SAHPRA
SOUTH AFRICAN
HEALTH PRODUCTS
REGULATORY AUTHORITY

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 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.

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1. INTRODUCTION

1.1 Purpose

The purpose of this guideline is to ensure that requests for access to unregistered veterinary medicines are received, processed effectively, 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 SAHPRA is mandated to regulate the quality, safety and efficacy of all registered medicines. Prior to registration of a medicine, access is limited to clinical trials authorised by the Authority and may in certain circumstances, and in accordance with 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. Authorisation of the importation and use of unregistered medicines used in clinical trials is also covered by this document. However another set of guidelines that accompanies use of unregistered medicines together with the protocol is provided as a separate document.

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

1.3 Objectives

This document is intended to clarify the mandate, intent and scope of access to unregistered veterinary medicines in terms of Section 21 of the Act) as per 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 veterinarians, persons submitting an application on behalf of an 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 Act;
c) the role and responsibilities of the veterinary medicines unit responsible for managing applications submitted in terms of Section 21 of the Act (Section 21 Unit); and
d) the information required to comply with Section 21 of the Act and regulation 29 of the General Regulations made in terms of the Act.

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 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 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).*

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,*
> - *(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 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 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 as per the provisions of regulation 12(5)(c).

1.5 Definitions

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

"adverse drug reaction" means a noxious and unintended response to a medicine;

"veterinarian" means a professional as defined in section 1 of the Veterinary and Para-Veterinary Professions Act no. 19 of 1982

"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; and

"medicine" means a medicine as defined in terms of the Act.

"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 utilised.

2. POSSIBLE ACCESS SCENARIOS

2.1 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, are unsuitable or unavailable as 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 the use of an unregistered medicine shall be submitted by the veterinarian responsible for the care of the patient. In this instance, the co-applicant/s for authorisation to sell an unregistered medicine shall be the applicable 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, responsible for supply of the product for which authorisation is requested.

2.2 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 spill over 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 as opposed to requesting it per patient.

In such cases, the co-applicant/s for authorisation to sell an unregistered medicine shall be the applicable 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 responsible for supply of the unregistered product for which authorisation is requested.

2.3 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 or Scheduled substance, 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 holder, for distribution when required in accordance with the conditions of the authorisation granted. The applicant should include a rationale or description of the clinical scenario with an explanation as to why this mechanism of supply is required as opposed to the submission of applications per individual patient. A dispensing record shall be submitted to the Authority by the license holder every six months and 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 or prescribers who shall submit an application to the Authority for use of such medicine on a named patient basis.

2.4 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(s) involved in the supply of the unregistered medicine.

3. ROLES AND RESPONSIBILITIES

3.1 Applicants

The scenarios outlined above 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. In all instances, the applicant and co-applicant should be the individuals who accept responsibility for the submission of the application and or use of the unregistered medicine.

Applicants are required to assume responsibility for the application process and submission thereof and must provide accurate information for submission with every 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;

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

Applicants and co-applicants are expected to ensure that significant new information about the quality, safety, and efficacy of a medicine for which authorisation has been granted in terms of Section 21 is made available to the Veterinary Medicines Unit once received.

3.2 Veterinarians

The veterinarian who submits an application for authorisation to use an unregistered medicine must ensure that the decision to use the medicine is supported by credible scientific evidence. Such evidence is usually found in the package insert, prescribing information from another regulatory authority, or publications in peer-reviewed literature.

A representative of an establishment will represent the institution as the applicant. This individual will be responsible for the actions and responsibilities of the institution associated with the application.

Veterinarians 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.

Furthermore, as per 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.

> ***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.*

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.*

3.3 Holders of a licence issued in terms of section 22C(1)(*b*) of the Act

After authorisation has been granted to 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, 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 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 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 the 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 licence 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 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.

3.4 Veterinary Medicines Unit

The Unit undertakes the following activities:

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

b) emphasising to veterinarians 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;

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 pertaining to medicines accessed in terms of section 21;

f) monitoring the trend in terms of frequency, extent, geographical location and potential risks and environmental impact of requests for a specific unregistered medicine, to enable the Authority to determine whether a recommendation should be made that an application for registration of the medicine be considered; and also

g) 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.

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

4. APPLICATION PROCESS

4.1 Initiation of requests

To initiate a Section 21 Request an applicant and co-applicant/s shall complete the Section 21 Application Form. A completed application form must be accompanied by the prescribed fee as per latest 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 where relevant should be sent by email to:
nonhlanhla.skosana@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 deny the request or refer the application for further expert consideration.

4.2 Hours of Operation

The Veterinary Medicines Unit operates 8 hours a day during the week only and not on weekends and public holidays.

5.3 Special Considerations

5.3.1 Medicine shortages and discontinued medicines

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 or discontinuation of the medicine on company letterhead;
- there are no other dosage forms of the medicine on the market that would be considered a reasonable alternative;
- there are no other medicines or therapies that would be considered to be reasonable alternatives; and
- in the case of a medicine shortage, the manufacturer demonstrates that efforts have been made to avoid and manage the shortage.

5.4 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. Authorised applications are sent by facsimile or email to the applicant and copied to the co-applicants where applicable.

Section 21 applications that are denied are returned by email to the applicant with an explanation of the reason/s for the decision. The applicant may respond in writing with any additional scientific information for clarity

6. 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 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 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 the unregistered medicine..

7. REPORTING

Applicants and co-applicants must provide progress reports to the Veterinary Medicines Unit on the use of the unregistered product and any ADRs encountered, using the forms provided by the Authority.

8. 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 Act. 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.

9. ADVERTISING

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