South African Health Products
Regulatory Authority
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ACCESS TO UNREGISTERED VETERINARY MEDICINES

This document provides guidance on access to unregistered medicines for animal 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 SAHPRA 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 veterinary 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 quality, safety, and efficacy.

Document History

Final Version	Reason for Amendment	Effective Date
1	3.11 Guideline on completing section 21 application form: for implementation	January 2004
2	– 3.11 Guideline for implementation, and – Logo updated to reflect SAHPRA	November 2019
3	– Replaces SE, – Administrative changes to align with the SAHPRA processes, and – Content was structured on the new SAHPRA Guideline Template.	January 2022
4	– Administrative changes include: ○ Content updated on the latest SAHPRA Guideline template, ○ Form No.: OF-PEM-VET-01E changed to GLF-PEM-VET-01A, ○ Form No.: OF-PEM-VET-01D changed to GLF-PEM-VET-01B, and ○ Form No.: OF-PEM-VET-01G changed to GLF-PEM-VET-01C.	March 2024

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Glossary

Abbreviation/ Term	Meaning
Adverse drug reaction	means a noxious and unintended response to a medicine
Institution	means any organisation that wishes to sell an unregistered medicine and includes the holder/s of a license 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 a medicine as defined in terms of the Act
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
Veterinarian	means a professional as defined in section 1 of the Veterinary and Para-Veterinary Professions Act no. 19 of 1982
Withdrawal period	means the interval between the time of last administration of the veterinary medicine and the time when the animal can safely be slaughtered for food purposes, or its products can be utilized

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1. INTRODUCTION

This document is intended to clarify the mandate, intent and scope of access to unregistered medicines for animal 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.

1.1 Purpose

The purpose of this guideline is to ensure that requests for access to unregistered veterinary medicines are received, processed 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.

1.2 Scope

The South African Health Products Regulatory Authority (SAHPRA)'s mandate is to regulate and control the quality, safety, and efficacy of all medicines or human and animal use. Prior to registration of a medicine, access is limited to clinical trials authorised by the Authority and SAHPRA may in accordance with Section 21 of the Act, authorise the sale of an unregistered medicine for use in individual patients during such period as the Authority may determine. Authorisation of the importation and use of unregistered medicines used in clinical trials is also covered by this document. However, another guideline that accompanies the use of the unregistered medicine in clinical trials is provided as a separate document (Add G/L number).

The importation of unregistered medicines for purposes of exhibitions is also not covered in this guideline (Refer to regulation 43 of the General Regulations).

1.3 Objectives

This document is intended to clarify the mandate, and scope of access to unregistered veterinary medicines in terms of Section 21 of the Medicines Act and outlines:

a) the process to be followed to enable access to an unregistered medicine in South Africa.

b) the responsibilities of sellers of the unregistered medicine such as the veterinarians, persons submitting the application on behalf of an establishment, and the holders of a license to manufacture, import or wholesale or distribute a medicine, issued in terms of section 22C(1)(b) of the Act.

c) the role and responsibilities of the veterinary medicines unit responsible for evaluation and

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processing section 21 applications and the information required to comply with requirements of the Act and regulation 29 of the General Regulations.

2. LEGAL PROVISION

Section 1(3) of the Act states:

In determining whether 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 or any animal, as the case may be.

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 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).

Regulation 29 of the General Regulations made in terms of the Act (Government Notice 859, 25 August 2017) 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,

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(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) declaration of informed consent, where applicable;

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

(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 or animal, if the Authority is of the opinion that the safety of any patient or animal is compromised, that the scientific reasons for administering the unregistered medicine have changed or for any other

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reason as determined by the Authority.

A medicine referred to in sub-regulation (1) shall be properly labelled and the package shall sufficiently identify the information as per the provisions of regulation 12(5)(c).

3. POSSIBLE ACCESS SCENARIOS

3.1 Individual Named Patient

This scenario considers access to unregistered medicines for the treatment, diagnosis, or prevention of conditions, diseases or disorders for an individual named patient, flock or herd when conventional therapies have been considered and ruled out, have failed or unavailable as registered marketed products or through enrolment of the patient in a clinical trial. It is recommended that Section 21 access should be an exception and where possible, post-trial, open label or compassionate access trials should be incorporated into medicine development plans to meet the needs of patients not eligible for enrolment in other pivotal trials. An application for authorisation for use of an unregistered medicine shall be submitted by the veterinarian responsible for the care of the patient or the holder of a license to manufacture, import or to act as a wholesaler of or distribute a medicine, issued in terms of section 22C(1)(b) of the Act.

3.2 Bulk stock held by an establishment

In exceptional circumstances, certain unregistered veterinary medicines need to be available urgently and an individual named patient application is not possible. In such circumstances, bulk stock of the unregistered medicine may need to be maintained at an establishment for use in, for example, a theatre or prevention of outbreaks or spillover of disease. An application may be submitted for authorisation to hold a certain amount of emergency stock in a pharmacy or approved facility of the establishment for use when an emergency arises.

In such cases, the applicant shall be the intended prescriber of such a medicine who is designated as a representative of the establishment requiring the stock. The applicant must provide a clinical rationale as to why the unregistered medicine is required as emergency stock.

3.3 Bulk stock held by the holder of a license issued in terms of section 22C(1)(*b*)

In exceptional circumstances, certain unregistered medicines may need to be maintained at a single point of storage for distribution on an urgent basis to one or more veterinarians or health establishments. In such cases, the applicant shall be a designated representative by the holder of a license to manufacture, import or to act as a wholesaler of or distribute a medicine, issued in terms of section 22C(1)(b) of the Act. The applicant may apply for a certain quantity of emergency stock to be held on the premises of the license

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holder, for distribution when required in accordance with the conditions of the authorisation granted using the "Bulk application form" form number (GLF-PEM-VET-01C).

The applicant should include a rationale or description of the clinical scenario with an explanation as to why this mechanism of supply is required. A dispensing record shall be submitted to the Authority by the license holder when the stock is depleted. No such medicines shall be exported or further compounded for animal use.

In such circumstances, co-applicants shall include the veterinarians who shall apply to the Authority for use of such medicine on a named patient basis.

3.4 State Procurement

The State may designate a representative to apply for authorisation for the supply or sale of an unregistered medicine. In such circumstances the co-applicants shall include veterinarians (if applicable), where these are known, and the license holder involved in the supply of the unregistered medicine.

4. ROLES AND RESPONSIBILITIES

4.1 Applicants

The scenarios outlined above require that various persons and/ or institutions need authorization in terms of Section 21 with all role-players assuming responsibility as applicant or co- applicant/s. In all instances, these individuals must accept responsibility for the submission of the application and or use of the unregistered medicine.

a. Applicants and co-applicants must 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;

c. comply with any other conditions imposed by the Authority; and

d. Applicants and co-applicants are expected to ensure that relevant scientific new information on the quality, safety, and efficacy of a medicine for which authorisation has been granted is submitted to the Veterinary Medicines Unit at SAHPRA.

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4.2 Veterinarians

The veterinarian who applies for authorisation to use an unregistered medicine must submit credible scientific evidence. Such evidence is usually found in the package insert from another regulatory authority that SAHPRA aligns with, or publications in peer-reviewed literature.

Veterinarians who prescribe an unregistered medicine must provide the owner with information on the potential risks, benefits, consequences, as well as the range of alternative therapies available.

As per regulation 29(3) of the General Regulations progress reports must be submitted on a six-monthly basis.

29. Authorisation for 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.

The provisions of regulation 40(3) of the General Regulations (as quoted below), which place an obligation on veterinarian 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. Adverse drug reactions

3) A health care provider, veterinarian 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.

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4.3 Holders of a license issued in terms of section 22C(1)(b) of the Act

After authorization has been granted to the holder of a license 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, the Authority may impose conditions on the sale of a medicine to ensure that it is used in accordance with the latest information available and 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 license in terms of section 22C(1)(b) who imports an unregistered medicine must comply with the provisions of section 22A(11)(a) of the Act (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 a valid Section 21 "Letter of Authorisation" 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.

In certain circumstances as determined by the Authority, a permit may be required from Animal Health (Act 35/1984).

Furthermore, a holder of a license in terms of section 22C(1)(b) must inform the Authority of any new or existing quality, safety, or effectiveness concerns as per the relevant Authority and must maintain records and case reports of such cases. Regarding any safety concerns, the provisions of regulation 40(1) and (2) of the General Regulations (as quoted below) apply to unregistered medicines authorised through Section 21.

4.4 Veterinary Medicines Unit

The Unit undertakes the following activities:

a. while evaluating and authorising applications checks that applicants have provided the information required in terms of regulation 29 (2);

b. emphasising to veterinarians that registered medicines should always be considered first and/or used before considering the use of an unregistered medicine;

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c. monitoring the compliance of applicants and co-applicants with the provisions of regulation 29(3) regarding the submission of progress reports;

d. monitoring the compliance of applicants and co-applicants with the provisions of regulation 29(3) regarding the reporting of adverse events;

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

f. Ensuring that banned and or undesirable substances are not accessed in terms of section 21;

g. monitoring the trend in terms of frequency of requests, extent, geographical location and potential risks and environmental impact of requests for a specific unregistered medicine and;

h. monitoring trends in the use of unregistered medicines accessed in terms of Section 21 in terms of food safety/toxicology and notifying and advising the Authority thereof.

i. seeking advice from relevant advisory experts and Departments when referrals are essential.

5. APPLICATION PROCESS

5.1 Initiation of requests

To initiate a Section 21 request, an applicant and co-applicant/s shall complete the Veterinary Medicines Section 21 Application Form (GLF-PEM-VET-01A). A completed application form must be accompanied by the prescribed fee as per latest Fees Gazette and must contain at least the following information as prescribed by regulation 29 (2).

Completed forms and proof of payment including the progress report (GLF-PEM-VET-01B) where relevant should be sent by email to: pervetS21@sahpra.org.za

Following consideration of the request, the Veterinary Medicines Unit may either authorise the sale of the unregistered medicine, request additional information from the applicant, or refer the application for further expert consideration or deny the request.

5.2 Hours of operation

The Veterinary Medicines Unit operates 8 hours a day (8.00 am to 4.00 pm) during the week only and not on weekends and public holidays.

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5.3 Special considerations

5.3.1 Medicine shortage

In circumstances where a medicine is in short supply or is discontinued from the market, the Veterinary Medicines Unit will consider if:

- the medicine is considered to be medically necessary for the treatment, diagnosis or prevention in an area of unmet medical need;
- the manufacturer has disclosed the reasons for the shortage of the medicine on their company letterhead. The applicant must submit this letter from the manufacturer.
- In the case of a medicine shortage, the manufacturer should indicate when stock will be available there are no other dosage forms of the medicine on the market that would be considered a feasible alternative;

5.4 Communication of the outcome of the application

Following consideration of the Section 21 application, the Veterinary Medicines Unit will either authorize or refer or deny the application, with reasons provided. Authorized applications are sent by email to the applicant and copied to the co-applicants where applicable within 24 working hours if all the required documentation has been included in the application.

For section 21 applications that are denied with an explanation of the reason/s for the decision the applicant may respond in writing with any additional scientific information for clarity.

5.5 Record keeping

The holder of a license issued in terms of section 22C(1)(b) of the Act is required to maintain complete and accurate records of all Section 21 transactions.

All records relating to unregistered medicines sold must be maintained for no less than five years, in a manner that permits rapid retrieval if necessary. The Authority 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 was granted, procured and used.

5.6 Progress and termination of use reporting

All section 21 permits allow the applicant a once-off six (6) months' supply of the imported product. Applicants are required to furnish this office with a written report on the use of the product and ADRs

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encountered 6 monthly and /or at the end of treatment. Failure to submit a progress report may negatively influence future applications for authorisation.

Unused permits expire after 6 months. A new application will therefore be required once the permit has expired.

A completed progress report (Form number) must accompany all repeat requests.

5.7 Unused medicines

As a rule, unused medicines should be returned to the holder of a license issued in terms of section 22C(1)(b) of the Act and must be disposed of in terms of regulation 44 of the General Regulations.

5.8 Advertising

Advertising and marketing of unregistered medicines accessed through Section 21 is strictly prohibited, in terms of Section 21 of the Act, read together with regulation 29(4)(a).

6. REFERENCES

The following related documents are referenced:

6.1 Medicines and Related Substances Act, 1965 (Act 101 of 1965),

6.1 General Regulations published in terms of the Medicines Act.

7. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the old revision (v3) of this guideline. It will be reviewed on this timeframe or as and when required.

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