South African Health Products
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GUIDELINE
AVAILABILITY OF MEDICINES FOR USE IN A PUBLIC HEALTH EMERGENCY

This guideline provides recommendations to applicants who intend to submit applications for the registration or authorisation of medicines intended to be available to those affected by a public health emergency. It represents the current thinking of the South African Health Products Regulatory Authority (the Authority) on approaches to determine the quality, safety, and efficacy of the medicines required in a public health emergency, and is not intended as an exclusive approach. The Authority reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used, but these should be scientifically and technically justified. The Authority is committed to ensuring that all registered or authorised medicines are of the required safety, quality and efficacy. It is important that applicants also adhere to administrative requirements to avoid delays in the processing and evaluation of applications.

This document should be read in conjunction with all other related guidelines and templates, available from the Authority's SAHPRA's website: www.sahpra.org.za.

Version 1: publication released for implementation and open for 30 day comment period ending 30 September 2021.	August 2021

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1. INTRODUCTION

1.1 Purpose

The purpose of this guideline is to guide how medicines that are not yet available in South Africa may become registered for use by, or authorised for sale to those who are affected by a Public Health Emergency (PHE). Such applications for registrations or authorisations would be received, processed and decided upon effectively, consistently, timeously and in accordance with the Medicines and Related Substances Act, 1965 (Act 101 of 1965), ["the Act"] and the General Regulations published in terms of the Act ["General Regulations"].

1.2 Scope of the document

The Authority is mandated to assess the safety, quality and therapeutic efficacy of all medicines in determining whether the availability of a medicine is in the public interest. Before registration of a medicine, access is usually limited to clinical trials. The Authority may, in certain circumstances, and in terms of section 21 of the Act, authorise the sale of an unregistered medicine for such purposes and in such manner and during such period as the Authority may determine.

PHEs represent a significant concern for their potential domestic and international impact. The unusual and unexpected nature of PHEs may lead to situations for which there is no or insufficient effective treatment, diagnosis, or prevention of the associated conditions, diseases or disorders associated with the PHE. The Authority, therefore, needs to consider mechanisms that would allow for the agile, expeditious and appropriate review of medicines required in a PHE.

The Authority seeks to expedite access to safe, good quality and efficacious medicines for the South African public. The processes encompassed in this document guide how applicants may position their applications to best facilitate the review of applications for the registration, or authorisation of the sale of a qualifying medicine in response to a PHE.

1.3 Objectives

This document is intended to clarify the scenarios for applications for the registration, or authorisation of the sale of medicines during a PHE in terms of the Act according to the scope of the document described in 1.2 and outlines:

a) the qualifying criteria for consideration of this pathway;
b) the application processes that apply to medicines that may address a medical need during a PHE in South Africa;
c) the responsibilities of applicants; and
d) the information required to comply with this pathway.

1.4 Legislative Provisions

Section 1 of the Act defines "sell" as follows:

> ***"sell"*** *means sell by wholesale or retail and includes import, offer, advertise, keep, expose, transmit, consign, convey or deliver for sale or authorize, direct or allow a sale or prepare or possess for purposes of sale, and barter or exchange or supply or dispose of to any person whether for a consideration or otherwise; and "sale" and "sold" have corresponding meanings;*

Section 1(3) of the Act states:

> *In determining whether or not the **registration** or **availability** of a medicine is in the public interest, regard shall be had **only** to the **safety, quality** and **therapeutic efficacy** thereof in relation to its effect on the health of a person, as the case may be.*

Section 14(1) of the Act states:

> *(1) Save as provided in this section or sections 21 and 22A, no person shall sell any medicine, medical device or IVD which is subject to registration by virtue of a declaration published in terms of subsection (2) unless it is registered.*

Section 15(1)-(3) of the Act states:

> *(1) Every application for the registration of a medicine, medical device or IVD shall be submitted to the Chief Executive Officer in the prescribed form and shall be accompanied by-*
> *(a) the prescribed particulars;*
> *(b) samples of the relevant medicines;*
> *(c) where practicable, samples of medical devices or IVDs; and*
> *(d) the prescribed registration fee.*
>
> *(2) As soon as possible after receipt by the Chief Executive Officer of an application contemplated in subsection (1), he or she shall inform the applicant in writing that the application is being considered.*
>
> *(3)*
> *(a) If after consideration of any such application and after any investigation or enquiry which it may consider necessary the Authority is satisfied that the medicine, medical device or IVD in question-*
> *(i) is suitable for the purpose for which it is intended;*
> *(ii) complies with the prescribed requirements; and*
> *(iii) is safe, efficacious and of good quality and, in the case of a medical device and IVD, performs as intended,*
> *the Authority shall issue the applicant with a certificate of registration to that effect.*

Section 21 of the Act states:

> *(1) The Authority may in writing authorize any person to **sell** during a specified period to any specified person or institution a specified quantity of any particular medicine, medical device or IVD which is not registered.*
>
> *(2) Any medicine, medical device or IVD sold in pursuance of any authority granted under subsection (1) may be used for such purposes and in such manner and during such period as the Authority may in writing determine.*
>
> *(3) The Authority may at any time by notice in writing withdraw any authority granted in terms of subsection (1) if effect is not given to any determination made in terms of subsection (2).*

1.5 Definitions

For the purposes of this guideline, any word or expression to which a meaning has been assigned in the Act or General Regulations shall have the meaning so assigned and, unless the context otherwise indicates-

"Authority" means the South African Health Products Regulatory Authority established by section 2 of the Act;

"institution" means any organisation that wishes to sell an unregistered medicine and includes a health establishment as defined in section 1 of the National Health Act, 2003 (Act No. 61 of 2003), or the holder/s of a licence to manufacture, import or to act as a wholesaler of or distribute a medicine or Scheduled substance, issued in terms of section 22C(1)(*b*) of the Act;

"medicine" means medicine as defined in terms of the Act; and

"public health emergency" means an extraordinary event which, in consultation with the National Department of Health of South Africa, has been determined to:

(a) constitute a serious health risk to members of the public of the Republic of South Africa; or
(b) cause or has the potential to cause an outbreak, epidemic or pandemic.

2. BACKGROUND INFORMATION

A PHE may lead to an unprecedented challenge to public health, resources and way of living, economic and social disruptions as well as possible loss of human life. To mitigate the effects of any disease or health risk, the impact of which is sudden, unexpected and is not readily addressed by existing therapeutic means, may potentially rely upon the availability of novel medicines or medicines not yet legally available in the country.

Due to the potential global impact of a PHE, the anticipated applications for registration in terms of section 15 of the Act or authorisation of the sale of an unregistered medicine in terms of section 21 of the Act need to be appropriately motivated, contextually applicable and guided.

The Authority's legislated mandate is to consider the safety, quality and efficacy of any medicine when deciding whether or not to make a medicine available for use in the country. All three elements must be ensured so that members of the public realise the inherent therapeutic or preventative benefits of a medicine but also that such medicines do not cause any harm because of their quality deficiencies or inherent safety concerns.

This guideline should be read together with other relevant guidelines determined by the Authority concerning information and application requirements for the authorisation for sale or registration of medicines as may be appropriate.

Despite the guidance provided herein, the Authority may request any other information as may be required by the Authority in terms of regulation 16(3)(*g*) (with respect to applications submitted for the registration of a medicine) or regulation 29(2)(*g*) (with respect to applications for the authorisation of the sale of an unregistered medicine) of the General Regulations.

3. POSSIBLE SCENARIOS FOR MEDICINES INTENDED FOR A PHE

In either of the possible scenarios provided in 3.1 and 3.2 below:

- a PHE as defined must have been appropriately identified;
- the medicine in question must be verified to be manufactured in compliance with Good Manufacturing Practices (GMP);
- in the case that the applicant is the original manufacturer of the medicine, a commitment to:
    - provide SAHPRA with all necessary information related to the safety, quality, and efficacy of the medicine, and all research and development of the medicine; and
    - complete the necessary research and development steps to comply with the requirements for registration;
- in the case of a medicine to be imported by an entity or person other than the original manufacturer the applicant must:
    - have demonstrable contractual agreements in place, without any hindrance or limitation, that empowers it to have access to and provide all necessary information required by the Authority relating to the safety, quality, and efficacy of the medicine and all research and development of the medicine; and
    - include an undertaking from the original developer and manufacturer to complete and make available the necessary information as well as the research and development steps to comply with the requirements for registration;
- based on the outcome of a risk-based analysis concerning the safety, quality and efficacy of the medicine in question, registration of that medicine or authorisation for sale as an unregistered medicine may be undertaken, with conditions that require the submission of outstanding information within a timeframe stipulated by the Authority; and
- in the case of applications for registration of a medicine in terms of section 15 of the Act:
    - motivations for a priority review should take account of the context of the defined PHE and its clinical and social impact; and
    - motivations for a rolling review, should include reference to the following minimum available evidence:
        - non-clinical and early clinical phase data that demonstrate promising evidence of safety and efficacy;
        - written confirmation that phase 2/3 trials have started and there are enough people enrolled to determine evidence of safety and efficacy within an appropriate and reasonable amount of time; and
        - a plan stipulating the proposed timelines for submitting the various components of the application.

3.1 Medicines that have been authorised for use by Medicines Regulatory Authorities (MRAs) recognised by the Authority

The Authority may consider the authorisation of an unregistered medicine for sale in terms of section 21 of the Act if the medicine has been authorised or registered for use in a PHE by any MRA recognised by the Authority (see **SAHPRA Guideline 2.01: General Information**).

In such instances, applicants must consult **SAHPRA Guideline 2.52: Access to Unregistered Medicines** (scenario 2.5.1) and submit an application in terms of section 21 of the Act.

In line with the commitment to continue the necessary research and development of the medicine, the applicant must, within a period stipulated by the Authority, after the submission of an application in terms of section 21 of the Act, apply for registration of the medicine in question in terms of section 15 of the Act (see **sections 4** and **5 below**) including suitable motivation for the application to be considered for (a) priority review; and/or (b) rolling review.

In the event of a successful application for registration, any active authorisation for the sale of the unregistered medicine will be withdrawn. The registration of the medicine may be subject to conditions in terms of section 15(6)(*a*) of the Act.

3.2 Medicines that have not been authorised for use by Medicines Regulatory Authorities (MRAs) recognised by SAHPRA

In the case of novel medicines which have not been authorised for use by an MRA recognised by the Authority (see **SAHPRA Guideline 2.01: General Information**) and which are intended to be used for the management of a PHE, an application for registration in terms of section 15 of the Act must be made to the Authority.

Applicants must ensure that applications meet minimum requirements for submission as stipulated by the Authority.

If required, applicants may submit together with the application motivation for the application to be considered for (a) priority review; and/or (b) rolling review. The type of review of such application will be determined after the screening phase with reference to the motivation and the completeness of the dossier submitted.

Based on the context of the PHE, the need for the medicine in question and the progress of the review of the application for registration, a positive risk-benefit analysis for its use may be achieved. In such instances, the availability of the medicine to the public may be best facilitated by way of authorisation in terms of section 21 of the Act before all the requirements for registration are met. Applicants must consult **SAHPRA Guideline 2.52: Access to Unregistered Medicines** (scenario 2.5.2) and submit an application in terms of section 21 of the Act.

In the event of the medicine being registered in terms of section 15, any active authorisation for the sale of the unregistered medicine will be withdrawn. The registration of the medicine may be subject to conditions in terms of section 15(6)(*a*) of the Act.

4. PRE-SUBMISSION MEETING

Applicants intending to make submissions for registration may face different challenges regarding their applications and their ability to comply with all administrative requirements for an application for registration.

To provide an opportunity for applicants to explain the nature of these challenges and to develop a preliminary review of the data required, SAHPRA encourages applicants to schedule a pre-submission meeting with the Authority to obtain guidance, in accordance with the requirements outlined in section 3 above.

4.1 How to make a pre-submission appointment?

Send an email to newmedicines@sahpra.org.za and section21@sahpra.org.za together with a summary of the information requested in 4.2, requesting an appointment and undertaking to supply all information stipulated in 4.2 in detail prior to the meeting.

The subject of the email should include "PHE PRE-SUBMISSION APPOINTMENT REQUEST".

4.2 What is required for the pre-submission discussion?

The following information must be supplied in writing at least five working days prior to the intended meeting date and must be presented during the pre-submission meeting:

- information on authorisation or registration status with other regulators and whether the medicine has been or is intended to be submitted to the WHO or other regulators;
- all details of the medicine including, but not limited to, the technology used, the data available, specific transport/storage, and labelling information;
- evidence which shows that manufacturing of the medicine is in compliance with GMP and that product quality and consistency are well controlled;
- information on testing for lot release, where applicable in terms of regulation 15 of the General Regulations; and
- requested type of review (e.g. priority and/or rolling) and its relevant motivation.

The applicant will be required to submit formal applications for consideration by the Authority subsequent to the pre-submission meeting.