South African Health Products
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GUIDELNE FOR SECTION 21 ACCESS TO UNREGISTERED MEDICINES

This document provides guidance on access to unregistered medicine for human use through the provisions of section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), and clarifies the mandate, intent and scope of this section and regulation 29 of the General Regulations published in terms of the Act. It outlines the process to be followed when requesting a medicine through Section 21, as well as the information required to comply with the provisions of the Act and Regulations.

The South African Health Products Regulatory Authority (the Authority) reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments to this document in keeping with knowledge which is current at the time of consideration of the data accompanying applications for access to and use of unregistered medicines. Alternative approaches may be used but these must be scientifically and technically justifiable.

The Authority is committed to ensuring that all medicines granted approval will be of the required safety, quality, and efficacy.

Document History

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1	First publication released for comment and issued for implementation	May 2019
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Contents

Glossary

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:-

Abbreviation/ Term	Meaning
Adverse Drug Reaction (ADR)	A noxious and unintended response to a medicine
Authority	The South African Health Products Regulatory Authority established by Section 2 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965)
Health Care Provider	A health care provider as defined in Section 1 of the National Health Act, 2003 (Act 61 of 2003)
Institution	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 Medicines and Related Substance Act, 1965 (Act 101 of 1965); and
Medicine	Medicine as defined in terms of the Medicines and Related Substance Act, 1965 (Act 101 of 1965)
Public Health Emergency	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.
Name Patient Application	A singular formal Named Patient specific request to be considered for a position or to be allowed to import unregistered products for treatment of single patient with a single product. The application is submitted a single application through the SAHPRA portal. A single Outcome report will be required for this patient within 6 months of the approval. Failure to submit this report will result in no further request being allowed until outstanding information has been submitted.
Multiple Patient Applications	Multiple Named Patient formal requests to be considered for a position or to be allowed to import unregistered products for treatment of multiple patients with a single product. The applications are submitted as multiple applications through the SAHPRA portal. Multiple Outcome reports will be required for all of these patients within 6 months of the approval. Failure to submit these reports will result in no further request being allowed until the information has been submitted. A different fee calculation will apply to applications ONLY for specific Use Cases such as Hospital/Clinic settings that require multiple packs for out-of-stock items that are normally used for routine treatment, or where we have a situation where a product, previously registered in South Africa, and now withdrawn, or where products are registered by local applicants but not marketed in local market (i.e. not accessible) or a product that is for “State Use” only, for One-Off use and also not locally available such as certain diagnostic

	materials, radiopharmaceuticals or emergency products used in theatre. This will be costed as an application per Use Case at the gazette fee.

1. INTRODUCTION

This document is intended to clarify the mandate, intent and scope of access to unregistered medicines in terms of Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) according to the scope of the document described in 1.2 and outlines:

a) the process to be followed to enable access to a medicine that is not registered for sale in South Africa;

b) the responsibilities of sellers of unregistered medicine including health care providers, persons submitting an application on behalf of a health establishment, and the holders 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 Medicines and Related Substances Act, 1965 (Act 101 of 1965);

c) the role and responsibilities of the organisational unit responsible for managing applications submitted in terms of section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) (Section 21 Unit); and

d) the information required to comply with Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) and regulation 29 of the General Regulations made in terms of the Act. Authorisation for the sale of an unregistered medicine in terms of Section 21 of the Act must be granted prior to any such medicine being imported into or manufactured in the Republic of South Africa.

No person may sell any unregistered medicine unless they have been so authorised as an Applicant or co-Applicant in terms of section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965). Conditions associated with the authorisation for the sale of an unregistered medicine may be imposed at the time of authorisation or during the authorisation as additional conditions in line with the provisions of Section 21 of the Act and regulation 29 of the General Regulations.

1.1 Purpose

The purpose of this guideline is to ensure that requests for access to unregistered medicines are 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

The Authority is mandated to regulate the safety, efficacy and quality of all medicines. Before registration of a medicine, access is usually limited to clinical trials authorised by the Authority. SAHPRA may, in certain circumstances, and in accordance with Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965), authorise the sale of an unregistered medicine for such purposes and in such manner and during such period as the Authority may determine.

Whilst clinical trials are authorised by the Authority in accordance with Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965), authorisation of the sale of unregistered medicines used in clinical trials is not covered by this document. Guidelines that detail authorisation for the use of unregistered medicines as part of a clinical trial can be accessed at SAHPRA website: https://www.sahpra.org.za/.

Post-trial access to an investigational medicine must be done in accordance with the relevant guideline issued by the Authority **(SAHPRA Guideline SAHPGL-CEM-CT-07: Post Clinical Trial Drug Access)**. In cases where it is not possible to adhere to that guideline, justification and motivation must be submitted with an application for authorisation to sell unregistered medicines in terms of Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965), which will be reviewed on a case-by-case basis, to ensure that participant safety and wellbeing is not compromised.

The main purpose of any authorisation granted in terms of Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) is to provide access to medicines on an exceptional basis, where conventional therapies have been ruled out, have failed or are unavailable. This must always have regard to the safety, efficacy and quality of medicines accessed through Section 21 which are set out in Regulation 29. Affordability on its own is not generally a significant reason to grant a Section 21 authorisation, however, applications will be considered on a case-by-case basis.

The importation of unregistered medicines for purposes of exhibitions is not covered in this guideline and must be done in accordance with Regulation 43 of the General Regulations.

Access to veterinary (Category C) medicines is **not** addressed in this guideline.

2. LEGAL PROVISION

2.1 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;*

2.2 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.*

2.3 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).

2.4 Regulation 6(2) of the General Regulations states:

(2) A person shall only import a medicine or scheduled substance if such person-

(a) is licensed in terms of the Act to import medicines; and

(b) in the case of unregistered medicines, is authorised by the Authority to import such unregistered medicines.

Regulation 29 of the General Regulations states:

29. Authorisation of sale of an unregistered medicine for certain purposes

(1) Subject to the provision of information, requirements and conditions as determined by the Authority, a person desiring to sell an unregistered medicine subject to registration in terms of section 14 of the Act, for purposes other than a clinical trial, shall apply to the Authority, on an application form obtainable from the office of the Chief Executive Officer, for authorisation in terms of Section 21 of the Act to sell such a medicine.

(2) An application referred to in sub-regulation (1) must be accompanied by the prescribed fee and must contain at least the following information-

(a) duly completed application form,

(b) product brochure containing relevant chemical, pharmaceutical, pre-clinical pharmacological and toxicological data and where applicable, human or animal pharmacological and clinical data with the medicine concerned;

(c) witnessed informed consent document, where applicable;

(d) details of registration or pending registration of the medicine with any other regulatory authority, if available;

(e) evidence of compliance of the manufacturer of the medicine with Good Manufacturing Practice standards as determined by the Authority;

(f) reasons why a South African registered medicine cannot be used; and

(g) any other information as may be required by the Authority.

(3) The person under whose supervision the unregistered medicine or substance is prescribed shall submit to the Authority-

(a) any adverse event report;

(b) progress reports after every six months from the date following commencement of the use of the unregistered medicine; and

(c) progress report 30 days after the completion or termination of the use of the medicine.

(4) The Authority may-

(a) impose any additional conditions;

(b) request additional information;

(c) inspect the site where the unregistered medicine is manufactured, stored or administered; or

(d) withdraw the authorisation to treat the patient, if the Authority is of the opinion that the safety of any patient is compromised, that the scientific reasons for administering the unregistered medicine have changed or for any other reason as determined by the Authority.

(5) A medicine referred to in sub-regulation (1) shall be properly labelled and the package shall sufficiently identify the information.

3. POSSIBLE ACCESS SCENARIOS

3.1 Individual named patient

3.1.1 Description

This scenario considers access to unregistered medicines for the treatment, diagnosis, or prevention of conditions, diseases or disorders for an individually named patient when conventional therapies have been considered and ruled out, have failed, are unsuitable or unavailable as marketed products. The Section 21 access should be an exception and, where possible, post-trial, open-label or compassionate access provisions should be incorporated into medicine development plans to meet the needs of patients not eligible for enrolment in clinical trials.

3.1.2 Applicants

An application for authorisation for the use of an unregistered medicine shall be submitted by the health care provider responsible for the care of the patient. A progress report must be submitted on completion of treatment or before a new application is submitted for the patient to continue treatment at most 6 (six) months later.

The Applicant must also provide the details for the duly licenced entity 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 Medicines and Related Substance Act, 1965 (Act 101 of 1965), responsible for the supply of the product for which authorisation is requested.

3.2 Multiple patient applications held by a health establishment/medical practice

3.2.1 Description

In **exceptional** circumstances, certain unregistered medicines need to be available urgently and an individually named patient application is not possible. In such circumstances, bulk stock of the unregistered medicine may need to be maintained at a health establishment for use in, for example, an intensive care unit or theatre. An application may be submitted for authorisation to hold a certain amount of emergency stock in the pharmacy of the health establishment for use when an emergency arises. Either the named patients' details are to be provided (in the case of planned treatments) or then previous 6 month's usage for the product and rationale for the planned number of patient treatments. Treatment plans should not exceed 6 month's requirements. Submit as well proof that all previous outcome reports for previous applications have successfully been submitted prior to making this application.

3.2.2 Applicants

In such cases, the Applicant shall be the health care provider who is the intended prescriber of such medicine or a health care provider who is designated as a representative of the health establishment requiring the stock. A progress report must be submitted per patient on completion of treatment or before a new application is submitted for the patient to continue treatment at most 6 (six) months later.

3.2.3 Additional information required

The Applicant must provide a clinical rationale as to why the unregistered medicine is required as emergency stock as opposed to requesting it per individual patient, in advance of use. The application fee required for multiple patient applications is the application fee for a Section 21 application (as per the latest gazetted fee schedule) multiplied by the number of patient applications that the aggregated quantity will be for. One application fee as per gazette fee will be applied for specific use cases such as:

- All registered equivalents are Out of Stock (OOS)
- All registered products have been withdrawn from the market/not marketed
- All registered products only available for supply to State/Public sector use
- Emergency Hospital Item for once-off use
- Radiopharmaceuticals
- Total Parenteral Nutrition (TPN)

The Applicant should also clearly indicate in the application which duly licenced entity (approved 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) will be responsible for the storage and supply of the unregistered product for which authorisation is requested.

3.3 State Procurement

3.3.1 Description

In exceptional circumstances, certain unregistered medicines may need to be procured by the State for distribution on an urgent basis to one or more public sector health establishments. These circumstances may arise where all other mechanisms of supply have been exhausted and where, without intervention, a significant public health risk may be realised. State will apply via the Multiple Patient application process stating that it is an application for State Procurement.

3.3.2 Applicants

The State may designate a health care provider as a representative to apply for authorisation for the supply or sale of an unregistered medicine to on behalf of the State institution, and held by the health establishments for distribution to patients on an individual patient basis.

3.4 Public health emergency (PHE)

In line with **SAHPRA Guideline 2.64: Availability of medicines for use in a Public Health Emergency (PHE)**, unregistered medicines may be authorised for sale which are intended for use for an identified PHE. All requirements as stated in **Section 3** of **SAHPRA Guideline SAHPGL-PEM-01** are applicable as qualifying criteria for consideration of authorisation for sale of an unregistered medicine. Apply via the Multiple Patient application process stating that it is an application made in terms of a Public health emergency (PHE). A progress report must be submitted per patient on completion of treatment or before a new application is submitted for the patients to continue treatment at most 6 (six) months later.

Additional considerations for the availability of such medicine by way of authorisation in terms of section 21 of the Act would include when there is an unmet medical need, where existing products have not been successful in eradicating the disease or preventing outbreaks and, in the face of the PHE there:

a) are no medicines available for the intended use or indication;

b) are no medicines available for a critical subpopulation (e.g., children); or

c) there is insufficient supply of registered medicines for the intended use or indication.

Despite any authorisation provided by the Authority, the sale of any medicine may only be permitted after

compliance with any other legislative or policy requirements that may be required outside of the mandate of the Authority.

Medicines that meet the criteria as stated above may be considered for authorisation based on their status of authorisation by other medicine regulatory authorities (MRAs) with which the Authority aligns:

3.5 Medicines that have been authorised or registered for use by MRAs recognised by the Authority

The Authority may consider the authorisation of an unregistered medicine for sale in terms of Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) 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 this instance, an application may be submitted before an application for registration in terms of Section 15 (see **Scenario 3.1** of **SAHPRA Guideline SAHPGL-PEM-01: Availability of medicines for use in a Public Health Emergency (PHE)**).

If authorised, a condition for sale shall include a time limitation for authorisation of a specified amount of medicine. The renewal of such authorisation shall only be considered if an application for registration in terms of Section 15 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) is made within a stipulated period of time from the date of submission of the application for Section 21 authorisation.

3.6 Medicines that have not been authorised or registered for use by Medicine Regulatory Authorities (MRAs) recognised by SAHPRA

An application for authorisation in terms of section 21 may only be submitted after an application for registration in terms of section 15 has been made in the case of novel medicines which have not been authorised for use by an MRA recognised by SAHPRA (see **SAHPRA Guideline 2.01: General Information**).

3.6.1 During the review of the section 15 application for registration a favourable risk-benefit analysis may indicate that the medicine should be made available, although there is insufficient data to support registration of the medicine. To allow for mitigation of the PHE, an application for authorisation in terms of section 21 may be submitted.

3.6.2 If authorised, a condition for sale shall include a time limitation and authorisation for the sale of a specified amount of medicine. The renewal of such authorisation shall only be considered provided that progress on the section 15 submission for application for registration is made within

a stipulated amount of time from the date of submission of the application for section 21 authorisation.

3.6.3 Applicants

Applicants must be a holder of a licence issued in terms of section 22C(1)(b) of the Medicines and Related Substance Act, 1965 (Act 101 of 1965).

The application fee required for multiple patient applications is the application fee for a Section 21 application (as per the latest gazetted fee schedule) multiple by the number of patients that the multiple patient stock will treat. The application fee required for multiple patient applications is the application fee for a Section 21 application (as per the latest gazetted fee schedule) multiple by the number of patients that the multiple patient stock will treat.

All sellers of the medicine up until the supply of such medicine to the end-user (including all designated holders of licences issued in terms of Section 22C(1)(b) of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) must be listed as co-Applicants and must be authorised to sell the medicine pertaining to the application.

The co-Applicants should also include the prescribers, where these are known.

4. ROLES AND RESPONSIBILITIES

The scenarios outlined in Section 2 require that various persons and/ or institutions need authorisation in terms of Section 21 to sell unregistered medicines, with all role-players assuming responsibility as Applicant or co-Applicant/s.

4.1 Applicants and their designated SAHPRA Manufacturing/ Import/ Export Licence Holder

In all instances, the Applicant should be the individual who accepts responsibility for the submission of the application, while co-Applicants will be all persons (including holders of licences issued in terms of section 22C(1)(b) or institutions) involved in the sale of the unregistered medicine.

Applicants are required to assume responsibility for the application process and submission thereof.

Their designated service provider – responsible for the import, storage and distribution of the health product must provide accurate information for submission with an application.

Both Applicants and co-Applicants must: -

a) ensure that the medicine for which authorisation is granted is sold, prescribed and dispensed in compliance with the provisions of the Act;

b) ensure that the medicine for which authorisation is granted, is used for the purpose, in the manner and for the duration for which authorisation is granted; and

c) comply with any other conditions imposed by the Authority.

Following the granting of authorisation by the Section 21 Unit, the Applicant and co-Applicant(s) is/are responsible for deciding whether or not to sell the medicine. An Applicant or co-Applicant is under no obligation to sell an unregistered medicine and cannot be compelled to do so, however, the Authority must be notified by the holder of authorisation when the authorised medicine will not be sold

Applicants and co-Applicants are expected to ensure that significant new information about the safety, quality and efficacy of a medicine for which authorisation has been granted in terms of Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) is made available to relevant role-players and in accordance with the relevant guideline issued by the Authority.

4.2 Health care providers

The health care provider who submits an application for authorisation to use an unregistered medicine must ensure that the decision to use the medicine is supported by credible evidence. Such evidence is usually found in an investigator's brochure, prescribing information from another jurisdiction, or publications in peer-reviewed, medical literature.

A health care provider designated as a representative of an institution will represent the institution as the Applicant. This individual will be responsible for the actions and responsibilities of the institution associated with the application.

Health care providers who prescribe an unregistered medicine must provide the patient with information about the potential risks, benefits, consequences and costs of the unregistered medicine as well as the range of any alternative therapies available. Health care providers must also comply with the provisions of section 6(1) of the National Health Act, 2003 (Act 61 of 2003) – as quoted below:

6. User to have full knowledge

(1) Every health care provider must inform a user of-

(a) the user's health status except in circumstances where there is substantial evidence

that the disclosure of the user's health status would be contrary to the best interests of the user;

(b) the range of diagnostic procedures and treatment options generally available to the user;

(c) the benefits, risks, costs and consequences generally associated with each option; and

(d) the user's right to refuse health services and explain the implications, risks, obligations of such refusal.

(2) The health care provider concerned must, where possible, inform the user as contemplated in subsection (1) in a language that the user understands and in a manner which takes into account the user's level of literacy.

Furthermore, according to Regulation 29(3) of the General Regulations (as quoted below) progress reports must be submitted on a six-monthly basis from the date of commencement of use of the unregistered medicine. A final report must be submitted 30 days after the use of the unregistered medicine has been stopped.

These reports should be sent by email to: **section21@sahpra.org.za** .

29. Authorisation of sale of an unregistered medicine for certain purposes

(3) The person under whose supervision the unregistered medicine or substance is prescribed shall submit to the Authority-

(a) any adverse event report;

(b) progress reports after every six months from the date following commencement of the use of the unregistered medicine; and

(c) progress report 30 days after the completion or termination of the use of the medicine.

(d) It is important that a progress report is submitted before new application(s) can be submitted on the treating Practitioner's profile.

The provisions of regulation 40(3) of the General Regulations (as quoted below), which place an obligation on health care providers or any other person to report suspected adverse drug reactions or new or existing safety, quality or effectiveness concerns, shall apply equally to unregistered medicines for which

authorisation has been granted in terms of Section 21.

40. Vigilance

…

(3) A health care provider, or any other person should inform the Authority, in the manner as determined by the Authority, of any-

(a) suspected adverse drug reactions; or

(b) new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.

4.3 Holders of a licence issued in terms of Section 22C(1)(b) of the Act – (being the designated service providers to the Applicant Health Care practitioner)

After authorisation has been granted to 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 Medicines and Related Substance Act, 1965 (Act 101 of 1965), the Authority may impose conditions on the sale/distribution of a medicine to ensure that it is used in accordance with the latest information available and in accordance with the conditions determined by the Authority.

These conditions may include but are not limited to the quantity of the medicine sold.

The holder of a licence in terms of Section 22C(1)(b) who imports an unregistered medicine must comply with the provisions of Section 22A(11)(a) of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) (as quoted below), namely:

11.

(a) No person shall import or export any specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substance or medicine prescribed for that purpose unless a permit has been issued to him or her by the Director-General of Health in the prescribed manner and subject to such conditions as may be determined by the Director-General.

Importers should clearly display the Letter of Authorisation issued in term of Section 21 of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) with other related documents, such as import permits,

to facilitate clearance by South African customs authorities.

Unregistered medicines which may be sold following the granting of an authorisation in terms of Section 21 may not be exported.

The importing company must provide evidence (an agreement) that the sponsor or patent holder is in agreement with the use of the unregistered medicine that is being applied for.

Any pharmaceutical company may inform the Authority that a patented unregistered medicine may not be brought in by another importing company without their consent. This must be accompanied by evidence that the aforementioned notification has also been sent to the importing company.

Furthermore, a holder of a licence in terms of Section 22C(1)(b) must also (in addition to the Healthcare Practitioners) inform the Authority of any new or existing quality, safety or effectiveness concerns according to the relevant Authority guideline and must maintain or have access to records and case reports of such cases. With regard to any safety concerns, the provisions of Regulation 40(1) and (2) of the General Regulations (as quoted below) apply to unregistered medicines authorised by way of Section 21.

40. Vigilance

(1) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C(1)(b) must inform the Authority, in the manner and within the time frame as determined by the Authority, of any-

(a) new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to adverse drug reactions; and

(b) risk management activities associated with paragraph (a).

(2) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C(1)(b) must maintain or have access to records of the reports and case reports referred to in sub-regulation (1) above.

4.4 Section 21 Unit

The Section 21 Unit undertakes the following activities:

a) while evaluating applications, check that Applicants have provided the information required in terms of regulation 29(2);

b) emphasising to health care providers that registered medicines should always be considered and/ or used before considering the use of an unregistered medicine;

c) monitoring the compliance of Applicants and co-Applicants with the provisions of regulation 29(3) regarding the submission of progress reports and the reporting of adverse events;

d) monitoring the compliance of Applicants and co-Applicants with any conditions imposed in terms of regulation 29(4);

e) monitoring safety issues and concerns pertaining to medicines accessed in terms of section 21;

f) monitoring the frequency and extent of requests for a specific unregistered medicine, to enable the Authority to determine whether a recommendation should be made that application for registration of the medicine be considered; and

g) monitoring trends in the use of unregistered medicines accessed in terms of Section 21.

5. APPLICATION PROCESS

5.1 Initiation of application

To initiate a Section 21 application an Applicant and co-Applicant/s shall complete the Section 21 Application. The latest fee schedule and relevant instructions may be accessed and downloaded from the SAHPRA website: www.sahpra.org.za. A completed application (submitted via the online submission portal) must be accompanied by the prescribed fee and must contain at least the information as prescribed by regulation 29(2).

The Authority has implemented a submission portal in order to process Section 21 applications.

These must be submitted via the **E-services** tab on the SAHPRA website homepage, www.sahpra.org.za and navigating to **Section 21 Applications**.

Supporting documents (e.g. proof of payment and informed consent) for online applications must be attached on the application.

Following consideration of the application, the Section 21 Unit may either authorise the sale of the

unregistered medicine, request additional information from the Applicant, or deny the application.

5.2 Hours of Operation

The Section 21 service is offered 24 hours a day, throughout the year. Regular business hours are weekdays from 08:00 to 16:00 South Africa Time (GMT +02:00). Outside of regular business hours and during public holidays, the cell phone numbers for Section 21 on the SAHPRA website: www.sahpra.org.za may be used.

5.3 After Hours Applications

Telephonic applications should be limited to life-threatening situations requiring immediate attention.

An application outside of regular office hours should be made to the designated official, who can be reached on the emergency number provided on the website.

In the case of telephonic applications, the Applicant should be prepared to provide all of the required information using the application form as a guide.

This must be followed by the process detailed in section *4.1 Initiation of application*.

6. EVALUATION PROCESS

6.1 Screening

Applications related to Scenario 2.1 are typically processed within 24 working hours of receipt. This timeframe is extended for other Scenarios (2.2 to 2.5) based on their complexity and amount of information to be reviewed. Requests are triaged to ensure that urgent matters take precedence over less urgent matters.

During initial screening, the application is checked to ensure that:

a) all sections of the form are complete;

b) all contact details of the Applicant and co-Applicant/ s are provided;

c) the information provided is legible;

d) a quantity of six months' supply or less is requested; and

e) the health care provider has provided his/ her registration number.

The Applicant will be requested in writing to respond to critical screening outcomes. Once a request has passed screening, it is forwarded to a designated official for review.

6.2 Evaluation

Evaluation is the process by which the Section 21 Unit decides whether authorisation is appropriate and justified. Each request represents a unique set of circumstances and is supported to varying degrees by information provided by the Applicant and co-Applicant/s.

A decision to authorise or deny a request is made on a case-by-case basis taking into consideration the nature of the unmet medical need, the availability of marketed alternatives and the information provided in support of the request regarding the use, safety and efficacy of the medicine.

Medicines accessed through Section 21 do not undergo the scrutiny of a benefit-risk assessment applied to medicine registration submissions or clinical trial applications. Accordingly, authorisation through Section 21 does not constitute an opinion that a medicine is safe, efficacious or of acceptable quality. Furthermore, approval of a Section 21 application does not constitute authorisation to sell a medicine outside the conditions stipulated by the Section 21 authorisation, nor does it compel a Licence Holder to sell the medicine so authorised.

Evaluation takes into account the information supplied in terms of Regulation 29(2) and balances the following factors to ensure that an unmet medical need exists and there is credible data to support the request:

a) Seriousness of disease based on a description of the unmet medical need for which the medicine is requested;

b) Clinical status of the patient/s, including prognosis for patient-specific applications;

c) Other therapies that have been tried and failed, or have been considered and ruled out, or are unavailable

d) Other current/ concomitant medication whether for diagnosis, treatment or concomitant disease;

e) Prior patient experience with the medicine, including evidence of efficacy and adverse drug

reactions;

f) Data provided with the application including quality and relevance of data regarding the unmet medical need. A hierarchy of available evidence may range from prescribing information/ professional information from the jurisdiction where the medicine may be marketed, preferably a regulatory authority with which SAHPRA aligns itself; published data to support the application; or unpublished reports;

g) Data available from medical literature, treatment guidelines, investigator's brochures, information obtained from the manufacturer, clinical trial reports, consultations with experts;

h) Regulatory status of the medicine;

i) Availability of clinical trials as an option for an individual patient; and

j) Where applicable, the availability of medicines for use in a Public Health Emergency (PHE).

6.3 Special Considerations

6.3.1 Medicine shortages and discontinued medicines

In circumstances where a medicine is in short supply or is discontinued from the market, the Section 21 Unit will consider authorising access to an alternative source in circumstances where:

a) the medicine is considered to be medically necessary for the treatment, diagnosis or prevention in an area of unmet medical need;

b) the manufacturer has disclosed the reasons for the shortage or discontinuation of the medicine;

c) there are no other dosage forms of the medicine on the market that would be considered a reasonable alternative;

d) there are no other medicines or therapies that would be considered to be reasonable alternatives; and

e) in the case of a medicine shortage, the manufacturer demonstrates that efforts have been made to avoid and manage the shortage.

6.3.2 Complementary Medicines

Medicines conforming to the definition of a Complementary Medicine (Category D) (CM) may be considered for authorisation for sale by way of section 21 based on, *inter alia,* the following criteria:

a) the medicine applied for is a bona fide CM in South Africa and complies with the definition of a CM in terms of the General Regulations;

b) consideration of the composition of the CM in its entirety would yield no overt safety concerns relevant to the intended benefit to the patient;

c) an indication whether the medicine is registered or licensed for sale in the country of origin or elsewhere. In such instances, proof of same should be provided in the form of registration certificates, licensing, market authorisation or appropriate legislative reference;

d) proof of manufacture preferably by a duly licensed manufacturer, and the provision of all contact details pertaining to the manufacturer;

e) an indication that the stated intended use of the CM matches the registered / licensed use of the product. A further motivation of the reasoning for its intended use based on bona fide medical / discipline principles may be provided;

f) demonstration that there is no South African registered medicine or equivalent available; and

g) relative to the nature of the medicine and condition it is intended for, the prescription of the CM should be overseen by the relevant duly legally authorised prescriber.

6.4 Communication of the Outcome of the Application

Following consideration of the section 21 application, the Section 21 Unit will either authorise or deny the application, with reasons provided if denied. Authorised applications are sent by e-mail to the Applicant and copied to the co-Applicants as required.

The Authority will inform Applicants by e-mail of any Section 21 application which is not granted with reason/s for the decision. The Applicant may also reply to the Section 21 Unit by e-mail to discuss the reasons and, if applicable, the process for submitting a new application with additional information.

6.4.1 Record Keeping

All records relating to unregistered medicines sold must be maintained in accordance with applicable legislation (recommended to be no less than five years), in a manner that permits rapid retrieval if necessary. The Section 21 Unit may at any time request that Applicants and co-Applicants account for all quantities of medicine received or supplied i.e. reconciliation of the quantities for which authority is granted, procured and used.

The holder of a licence issued in terms of Section 22C(1)(b) of the Act is required to maintain complete and accurate records of all Section 21 transactions in a manner that permits rapid response to specific requests to verify the distribution of medicine supplies to health establishments or health care providers.

6.4.2 Reporting

Applicants and co-Applicants must provide reports to the Section 21 Unit on the use of the unregistered product and any adverse drug reactions (ADRs) encountered, using the tools and/ or forms provided by the Authority.

The SAHPRA ADR reporting guideline must be followed regarding what should be reported, and the associated timeframes. Specifically, the health care provider shall inform the Section 21 unit of any serious unexpected adverse medicine reaction within:

a) 15 days after becoming aware of the information if the reaction is neither fatal nor life-threatening; or

b) seven (7) days after becoming aware of the information if the reaction is fatal or life-threatening.

6.4.3 Unused Medicines

As a general rule, unused supplies of a medicine should be returned to the holder of a licence issued in terms of Section 22C(1)(b) of the Medicines and Related Substance Act, 1965 (Act 101 of 1965). Health care providers may, however, request that unused supplies of a medicine be transferred to a new patient by submitting a new Section 21 application.

Unused medicines for which authorisation has been granted in terms of Section 21 of the Act must be disposed of in terms of Regulation 44 of the General Regulations.

6.4.4 Advertising

A general condition of authorisation under section 21 of the Act, read together with regulation 29(4)(a) is that advertising and marketing of unregistered medicines accessed through Section 21 authorisation is strictly prohibited.

7. REFERENCES

The following related documents are referenced:

7.1 Medicines and Related Substances Act, Act 101 of 1965, as amended.

7.2 General Medicines Regulations August 2017

7.3 SAHPGL-CEM-CT-07_v4-Guideline-for-Post-Clinical-Trial-Access

7.4 SAHPGL-PEM-01-_Availability_of_medicines_for_use_in_a_PHE_June-2022_v2-004

8. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the old Guideline for Section 21 Access to Unregistered Medicines, Doc no.: 2.52. It will be reviewed on this timeframe or as and when required.