

## Guidelines for drafting a Site Master File (SMF)

A Site Master File for **each manufacturing site listed in a product dossier**, must be submitted to World Health Organization, HTP/EDM/QSM, 20 Ave Appia, 1211 Geneva, 27 Switzerland. Mark the envelope: For attention: Mrs. C. Doucelin (Prequalification).

A site master file should be succinct and, as far as possible, **not exceed 25 A4 pages**.

A site master file is a document 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 and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, the site master file need describe only those operations, e.g., analysis, packaging.

### GENERAL RECOMMENDATION

Read the relevant part and use the terminology of the WHO-GMP before you complete the information requested under a specific point in the SMF. For instance, read 8. Self-inspection and quality audits in the current WHO-GMP before you draft 9.1 Short description of the self-inspection system in this SMF.

### Layout of the SMF:

Front page

In the header: Name and address of the applicant (repeated on each page)

Document number

Effective date

A bird view of the manufacturing site (photo)

Date

Stamped: MASTER COPY

CONTROLLED/UNCONTROLLED COPY

### Table of contents

**Generate by WinWord**

### Approval page signed and dated by person(s):

- Prepared by
- Reviewed by
- Approved by

### Distribution of copies

### Change control

### Structure of the SMF

#### 1. General information

1.1 Brief information on the firm (including name and address), relation to other sites, and, in particular, any information relevant to understanding the manufacturing operations

Name and Address	Responsibility	Drug Master File Number
Drugs 'R' Ltd. 111 First Avenue City 1, Country A	Manufacturing, packaging, labeling, testing, storage, distribution (for FPPs intended for the requalification market)	N/A
Testy Inc. 789 High Road City 2, Country A	testing of the API (particle size testing only)	N/A

1.2 Pharmaceutical manufacturing activities as licensed by the national authority

The above manufacturing facilities have a valid Manufacturing License (MfgL), No. ...., issued by the national DRA and valid until ..... for the manufacture of the following pharmaceutical dosage forms:

- Tablets
- Hard capsules
- Oral solutions, and so on.

In addition, the contract testing facility also has a valid Establishment License.

1.3 Any other manufacturing activities carried out on the site

Only pharmaceutical finished products (FPPs) are manufactured on the site.

1.4 Name and exact address of the site, including telephone, fax, and 24-hour telephone numbers

Registered office and factory:

Drugs 'R' Ltd.  
111 First Avenue  
City 1, Country A

Phone:

Fax:

E-mail:

Contact person(s):

24-hour telephone numbers:

Testy Inc.  
789 High Road  
City 2, Country A

Phone:

Fax:

E-mail:

1.5 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 a **campaign basis**)

Except the QC laboratory, specifically toxic, hazardous or sensitizing APIs –like for instance beta-lactams, cytotoxic or contraceptive hormones– are not handled on the site.

Poisons and narcotics are kept in locked safes. Organic solvents as well as medical and utility gases are stored in separate areas outside the buildings, respectively.

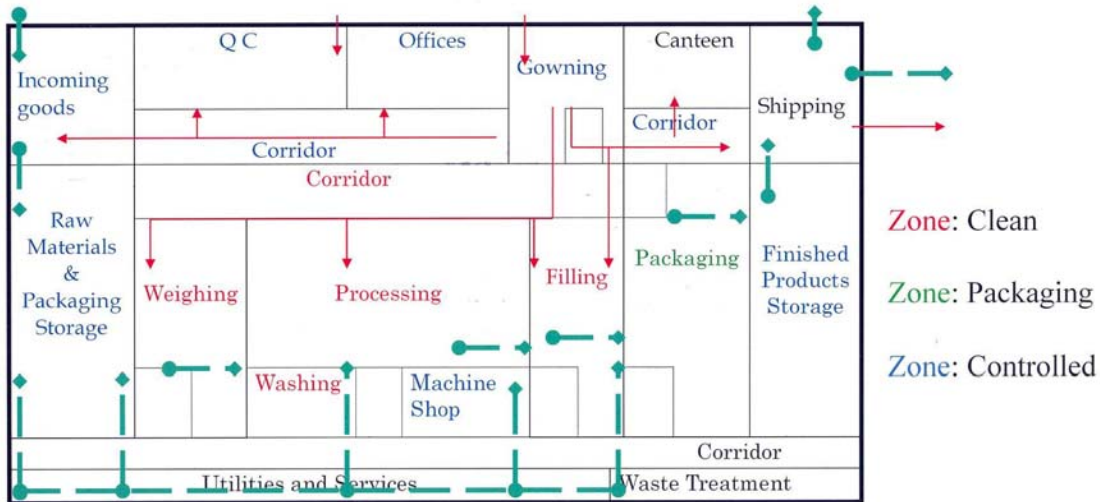
1.6 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site)

Infrastructure such as roads, power and municipal drinking water supply are good and reliable. A map of the factory area is copied into the SMF below, which shows surrounding industries and indicate sources of potential sources of pollution, e.g., from the dominant direction of the wind.

The buildings and other facilities inside the site are numbered and identified in the map.

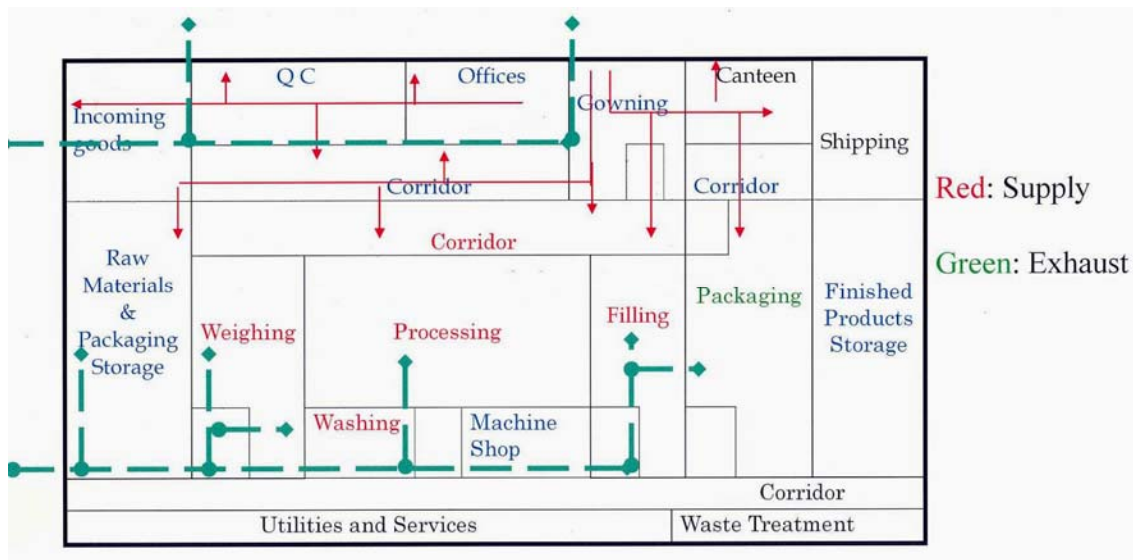
Short description of the buildings:

- Management and administration
- Material, personnel movements and technological order



Source: Dr. Adriaan J. Van Zyl

- Starting material stores
- Packaging material stores
- Capsule and tablet manufacturing plant
- Utility building (HVAC system, water purification, steam boiler, compressed air, etc.)



Source: Dr. Adriaan J. Van Zyl

1.7 Number of employees and workers engaged in:

- Production :
- Quality control :
- Storage :
- Other (e.g., security) :
- Distribution :
- Total :

1.8 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis

Testy Inc., 789 High Road, City 2, Country A: Testing the particle size of APIs.

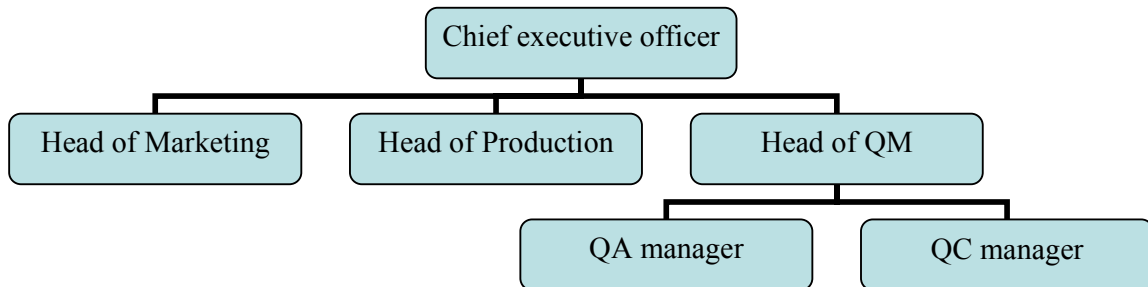
1.9 Short description of the quality management (QM) system of the firm responsible for manufacture.

Brief description of the quality policy of the company (with reference to the Quality Manual).

Responsibilities of the QM [briefly, e.g., audit programs, approval of starting and primary packing material suppliers, FPP batch release, document control (in particular SOPs)]

- Head of QM
- QA manager
- QC manager

QA system organization chart



From this part on, please refer always to the relevant SOP(s) and declare responsibilities.

## 2. Personnel

2.1 Organization chart showing the arrangements for quality assurance, including production and quality control.

See diagram under 1.9

2.2 Qualifications, experience, and responsibilities of key personnel.

Head of Production

Head of QM

Authorized person

Persons with delegated functions (but not responsibilities)

2.3 Outline of arrangements for basic and in-service training and how records are maintained

Organization plan of identified training needs, in particular GMP introduction and reinforcement/upgrading, job related skills, in-house and external training, etc.

Evaluation (open ended question tests, score ranges for fail/pass, trainees opinion) of the effectiveness of training.

2.4 Health requirements for personnel engaged in production

Medical examination prior to and during employment.

2.5 Personnel hygiene requirements, including clothing.

Describe briefly change room procedures in relation to rest room and laundry room procedures.

Describe procedures with protective clothing, shoes, hand shoes, etc.

State rules on eating, drinking, smoking, chewing gum or tobacco, etc.

## 3. Premises and equipment Premises

3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required)

Attach layout of the plant.

3.2 Nature of construction and finishes.

Describe wall construction, nature of finishes, floors, ceilings, doors and windows, lighting, piping and drainage system(s).

3.3 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.

Outline the HVAC system, areas with different classes of air, pressure differential principles to prevent cross-contamination, dedicated air handling units (AHUs), forced ventilation systems, etc.

3.4 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.

Such materials are handled only in the QC laboratory. Solids are neutralized and collected in separate containers. Extracted gases from the fume hood are neutralized and scrubbed before they are allowed to exit into the external environment.

3.5 Brief description of water systems (schematic drawings of the systems are desirable), including sanitation.

Source of raw water, storage tanks, preparation of purified water and its distribution system (construction material), capacity/day, sanitation procedures should be described.

3.6 Description of planned preventive maintenance program for premises and of the recording system.

Critical activities of the annual planned preventive maintenance program for premises should be summarized.

### **Equipment**

3.7 Brief description of major equipment used in production and control laboratories (a list of equipment is not required).

Major pieces of equipment used in:

- Capsule plant
- Tablet plant
- Packing plant
- QC laboratory

3.8 Description of planned preventive maintenance programs for equipment and of the recording system.

The annual planned preventive maintenance program for equipment should be summarized in accordance with machine/instrument manufacturers' requirements.

3.9 Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

Refer to the Validation Master Plan (VMP) and outline qualification, calibration and revalidation as well as cleaning validation schedules/annual plans.

### **Sanitation**

3.10 Availability of written specifications and procedures for cleaning manufacturing areas and equipment

Summarize facility cleaning and sanitization strategy, schedules and documentation with an illustrative list (examples) of SOPs and log books.

## **4. Documentation**

4.1 Arrangements for the preparation, revision, and distribution of necessary documentation for manufacture

Master documents (directly related to product and process quality).

Batch manufacturing and quality records are controlled documents [design (title, number, version, date, signature, etc.), preparation, review, approval, reproduction, entry of data and information, storage, destruction, and so on).

4.2 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water)

Validation protocols, records, job descriptions, contracts with suppliers and customers, etc.

## **5. Production**

5.1 Brief description of production operations using, wherever possible, **flow sheets and charts** specifying important parameters.

E.g., general steps in capsule filling and in tableting, including packing, and indicating equipment and critical in-process control parameters regularly measured.

5.2 Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage

Purchasing procedures (approval of suppliers of APIs, excipients and primary packing materials), material requisition procedures from stores to manufacturing plant and *vice versa*, including sampling, quarantine, release, and storage.

5.3 Arrangements for the handling of rejected materials and products.

Procedures for rejected starting materials and FPPs.

5.4 Brief description of general policy for process validation.

Refer to parts of VMP on (analytical and manufacturing) process validation.

## **6. Quality control**

6.1 Description of the quality control system and of the activities of the quality control department. Procedures for the release of finished products.

Refer to the Quality Manual cited under 1.9 and summarize batch release procedures (review of BMR, IPC and QC data, final approval by Authorized person or QA/QC manager).

## **7. Contract manufacture and analysis**

7.1 Description of the way in which the GMP compliance of the contract acceptor is assessed

Only the X-ray diffraction analysis is contracted to Testy Inc. The contract acceptor is authorized and inspected by the national DRA to perform X-ray diffraction testing. We also audit the laboratory of Testy Inc (every two years). The Authorized Person of Drugs 'R' Ltd.

Reviews the certificates of analysis of Testy Inc. before releasing the batches concerned.

## **8. Distribution, complaints, and product recall**

8.1 Arrangements and recording system for distribution

The distribution records are readily available to the Authorized Person, and they contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

8.2 Arrangements for the handling of complaints and product recalls

Complaints about marketed FPPs are examined according to SOP No. ..., the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

## **9. Self-inspection**

9.1 Short description of the self-inspection system

Written instructions for self-inspection have been established to provide a minimum and uniform standard of requirements. These include GMP requirements covering all the items listed under 8.2 in the WHO-GMP.

Self-inspections are conducted every six (6) months. The management of Drugs 'R' Ltd. Always evaluates both the self-inspection report and the corrective actions, as necessary.

## **THE MAIN POINTS AGAIN**

1. Keep the SMF short (NMT 25 pages).
2. Reference should be made to the document, which describes the Quality Policy and System of the Company. The Quality Manager must be independent from the Production manager.
3. Document that premises have been designed, constructed and maintained to prevent contamination and cross-contamination of pharmaceutical products during the manufacturing process.
4. Describe the validation policy of the Company in the VMP (DQ, IQ, OQ and PQ of equipment (systems) including utilities and analytical instruments) and outline essential steps of the manufacturing process validation and cleaning validation.

**Reference: GMP: World Health Organization**

**WHO Technical Report Series, No. 908, 2003, Annex 4. Good Manufacturing Practices for pharmaceutical products: main principle**