methods?
    - What are the cleaning methods (and their frequency) for the water supply system, and air handling system and dust extraction systems?
    - Is an equipment-use log maintained?
    - Are cleaning procedures validated for multi use equipment?

Requirement, Division 2, C.02.009, C.02.010

7. RAW MATERIAL TESTING

- A brief description of the handling and testing of raw materials, including sampling, quarantine, release, storage and handling of rejected materials.

Requirement, Division 2, C.02.011, C.02.012

8. MANUFACTURING CONTROL

A brief description of:

- Production flow sheets/charts
- Identification of materials
- In process storage
- In process testing
- Manufacturing and Packaging Master formulaes
- Handling and control of components, in process and finished products (sampling, quarantine, release, storage)
- Handling of printed packaging materials
- Reprocessed/ recycled/ rejected materials
- Description of computer systems
- Logic flow diagrams
- Development of software
- Validation of computer systems
- Recall system (distribution system, responsibilities, phases)
- Self inspection
- Qualification of contractors and suppliers
- Process validation

Requirement, Division 2, C.02.013, C.02.014, C.02.015

9. QUALITY CONTROL

- Description of the Quality Control systems and of the activities of the Quality Control Department including:
  - general list of equipment,
  - quality policy
  - organization and principles of quality assurance
  - responsibilities
  - control of design and development
  - change control
  - release of finished products
  - complaint handling
  - involvement of QC Dept. in preparation, review, distribution of documents in particular those for specification test methods and release criteria.
  - release of raw materials and packaging materials
  - returned goods policy
  - reprocess/recovery
  - transportation and storage methods
  - competent laboratory

Requirement, Division 2, C.02.016, C.02.017

10. PACKAGING MATERIAL TESTING

- A brief description of the handling and testing of packaging materials including quarantine, sampling, release, storage and handling of rejected materials.
- Description of the vendor certification program, if in place. Description of the procedure in cases of non-compliance, re-certification of vendors, etc.

Requirement, Division 2, C.02.018, C.02.019

11. FINISHED PRODUCT TESTING

- A brief description of the handling and testing of finished products including quarantine, sampling, release, storage and handling of rejected products.

Requirement, Division 2, C.02.020, C.02.021, C.02.022, C.02.023, C.02.024

12. RECORDS

A brief description of the system for:

- SOP (preparation, revision, distribution)
- Responsible person
- Master production documents
- Retention times
- Microfilms
- Electronic records
- Batch numbering system
- Documentations on individual lots
- Distribution records

Requirement, Division 2, C.02.025, C.02.026

13. SAMPLES

A brief description for:

- Storage
- Retention time

Requirement, Division 2, C.02.027, C.02.028

14. STABILITY

- Description of programme
- Shelf life evidences

Requirement, Division 2, C.02.029

15. STERILE PRODUCTS

(If previously addressed, cross references suffice)

- Premises (classification of rooms/areas)
- Equipment
- Personnel
- Sanitation
- Manufacturing control

APPENDIX 1

Please submit domestic Site Reference Files to:

Atlantic Operational Centre
Health Products and Food Branch Inspectorate
1505 Barrington Street, Suite 1625
Halifax, Nova Scotia B3J 3Y6
Operational Manager
Telephone: (902) 426-2160

Quebec Operational Centre
Health Products and Food Branch Inspectorate
1001 St-Laurent Blvd.
Longueuil, Québec J4K 1C7
Operational Manager
(450) 646-1353

Ontario & Nunavut Operational Centre
Health Products and Food Branch Inspectorate
2301 Midland Avenue
Scarborough, Ontario M1P 4R7
Operational Manager
Telephone: (416) 973-1600

Manitoba & Saskatchewan Operational Centre
Health Products and Food Branch Inspectorate
510 Lagimodiere Blvd.
Winnipeg, Manitoba R2J 3Y1
Operational Manager
Telephone: (204) 984-1341

Western Operational Centre
Health Products and Food Branch Inspectorate
4595 Canada Way, 4th Floor
Burnaby, British Columbia V5G 1J9
Operational Manager
Telephone: (604) 666-3704

Please submit *Foreign* Site Reference File to:
Health Products and Food Branch Inspectorate
Inspectorate Ottawa
Graham Spry Bldg, 2nd Floor
250 Lanark Avenue
P.L. 2002B
Ottawa, Ontario K1A 0K9
Head, Drugs GMP Inspection Unit
(613) 957-1492

GMP Committee members

Name	Title / Office / Bureau	Location
Riaz Akhtar	Drug Inspector, Atlantic Region, BCE	Moncton, NB
Benoit Binette, Secretary	Drug Inspector, Quebec Region, BCE	Longueuil, Que.
Jack Basarke	MRA Topic Leader, BCE	Scarborough, Ont.
Lauraine Begin	Officer, B PC	Ottawa, Ont.
Sheila Weilock	Drug Inspector, Western Region, BCE	Burnaby, B.C.
Cara Murray	Drug Inspector, Ontario Region, BCE	Scarborough, Ont.
Raymond Giroux	Drug Inspector, Quebec Region, BCE	Longueuil, Que.
Jean Saint-Pierre	Compliance Officer, OCPC, BCE	Ottawa, Ont.
Sultan Ghani	Manager, Division of Pharmaceutical Quality, BPA	Ottawa, Ont.
Daryl Krepps	Senior Regulatory Advisor, BBR	Ottawa, Ont.
Randy Stephanchew	GMP Specialist, Central Region	Winnipeg, Man.
France Dansereau, Chair	Head, Office of Compliance, Planning and Coordination, BCE	Ottawa, Ont.
Stephane Taillefer	Compliance Officer, OCPC, BCE	Longueuil, Que.
Yves Roy	Compliance Officer, OCPC, BCE	Ottawa, Ont.

BCE Bureau of Compliance and Enforcement changed to Health Products and Food Branch Inspectorate (HPFBI).
BPA Bureau of Pharmaceutical Assessment now part of Therapeutic Products Directorate (TPD).
BBR Bureau of Biologics and Radiopharmaceuticals changed to Biologics and Genetic Therapies Directorate (BGTD).
BPC Bureau of Policy and Coordination now part of Therapeutic Products Directorate (TPD).
OCPC Office of Compliance, Planning and Coordination changed to National Coordination Centre (NCC).