South African Health Products
Regulatory Authority
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VETERINARY MEDICINES EXEMPTIONS FROM CERTAIN MEDICINE REGISTRATION REQUIREMENTS

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of veterinary medicines. It represents the South African Health Products Regulatory Authority's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used, but these should be scientifically and technically justified. The SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to all administrative requirements to avoid delays in the processing and evaluation of applications.
guidelines and application forms are available from the SAHPRA website.

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ABBREVIATIONS AND ACRONYMS

Act	Medicines and Related Substances Act, 1965 (Act 101 of 1965, as amended)
API	Active Pharmaceutical Ingredient
IVD	In Vitro Diagnostics
P&A	Pharmaceutical and Analytical
PSUR	Periodic safety update report
SAHPRA	South African Health Products Regulatory Authority

INTRODUCTION

The Medicines and Related Substances Act (Act 101 of 1965) (hereinafter 'the Act') makes provision for the registration of medicines based on quality, safety and efficacy. In addition, the registration process for veterinary medicines includes evaluation of toxicity, target animal safety, withdrawal period data, operator safety and possible environmental impact.

Whilst the Act stipulates that only the quality, safety and therapeutic efficacy of a medicine may be considered to determine whether or not the registration or availability of a medicine is in the public interest, the Act also makes provision for consideration of registration of medicines by exemption from certain registration requirements or exemption from registration in special circumstances.

The relevant legislation includes the following provisions:

The Act:

Section 1(3)

1.3 (a) *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 man or any animal, as the case may be.*

Section 14(3)

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

(3) In the case of a medicine, medical device or IVD which was available for sale in the Republic immediately prior to the date of publication in the Gazette of the declaration by virtue of which it is subject to registration in terms of this Act, the provisions of subsection (1) shall come into operation—

(a) if no application for the registration of such medicine, medical device or IVD is made within the period of six months immediately succeeding that date, on the expiration of that period; or

(b) if an application for the registration of such medicine, medical device or IVD is made within the said period, on the date one month after the date on which a notice in respect of such medicine, medical device or IVD is published in the Gazette in terms of section 15(9) or section 17).

Section 36 Exclusion of any medicine, scheduled substance, medical device or IVD from operation of the Act

(1) The Minister may, on the recommendation of the Authority, by notice in the Gazette exclude, subject to such conditions as he or she may determine, any medicine, scheduled substance, medical device or IVD from the operation of any or all of the provisions of this Act, and may in like manner amend or withdraw any such notice.

Regulations made in terms of the Act:

The following General Regulations issued in terms of the Medicines Act enable the Authority to stipulate the technical requirements for the registration of medicines for both human and veterinary use and ensure continued compliance with the accepted standards and specifications.

Regulation 16 (6)

(6) A medicine, in respect of which an application for registration is made, must comply with the technical requirements as determined by the Authority.

Regulation 16 (9)

(9) The provisions of this regulation shall, with the necessary changes, apply to the application for the registration of veterinary medicines.

Regulation 53 (1)

(1) Every medicine must continue to comply with the standards and specifications which were furnished to the Authority and which have been accepted by the Authority with regard to such medicine.

(2) Any proposed deviation from accepted standards and specifications referred to in sub-regulation (1) must be submitted to the Authority for prior approval and such deviation shall not be introduced before the said approval has been granted.

In recognition of the scarcity of approved veterinary medicines in South Africa for minor use including use in wildlife, special provisions in this guideline are included to facilitate the registration of such products.

OBJECTIVES

The objective of this guideline is to clarify the provisions of the Act that allow for exemptions from certain requirements and to encourage applicants to register much needed medicines for which the regulatory burden may be perceived as being too high e.g. minor use minor species.

DEFINITIONS

3.1 Well-established APIs, API combinations and products (medicines)[1]

APIs/API combinations and products, which have been marketed for at least five years in countries that undertake active post-marketing monitoring

3.2 Human food safety

This is a process of ensuring that a product or chemical will not cause appreciable harm to a person exposed to a chemical in the food for a defined period of time.

3.3 Major Species

Animals that contribute to a large extent to human food security or, animals of which a large number is treated such as: cattle, pigs, sheep, goats, chickens, ostriches, farmed fin fish, horses, dogs and cats

3.4 Maximum Residue Limit (MRL)

The maximum residue limit of a chemical allowed in food destined for human consumption

[1] This definition does not take into account possible sensitivities to excipients and other factors relevant to therapeutic equivalence. It also does not take into account species differences with regard to use in animals.

3.5 Minor Species

Any species other than those already named under major species.

3.6 Minor Use

Either the use of a veterinary medicine in a minor species, or the use of a veterinary medicine in any animal species for which it is not registered or for an infrequently occurring or geographically limited disease.

3.7 Target animal safety study

Includes in vivo studies under controlled conditions which identify the toxicity syndrome(s) associated with the final formulation and the margin of safety of use of the product in the treated animal species for which approval is being sought.

3.8 Wildlife species

Undomesticated animals living in the wild or in captivity, excluding animals named as major species.

3.9 Withdrawal period

The interval between the time of last administration of a veterinary medicine and the time when the animal product can be safely used as determined by a validated method.

GENERAL REQUIREMENTS

All applications for exemptions from requirements must be addressed to the Authority.

4.1 **Letter of application**

4.1.1 Indicate clearly in the letter of application:

- the requirement(s) for which exemption is sought;
- justification for such exemption including the basis for concluding that alternative approaches may be used or certain technical requirements waived
- where the relevant justification is located in the dossier.

4.1.2 Where information is available, at least the following should be addressed in the dossier:

(i) Details of registration or pending registration of the medicine with any other regulatory authority, and the history of the medicine;

(ii) Any sale in the Republic of South Africa;

(iii) Known marketing experience in other countries;

(iv) A description of the disease or condition for which the medicine is proposed to be used;

(v) The basis for concluding that the medicine is:

- in the interest of animal well-being; or
- for use in a pandemic or high impact situation;
- for animal welfare or clinical management, or unmet need or

- for a rare disease or condition.

(vi) The size and other demographic characteristics of the target population affected in RSA and the source of the information.

(vii) The proposed minor species for use or the proposed minor use in the case of a veterinary medicine.

(viii) Data on user and environmental safety (if applicable)

(ix) Periodic Safety Update Reports (PSUR) to be monitored.

4.2 Application for registration

The current version of the VMRF1 application form/CTD format must be used for veterinary medicines.

SITUATIONS WHEN EXEMPTION FROM CERTAIN REQUIREMENTS MAY BE CONSIDERED

5.1 Transcription from MBR1 to VMRF1

Conversion of MBR1 to VMRF1 requires transcription of the currently approved information to the VMR1 format. Where information was not required at the time of submission of the original application, or for the registration of the medicine, or for subsequent amendments when these were applied for, it is not necessary to populate those sections of the VMRF1 (e.g. pharmaceutical development report). Resubmission of non-clinical and clinical data (Annexures 13, 14 & 15 / PARTs 4 & 5) is not required when transcribing from MBR1 to VMRF1.

5.2 Medicines where limited clinical data are available

Promising medicines, based on 4.1.2 (v), with limited clinical data in support of safety and efficacy may be considered provided that there is a prospectively planned for gathering of information.

5.3 Medicines that are well established but the moiety has not previously been registered in South Africa

In such circumstances literature based evidence in support of the safety and efficacy could be considered.

In terms of quality, pharmacopoeial requirements, as well as compliance with the minimum requirements stipulated in the Quality guideline, could be considered. The influence of the formulation on the release of the API may be demonstrated as no locally registered reference product would be available. Where a reference product can be obtained from a country the regulatory authority of which the Authority aligns itself with, this product can be used for comparative studies.

5.4 Medicines where the innovator product is no longer marketed in South Africa

In such circumstances literature based evidence in support of the safety and efficacy could be considered.

In terms of quality, pharmacopoeial requirements, as well as compliance with the minimum requirements stipulated in the Quality guideline, could be considered. The influence of the formulation on the release of the API may be demonstrated as no locally registered reference product would be available.

Where a reference product can be obtained from a country, the regulatory authority of which SAHPRA aligns itself with, this product can be used for comparative studies.

5.5 **Medicines where the innovator product is no longer marketed in South Africa but for which there are pharmacopoeial monographs available**

In such circumstances literature based evidence in support of the safety and efficacy could be considered.

In terms of quality, pharmacopoeial requirements, as well as compliance with the minimum requirements stipulated in the Quality guideline, could be considered. The influence of the formulation on the release of the API may be demonstrated as no locally registered reference product would be available. Where a reference product can be obtained from a country, the regulatory authority which SAHPRA aligns itself with, this product can be used for comparative studies.

5.6 **Specific veterinary medicines scenarios**

5.6.1 Registered veterinary medicine for use in a minor species

Extrapolation of interspecies data of a medicine already approved for use in a major species if relevant could be considered. If a commitment to collect safety and efficacy information as part of the post marketing surveillance initiative is made, the motivation may be considered.

5.6.2 Registered veterinary medicine for a minor use

Extrapolation of the effect may be considered when the medicine is already approved for use in another species, and if relevant. If a commitment to collect safety and efficacy information as part of the post marketing surveillance initiative is made, the motivation may be considered.

5.6.3 Entirely new medicine for use in a minor species or for a minor use

In such circumstances, limited clinical data or literature based evidence in support of safety and efficacy or extrapolation of data pertaining to a similar class medicine already approved, and/or if relevant a commitment to collect safety and efficacy information as part of the post marketing surveillance initiative is made, the motivation may be considered.

5.6.4 Medicine registered for human use but not registered for use in a minor species or for a minor use

In such circumstances limited clinical data or literature based evidence in support of the safety and efficacy, or extrapolation of human data when adequately justified and/or and if relevant a commitment to collect safety and efficacy information as part of the post marketing surveillance initiative is made, the motivation may be considered.

6. PARTs 4 and 5/Module 4 and 5

Efficacy

The applicant is required to conduct pilot studies for proof of concept for minor use/minor species status designation. As an example, proof of efficacy in 1 to 5 of the target species with the following sample size is suggested: 1 species n = 6 to 10 animals and for 3 to 5 species n = 3.

The applicant needs to commit to collect safety and efficacy information as part of the post marketing surveillance initiative.

Withdrawal Periods

Submit results of residue depletion studies and recommended withdrawal period for veterinary medicines intended for use in food producing animals. In the case of wildlife, lot of products from immobilised animals end up in the food chain as 20% of meat consumed by the population is from wildlife.

Where there are no MRLs yet, extrapolation from a major species (Refer to FDA and EMA MUMS guidelines) on a case by case basis using a worst case scenario can be considered. In South Africa, a default withdrawal period of 90 days for conventional formulations is acceptable unless determined.

7. UPDATE HISTORY

New Guideline: Date of implementation	March 2020