

# SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY



## GUIDELINES FOR LICENCE TO MANUFACTURE, IMPORT or EXPORT

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 medical device. It is not intended as an exclusive approach leaflet 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 medical device in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines or medical devices 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.

The guidance in this Guidelines and application forms are available from the office of the Chief Executive Officer and the website.

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**THE CHIEF EXECUTIVE OFFICER (CEO)**

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## 1 INTRODUCTION

South African Health Products Regulatory Authority (SAHPRA) regulates medicines, scheduled substances and medical devices for human and animal use, on behalf of the Department 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 there under. (Hereafter referred to as the Act or the Medicines Act.)

Amongst other things, the Act provides for a system of licences, certificates and exemptions from the regulation and control of the manufacture of medicines, scheduled substances and medical devices in South Africa. Legislation in respect of medicinal products is in accordance with the provisions of the Medicines and Related Substances Act, 1965 (Act 101 of 1965). These medicines and medical devices 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 license. The manufacturer’s license 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 the Act and the regulations.

The manufacture of veterinary medicines or medical devices for animal use, registered with South Health Products Regulatory Authority in terms of the provisions of the Medicines and Related Substance Act, 1965 (Act 101 of 1965), is subject to the same legislation and the requirements are similar.

A manufacturer’s license 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 Act, or additionally, in the case of a hospital pharmacy, when performed in terms of the provision of Regulation 36 of the Act.

## 2 MANUFACTURE AND PACKAGING

2.1 A Manufacturer Licence (ML) can be granted for the manufacture and packing of medicinal products or for the packaging of medicinal products. Section 22C of the Medicines Act read together with Regulation 1 provides that:

“**manufacture**” means 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” and

“**manufacturer**” means a person manufacturing a medicine and includes a manufacturing pharmacy.

2.2 The over-labelling of medicinal products (including parallel imports) is a packing activity and therefore licensable.

### 3 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 Act. An application for exemption should be submitted to the Registrar together with an appropriate motivation. The Minister may, on the unanimous recommendation of the members present at any meeting of SAHPRA, 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 of the provisions of this Act, and may in like manner amend or withdraw any such notice.

Advice on the exemptions from licensing can be obtained from Program 3: Inspectorate & Regulatory Compliance.

### 4 HOW TO OBTAIN A LICENCE APPLICATION FORM AND INFORMATION TO SUBMIT

- 4.1 Standard application forms for manufacturer's licences (ML) are available from the Chief Executive Officer (CEO) or the SAHPRA website: [www.sahpra.org.za](http://www.sahpra.org.za).
- 4.2 An application for ML should be accompanied by the prescribed application fee and in the case of a new Manufacturer an inspection fee. The application shall provide acceptable documentation proof obtained from:
  - 4.2.1 the SA Pharmacy Council, of:
    - 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.
  - 4.2.2 the Director-General of Health:
    - a licence for the premises 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.
- 4.3 The application for ML should include the qualification of staff to manufacture, store, distribute and sell medicines, scheduled substances or medical devices and documentary proof of the ability to comply with good manufacturing practices (GMP) as determined by SAHPRA.
- 4.4 The application should include, as proof of the compliance with GMP, a Site Master File (SMF). This should contain specific and factual information about the production and/or control of the pharmaceutical manufacturing operations to be carried out. Guidance on what information should be included in the SMF can be obtained on request from the Chief Executive Officer (CEO) or the SAHPRA website: [www.sahpra.org.za](http://www.sahpra.org.za)
- 4.5 The application should include:
  - A copy of the local area plans 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 or medical devices to be manufactured or distributed and sold.
- 4.6 The application should specify the medicines, scheduled substances or medical devices to be manufactured or distributed and sold.
- 4.7 Some of the information required to complete the application form also appears in the SMF.

**4 How to obtain a licence application form and information to submit***continued*

- 4.8 SAHPRA 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.
- 4.9 Where appropriate, SAHPRA may refuse to grant a licence. In such cases the CEO will notify the applicant to furnish the Authority 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 28 days to respond. The applicant may make written representations. Before making a final decision on its proposal SAHPRA will take the applicant's written representation into consideration.
- 4.10 The legislative basis for the information required when applying for a ML may be found in the Medicines Act.

**5 MANUFACTURERS' OBLIGATIONS**

- 5.1 The standard provisions for manufacturer's licences (MLs) are set out in Regulation 19 to 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 medicinal product which he currently handles, stores or distributes;
  - (c) inform the Chief Executive Officer 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 medicinal products;
  - (f) withhold any batch of medicinal product from sale or export when informed that it does not comply with its licence specifications or with provisions of the Act or of any regulations under the Act;
  - (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 disposal the service of a Responsible Pharmacist who must control the manufacturing of medicines or medical devices;
  - (k) appoint and designate a natural person who resides in the Republic who shall be responsible to SAHPRA for compliance with the Act;
  - (l) distribute products only to licensed wholesale dealers whose licences relate to those products or to persons who may lawfully sell those products by retail or to persons who may lawfully administer those products;
  - (m) pay the annual fee as determined by SAHPRA for continued registration;
  - (n) comply with the Act and the conditions of the licence.
  - (o) Apply for the renewal of the license every 5 years at least 90 days before the expiry of the existing licence.
- 5.2 Inform the Chief Executive Officer of any changes to any of the particulars furnished in the application or entered in the register, which occurred after the issue of the licence.
- 5.3 On application for the renewal of the licence the application should be accompanied by the prescribed fee and contain the information and documentation required by points 4.2 - 4.5 above.

**6. COMPLIANCE WITH GOOD MANUFACTURING PRACTICE**

- 6.1 The SA Guide to GMP sets out the “principle and guidelines of Good Manufacturing Practice” (GMP) for medicinal products.
- 6.2 The SA Guide to GMP is published on the SAHPRA website at [www.sahpra.org.za](http://www.sahpra.org.za)
- 6.3 To comply with GMP, holders of manufacturer’s licences (MLs) should:
- (a) establish and implement an effective pharmaceutical quality assurance system;
  - (b) have competent and appropriately qualified personnel, sufficient in number to achieve the pharmaceutical quality objective(s);
  - (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);
  - (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 for at least one year after the expiry date of the batch to which it relates;
  - (h) provide and maintain an independent quality control department, under the authority of a person nominated as responsible for overall quality control;
  - (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 programme of regular self-inspection.

**7. PERSONNEL****The Responsible Pharmacist**

- 7.1 It is required that the holder of a manufacturer’s licence (ML) should appoint at least one Responsible Pharmacist (RP), to be named on the licence. The RP’s duties are specific and are intended to ensure that every batch of medicinal product has been manufactured and/or packed and checked in accordance with legal requirements. A RP has a personal responsibility for ensuring that the required test and control 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. More than one RP may be named on the licence.
- 7.2 The Pharmacy Act and Regulations, 1974 (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 medicine, scheduled substances or medical device manufacturing as applicable.
- 7.3 The RP’s tasks are to:
- (a) ensure that each batch of the medicinal product to which the licence relates has been manufactured or packed and checked in compliance with section 19 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 medicinal product satisfies the conditions set out in the authorisation or certificate of registration before the batch is released for sale;

**7 Personnel - The Responsible Pharmacist continued**

- 7.4 A RP is required to be named on a licence which relates to manufacture of unregistered medicinal products intended solely for export;
- 7.5 Further guidance on the professional duties and responsibilities of a RP is given in the Ethical Rules and responsibilities of a pharmacist issued by the SA Pharmacy Council and in the guidelines on GMP.

**Production Manager**

- 7.6 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.

**Quality Controller**

- 7.7 An applicant for a ML should have a suitably qualified Quality Controller or Head of Quality Control independent of the Production Department. This person may not act as the Production Manager, but can be named the RP.
- 7.8 The Quality Controller 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.

**8. INSPECTION**

- 8.1 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. Inspection enables the Inspectorate 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).

**8 Inspection continued**

- 8.2 Amongst other things, Inspectors are empowered to:
- (a) enter any place or premises from which
    - The holder of a licence to manufacture, import or export conducts business
    - 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 medicinal products and inspect any documentation or records relating to the manufacture, packing, storage and distribution of medicinal products
  - (c) take samples
  - (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.

- 8.3 Following an inspection, the Inspector prepares a report of his/her findings. A letter 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.
- 8.4 Where quality control testing is contracted to a third party, the testing site should also be made available for inspection and should obtain a licence.

**9. POWERS TO SUSPEND OR REVOKE MANUFACTURER'S LICENCES**

- 9.1 SAHPRA may revoke, amend or suspend a licence when a statutory condition of that licence is no longer being met. SAHPRA 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 SAHPRA of his/her desire to be heard, or make written representation to SAHPRA with respect to the proposals.
- 9.2 Where it appears to SAHPRA that public safety is at risk, SAHPRA may suspend a licence with immediate effect for such a period as the Authority may determine, or revoke the licence in question.
- 9.3 Licence provisions may be varied on the application of the licence holder.
- 9.4 A licence holder or applicant may at any time within the period of 30 days from the date on which the decision is served on him/her appeal to the Minister to question the validity of SAHPRA's decision.

**10. FEES**

- 10.1 The Medicines Act introduced provisions for the payment of fees for licences, certificates and inspections. The current fees legislation for medicinal products is contained in the Medicines Regulations as amended.
- 10.2 Fees are currently payable for the following:
- (a) Licence applications
  - (b) Licence renewal
  - (c) Licence issue
  - (d) Performance of an inspection
- An annual service charge is also payable during the currency of a licence.



**10 Fees continued**

- 10.3 A schedule of the current fees is available from the office of the Chief Executive Officer or on the SAHPRA website at [www.sahpra.org.za](http://www.sahpra.org.za)
- 10.4 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 SAHPRA website at [www.sahpra.org.za](http://www.sahpra.org.za)

**11. CONTACT DETAILS**

SAHPRA and Program 3: Inspectorate and Regulatory Compliance can be contacted at:

The office of The Chief Executive Officer  
 South Health Products  
 Regulatory Authority  
 CSIR Campus, Building  
 10F, Meiring Naude Road  
 Brummeria, Pretoria 0001

**12. UPDATE HISTORY**

| Date    | Reason for update   | Version & publication |
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| Nov2019 | Authority: "MCC" to "SAHPRA"<br>Authority Logo: "MCC Logo" to "SAHPRA Logo"<br>Council to SAHPRA<br>Registrar of Medicines to the Chief Executive Officer (CEO)<br>Directorate: Inspectorate and Law Enforcement to<br>Program 3: Inspectorate and Regulatory Compliance<br>Director-General to CEO | v1.1 November2019     |