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GUIDELINE ON HOW TO APPLY FOR A LICENCE TO MANUFACTURE, IMPORT AND/OR EXPORT MEDICINES AND SCHEDULED SUBSTANCES

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This guideline is intended to provide recommendations to applicants wishing to submit an application for a licence to manufacture, import or export a medicine or scheduled substances. It is not intended as an exclusive approach and should not be taken as a complete or authoritative statement of the law. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine or scheduled substance in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all scheduled substances and registered medicines will be of the required quality, safety, and efficacy and that the manufacturer complies with acceptable quality assurance principles and good manufacturing practices as determined by SAHPRA to manufacture, import, or export. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Document History

Version	Implementation Date	Reason For Amendment
Version 0	November 2003	First Publication released for implementation and Industry comments.
Version 1	January 2004	Date of finalization/Implementation
Version 2	November 2019	Authority: “MCC” to “SAHPRA” Registrar of Medicines to the Chief Executive Officer (CEO) Directorate: Inspectorate and Law Enforcement to Program 3: Inspectorate and Regulatory Compliance Director-General to CEO
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Table 1: List of Abbreviations

Act 53 of 1974	The Pharmacy Act 53 of 1974 as amended
Act 101 of 1965/Medicines Act	Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended
CEO	Chief Executive Officer
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
ML	Manufacturer Licence (Manufacture, Import or Export)
NDOH	National Department of Health
RP	Responsible Pharmacist
SAHPRA	South African Health Products Regulatory Authority (also known as The Authority)
SAPC	South African Pharmacy Council
SMF	Site Master File

Table 2: List of Definitions

Holder of a certificate of registration	a person in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality and safety and compliance with conditions of registration
Importer and/or Exporter	(i) A manufacturer wherein the manufacturing is contracted out to a third-party manufacturer. The third-party manufacturer could be located within or beyond the borders of South Africa. (ii) Wherein the product is registered by SAHPRA. Wherein the scheduled substance is to be used in the manufacture of a SAHPRA registered product.
Manufacture	all operations including purchasing of material, processing, production, packaging, releasing, storage and shipment of medicines and related substances in accordance with quality assurance and related controls
Manufacturer	a person manufacturing a medicine and includes a manufacturing pharmacy
Responsible Pharmacist	a Responsible Pharmacist as defined in Section 1 of the Pharmacy Act

1 Introduction

The South African Health Products Regulatory Authority (SAHPRA) regulates medicines and scheduled substances for human and animal use, on behalf of the Minister of Health and in accordance with the provisions of the Medicines and Related Substances Act,1965 (Act 101 of 1965) and the relevant Regulations made thereunder. (Hereafter referred to as Act 101 of 1965 or the Medicines Act.)

Amongst other things, Act 101 of 1965 provides for a system of licences, certificates and exemptions from the regulation and control of the manufacture of medicines and scheduled substances in South Africa. Legislation in respect of medicines and scheduled substances is in accordance with the provisions of the Medicines Act. These medicines and scheduled substances must, unless exempt, be registered by SAHPRA, or must have an application number (regarded as "old Medicines") and their manufacturer must hold an appropriate manufacturer's licence. The manufacturer's licence is required by Section 22C of the Medicines Act.

Manufacturers of unregistered medicinal products e.g., investigational medicinal products, or medicine solely for export purposes, are also controlled in accordance with the relevant provisions of Act 101 of 1965 and its regulations.

The manufacture of veterinary medicines or scheduled substances for animal use, registered with the SAHPRA in terms of the provisions of the Medicines Act, is subject to the same legislation and the requirements are similar.

A manufacturer's licence is required for both total and partial manufacture, and for the various processes of dividing up, packaging, or presentation. However, such a licence is not required for preparation, dividing up, and changes in packaging or presentation where these processes are carried out, solely for retail supply, by or under the supervision of a pharmacist in a registered community pharmacy or hospital pharmacy when such activity is performed in terms of the provisions of Section 14(4) of the Medicines Act, or additionally, in the case of a hospital pharmacy, when performed in terms of the provision of Regulation 36 of the Medicines Act.

2 Purpose

This guideline is intended to provide recommendations to applicants wishing to submit an application for a licence to manufacture, import or export a medicine or scheduled substances.

3 Background

Licence to manufacture, import or export, medicines and/or scheduled substances are issued in accordance with the requirements of Section 22C read with Regulation 23 and 24 of the Medicines Act.

4 Scope

This document lays down guidelines on how to apply for a licence to Manufacture, Import and/or Export medicines and /or scheduled substances. It applies equally to medicines and/or scheduled substances for human and for veterinary use as per Act 101 of 1965 and exclude applications for Complementary Medicines licenses (Category D medicines). Information relevant to the Complementary Medicines licensing can be accessed on the website: https://www.sahpra.org.za/e-services/complementary medicines licensing

In this Guideline, the word "should" indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative, demonstrated to provide at least an equivalent level of quality assurance.

The scope covers all the operations which include but are not limited to purchasing of raw materials, processing of these raw materials, production of medicines and/or scheduled substances, packaging of medicines and/or scheduled substances, releasing of the medicines and /or scheduled substances, storage of medicines and scheduled substances, importation and/or exportation of medicines and scheduled substances and all the related quality management system controls.

The scope also covers the licensing of Testing Laboratories and Holders of Certificates of Registration (HCR) wherein the actual manufacturing is contracted out to third parties.

5 Who must apply or not apply for a Manufacturing Licence

5.1 Granting/Re-granting of a Manufacturing and Packing Licence

5.1.1 A manufacturer licence (ML) can be granted for the manufacture and packing of medicines and/or scheduled substances or for only the packaging of medicines and/or scheduled substances. Section 22C of the Medicines Act read together with Regulation 1 of the same Act provides that:

- "Manufacture" means all operations including purchasing of raw materials, processing, production, packaging, releasing, storage and shipment of medicines and related substances in accordance with quality assurance and related controls and
- "manufacturer" means a person manufacturing a medicine and includes a manufacturing pharmacy.

5.1.2 The over-labelling of medicines and scheduled substances (including parallel imports) is a packaging activity and is therefore licensable.

5.2 Exemptions from a Licence to Manufacture, Import or Export

A manufacturer can apply for an exemption from the requirements to obtain a licence to manufacture, import or export in terms of the provisions of Section 36 of the Medicines Act. An application for exemption should be submitted to the Office of the Chief Executive Officer of SAHPRA together with an appropriate motivation. The Minister may, on the recommendation of SAHPRA (The Authority), by notice in the Government Gazette exclude, subject to such conditions as he/she may determine, any medicine from the operation of any or all the provisions of Act 101 of 1965 and may in like manner amend or withdraw any such notice. Advice on the exemptions from licensing can be obtained from Program 3: Inspectorate and Regulatory Compliance(refer to SAHPRA website).

6 How to obtain a Licence Application Form and Information to submit.

6.1 Standard application forms for manufacturer's licences (ML) are available from The Office of the Chief Executive Officer of SAHPRA or from the SAHPRA website www.sahpra.org.za or https://www.sahpra.org.za/inspectorate-and-regulatory-compliance

6.2 An application for a ML should be accompanied by the prescribed application fee (see the

gazetted published fees on the SAHPRA website) and, in the case of a new Manufacturer Licence, an additional inspection fee will be required as per the SAHPRA gazetted fees published on the SAHPRA website. The Applicant shall provide acceptable documentation proof obtained from the following institutions:

6.2.1 The SA Pharmacy Council, namely:

- The particulars of the owner of the business which includes the Certificate of recording of a Pharmacy Owner
- The registration of the responsible pharmacist
- Certificate of recording of a Pharmacy.

6.2.2 The Director General of Health, namely:

- A licence for the premises (NDOH Licence) wherein or from which such business shall be carried on.

NOTE: All manufacturers in operation prior to 2 May 2003 are deemed to have a premises licence.

6.3 The application for ML should include the qualification of staff to manufacture, store, distribute and sell medicines and/or scheduled substances and documentary proof of the ability to comply with good manufacturing practices (GMP)/or proof of compliance with GMP as determined by SAHPRA.

6.4 The application should include, amongst other documents, a Site Master File (SMF) as outlined in regulation 23 of the Regulations to Act 101 of 1965. This should contain specific and factual information about the production and/or control of the medicines and/or scheduled substances manufacturing operations to be carried out at that site (facility). Guidance on what information should be included in the SMF can be obtained on request from the Office of the Chief Executive Officer of SAHPRA or the SAHPRA website www.sahpra.org.za in the guideline 4.08 for the SMF

6.5 The SMF, attached to the application form should include:

- A copy of the local area plan of the location of the business premises indicating all adjacent properties and the nature of the business being carried out on such premises
- A floor plan of the building in which the business premises are situated
- A plan of the actual layout of the business premises
- An inventory of equipment to be used in conducting the business
- A manual of procedures and practices to be implemented to ensure the safety, efficacy and quality of medicines or scheduled substances to be manufactured or distributed and sold.

6.6 The application should specify the Medicines and/or scheduled substances to be manufactured, distributed, or sold from that site as per the provided SAHPRA application form.

6.7 Some of the information required to complete the application form also appears in the SMF.

6.8 The Authority will only issue a ML when it is satisfied, usually following an inspection of a site by the GMP Inspectors, that the information contained in the application is accurate and in compliance with requirements of the legislation and good manufacturing or distribution practices.

6.9 Where appropriate, The Authority may refuse to grant or re-grant a licence. In such cases the

Chief Executive Officer will notify the applicant to furnish SAHPRA with such additional documentation or information as SAHPRA may require. The notification will set out the reason for the proposal and give the applicant a period of not less than 20 days to respond as per Section 22E of Act 101 of 1965. The applicant may make written representations. Before making a final decision on its proposal SAHPRA will take the applicant's written representation into consideration.

6.10 The legislative basis for the information required when applying for a ML may be found in the Medicines Act.

7 Manufacturer's-Obligations

7.1 The standard provisions for manufacturer's licences (MLs) are set out in Regulation 23 of the Medicines Act. These require a licence holder to:

a) Provide and maintain suitable staff, premises, equipment, and facilities.

b) Provide information as requested by SAHPRA regarding the type and quantity of any medicines or scheduled substances which he currently handles, stores, or distributes.

c) Inform the Chief Executive Officer of SAHPRA of any proposed structural alterations to or discontinuance of use of approved licensed premises.

d) Comply with current Good Manufacturing Practice.

e) Retain such transaction documents as are necessary to facilitate the withdrawal or recall of medicines or scheduled substances.

f) Withhold any batch of medicines or scheduled substances from sale or export when informed that it does not comply with its licence specifications or with provisions of Act 101 of 1965 or of any regulations under Act 101 of 1965.

g) Notify SAHPRA of any changes to the premises, operations, listed personnel, or products to which the licence relates.

h) Permit SAHPRA to carry out inspections, take samples or copies of documents as necessary.

i) Manage and provide suitable housing for any animals.

j) Have at his/her disposal the service of a Responsible Pharmacist who must control the manufacturing of medicines or scheduled substances.

k) Appoint and designate a natural person who resides in the Republic who shall be responsible to SAHPRA for compliance with Act 101 of 1965.

l) Distribute products only to licensed wholesale dealers whose licences relate to those medicines or scheduled substances, or to persons who may lawfully sell those medicines or scheduled substances by retail or to persons who may lawfully administer those medicines or scheduled substances.

m) Pay the annual licence retention fee as determined by SAHPRA in the gazetted fees published on the SAHPRA website www.sahpra.org.za for continued licensing.

n) Comply with Act 101 of 1965 and the conditions of the licence.

o) Apply for the renewal of the licence every 5 years at least 180 days before the expiry of the existing licence.

7.2 Inform the CEO of SAHPRA of any changes to any of the particulars furnished in the application or entered in the register, which occurred after the granting/re-granting of the licence, within 30 days of such change.

On application for the re-granting (renewal and/or amendment) of the licence, the application should be accompanied by the prescribed fee (see the gazetted published fees on the SAHPRA website) and contain the information and documentation required by points 6.2—6.5

8 Compliance with Good Manufacturing Practices

8.1 The SA Guide to GMP sets out the "principles and guidelines of Good Manufacturing Practice" (GMP) for medicines and scheduled substances.

8.2 The SA Guide to GMP is published on the SAHPRA's website at www.sahpra.org.za

8.3 To comply with GMP, holders of manufacturer's licences (MLs) should:

a) Establish and implement an effective pharmaceutical quality management system;

b) Have competent and appropriately qualified personnel, sufficient in number to achieve the pharmaceutical quality objective(s) of their organisation;

c) Define the duties of managerial and supervisory staff responsible for implementation and operating GMP in their job descriptions;

d) Give personnel sufficient authority training to meet the pharmaceutical quality objective(s) of their organisation;

e) Institute and maintain hygiene programmes relating to health, hygiene, and clothing;

f) Provide and maintain premises and equipment appropriate to the intended operations;

g) Have system(s) of documentation covering all process specifications of the various operations. Batch documentation should be retained at least one year after the expiry date of the batch to which it relates or at least five years after certification of the batch by the Authorized Person, whichever is the longer;

h) Provide and maintain an independent quality control department, under the authority of a person nominated as responsible for overall quality control/quality assurance;

i) Retain records and samples of starting materials and finished products for the required periods;

j) Ensure that any work contracted out is the subject of a written contract;

k) Maintain an effective system whereby complaints are reviewed, and products may be recalled;

l) Carry out a program of regular self-inspection.

9 Personnel (Refer to Annex 16 of the 4.01 Guide to GMP)

A. The Responsible Pharmacist

9.1 It is required that the holder of a manufacturer's licence (ML) should appoint a Responsible Pharmacist (RP), who is to be named on the licence. The RP's duties are specific and are intended to ensure that every batch of medicines or scheduled substances that have been manufactured and/or packed are checked in accordance with legal requirements. A RP has a

personal responsibility for ensuring that the required tests and controls are carried out and must sign or certify, for each batch, that the appropriate tests have been carried out and that it complies with the relevant product or certificate of registration. Not more than one RP may be named on the licence.

9.2 The Pharmacy Act 53 of 1974, Rules and Regulations (Act 53 of 1974) prescribes the qualifications for a RP as well as the acts pertaining to the profession of a pharmacist. Candidates for appointment as RP must meet specific educational requirements. Candidates are expected to be a pharmacist, registered with the SA Pharmacy Council, with appropriate experience in medicines or scheduled substances manufacturing as applicable. The RP's tasks are *inter alia* to:

a) ensure that each batch of the medicines or scheduled substances to which the licence relates has been manufactured or packed and checked in compliance with section 18 of the Medicines Act and associated regulations;

b) certify in a register or other appropriate record before the batch is released for sale that each batch of medicines or scheduled substances satisfies the conditions set out in the authorisation or certificate of registration before the batch is released for sale.

9.3 A RP is required to be named on a licence which relates to manufacture of medicines and/or scheduled substances including unregistered medicines and scheduled substances intended solely for export.

9.4 Further guidance on the professional duties and responsibilities of a RP is given in the Rules Relating to Good Pharmacy Practice document and these include the Ethics and Professional Standards plus the Responsibility of a Pharmacist as per the SAPC requirements. The document is issued by the SA Pharmacy Council. The SA-GMP guide also lists some of the duties and responsibilities of the Responsible Pharmacist.

B. The Production Manager

9.5 An application for ML should have a suitably qualified Production Manager or Head of the Production Department. The Production Manager is responsible for:

a) Ensuring that the products are produced and stored according to the appropriate documentation so that they reach the appropriate standards of quality;

b) Approving the instructions relating to production operations and to ensure their strict implementation;

c) Ensuring that production records are evaluated and signed by an authorised person before they are sent to the Quality Control (QC) Department;

d) Checking the maintenance of his/her department, premises, and equipment;

e) Ensuring that appropriate validation is done;

f) Ensuring that the required initial and continuing training of his/her department's personnel is carried out and adapted according to the need.

C. The Quality Control Manager Quality Assurance Manager (Refer to Annex 16 of the 4.01 Guide to GMP)

9.6 An applicant for a ML should have a suitably qualified Quality Control Manager or Head of Quality Assurance independent of the Production Department. This person may not act as the Production Manager but can be named the RP.

9.7 The Quality Control/Assurance Manager is responsible for:

a) Approving or rejecting, as he/she sees fit, starting materials, packaging materials and intermediate, bulk, and finished products;

b) Evaluating batch records;

c) Ensuring that all necessary testing is carried out;

d) Approving specifications, sampling instructions, test methods and other quality control procedures;

e) Approving and monitoring contract analysts;

f) Checking the maintenance of the department, premises, and equipment;

g) Ensuring that the appropriate validations are done;

h) Ensuring that the required initial and continuing training of his/her department's personnel is carried out and adapted according to the need.

10 Inspections [as stipulated by Section 28 of Act 101 of 1965 read together with Regulation 23(3)].

10.1 The Program 3: Inspectorate and Regulatory Compliance carry out regular and repeated inspection of manufacturing sites both in South Africa and in countries with which SAHPRA does not have a Mutual Recognition Agreement. The Inspection enables the Inspectorate Unit to confirm that licence holders are complying with the conditions of their licence, with the provisions of the Medicines Act and with Good Manufacturing Practice (GMP).

10.2 Amongst other things, Inspectors are empowered by Section 28 of the Medicine Act to:

a) Enter any place or premises from which

i. The holder of a licence to manufacture, import or export conducts business

ii. The holder of a certificate of registration of a medicine conducts business

b) Inspect the premises used in the manufacture, packing, testing, storage, and distribution of medicines and scheduled substances and inspect any documentation or records relating to the manufacture, packing, storage and distribution of these medicines and scheduled substances

c) Take samples of any medicine or schedule substance for the purpose of testing or analysis

d) Seize any book, record, documentation or medicine or scheduled substances.

It is required by legislation that licence holders shall make their premises available for inspection by the Inspectorate at any reasonable time.

10.3 Following an inspection, the Inspector prepares a report of his/her findings. A report is sent to the licence applicant or holder noting any deficiencies found and asking for proposals to remedy them. In the event of serious non-compliance with GMP, the report is referred to SAHPRA for

formal action, which can include the refusal, suspension or revoking of a licence, or part of a licence.

10.4 Where quality control testing is contracted to a third party, the testing site should also be made available for inspection and should also obtain a licence authorizing it to test medicines and/or scheduled substances.

11 Powers to Suspend or Revoke Manufacturer's Licence (as per the provisions of Section 22E of Act 101 of 1965)

11.1 SAHPRA (The Authority) may revoke, amend, or suspend a licence when a statutory condition of that licence is no longer being met. The Authority will give the licence holder notice of its proposal and set out the reasons. In most cases the licence holder will be given a period of not less than 20 days to respond. The licence holder may give notice to the Authority of his/her desire to be heard or make written representation to the Authority with respect to the proposals.

11.2 Where it appears to SAHPRA that public safety is at risk, SAHPRA may suspend a licence with immediate effect for such a period as SAHPRA may determine or revoke the licence in question.

11.3 Licence provisions may be varied based on the application of the licence holder.

11.4 A licence holder or applicant may at any time within the period of 30 days from the date on which the decision of the SAHPRA's CEO is served on him/her appeal to the Minister to question the validity of SAHPRA's decision as per Section 24A of Act 101 of 1965.

12 Process to follow when a SAHPRA licenced site ceases to exist

If a SAHPRA licenced site ceases to exist due to any business conditions, the process outlined below shall be followed:

12.1 The Company's CEO/MD together with the RP must write a letter on their company's letter head addressed to the CEO of SAHPRA in not less than 30 days prior to the closure of the site as per Regulation 23(9) of Act 101 of 1965. The letter must confirm to SAHPRA the proposed date of closure. Licence provisions may be varied based on the application of the licence holder.

12.2 The Company must confirm to SAHPRA that the intended closure has been communicated to NDOH and to the SAPC.

12.3 The Company shall return to SAHPRA the original licence with all its Annexures within 10 days of closure of the business.

13 Fees Payable(Refer to the gazetted fees on the SAHPRA website)

13.1 The Medicines Act introduced provisions in terms of Section 35 (1) (xxxi) and (xxxii) read together with Section 35 (4) for the payment of fees for licences, certificates, and inspections.

The current fees legislation for medicines and scheduled substances is contained in the Medicines Regulations as amended.

13.2 The fees are currently payable for the following:

a) Licence applications (new and amendment applications)

b) Licence renewal

c) Licence issue

d) Performance of an inspection

e) Annual fees applicable for the retention of the licence as per regulation 24 of the Regulations to the Medicines Act.

13.3 A schedule of the current fees is available from the Office of the Chief Executive Officer of SAHPRA or on the SAHPRA website at www.sahpra.org.za

13.4 When SAHPRA plans to make changes to the amount or frequency of fees, licence holders are consulted and given the opportunity to comment on the new fee proposals. Details of the new fees are published in the government gazette and on the Authority's website at www.sahpra.org.za

14 Contact Details

Refer to SAHPRA website: https://www.sahpra.org.za/key-contacts/ and

https://www.sahpra.org.za/inspectorate-and-regulatory-compliance/

15 References

15.1 Related Regulations

- The Pharmacy Act 53 of 1974
- Medicines and Related Substances Act, 1965 (Act 101 of 1965)