South African Health Products
Regulatory Authority
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WAIVERS FROM CERTAIN MEDICINE REGISTRATION REQUIREMENTS FOR MEDICINES FOR HUMAN USE

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the SAHPRA'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. 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.

Document History

Final Version	Reason for Amendment	Effective Date
1	New	July 2022

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Contents

Glossary

Abbreviation/ Term	Meaning
Act	Medicines and Related Substances Act, 1965 (Act 101 of 1965, as amended)
API	Active Pharmaceutical Ingredient
CTD	Common Technical Document
IVD	*in vitro* diagnostic
PBRER	Periodic Benefit Risk Evaluation Report
PHE	Public Health Emergency
PSUR	Periodic Safety Update Report
Q-BE	Quality and Bioequivalence
RMP	Risk Management Plan
RRA	Recognised Regulatory Authority
RSA	Republic of South Africa
SAHPRA	South African Health Products Regulatory Authority
USA	United States of America

1. INTRODUCTION

The Medicines and Related Substances Act (Act 101 of 1965) (hereinafter 'the Act') makes provision for the registration of human medicines based on quality safety and efficacy.

Whilst the Act stipulates that only the safety, quality 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 does make provision for consideration of registration of medicines, or exemption from certain registration requirements or exemption from registration in special circumstances.

1.1 Purpose

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.

1.2 Scope

This guideline is applicable to applications for chemically synthesized and biological medicines for human use and excluding complementary and veterinary medicines.

This guideline is not applicable to rolling reviews and applications for PHE with limited data available at the time of application. (Refer to the PHE GL - SAHPGL-PEM-01 **Availability of medicines for use in a Public Health Emergency (PHE)**.

2. LEGAL PROVISION

The relevant legislation includes the following provisions:

The Act:

Section 1(3)

1.3 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

(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(a).

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.

(2) Notwithstanding subsection (1), the exclusion of any medicine or Scheduled substance, from the operation of sections 18A and 22G shall be effected by the Minister on the recommendation of the Pricing Committee.

Regulations made in terms of the Act:

The following General Regulations issued in terms of the 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 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.

Therefore, although South African law does not have specific enabling provisions for an "Orphan Drug" programme such as that applied in the USA, Europe or Australia, the possibility does exist to stipulate alternative requirements for medicines required by small patient populations (human).

3. DEFINITION(S)

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

APIs, API combinations and products, which

- When an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature. (from EMA definition)
- General recognition of safety through scientific procedures is based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of scientific data, information, or methods (US FDA definition)
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known in the context of local disease burden and population; and
  have the same route of administration and strength, and the same or similar indications as the initially registered product.

4. GENERAL REQUIREMENTS

All applications for exemptions from requirements must be addressed to the Chief Executive Officer.

4.1 Letter of application

4.1.1 Indicate clearly in the letter of application:

- the requirement(s) for which exemption is required;
- justification for such exemption;
- where the relevant justification is located in the dossier.

4.1.2 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 RSA;

(iii) Known marketing experience in other countries with which SAHPRA aligns

(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 public health;
- for use in a pandemic or high impact situation;
- for an unmet clinical/health need; or
- for a rare disease or condition.

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

(viii) The basis for concluding that alternative approaches may be used or requirements waived

(ix) Confirmation that the application is supported by a Risk Management Plan describing pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks related to that medicine and the assessment of the effectiveness of those interventions.

(x) Confirmation that a Periodic Safety Update Reports (PSUR) and/or Periodic Benefit Risk Evaluation Reports (PBRER) will be submitted as per the relevant requirements.

4.2 Application for registration

The ZA eCTD dossier format must be used for all applications for registration of human medicines.

Refer to the roadmap document **eCTD-Roadmap-communication-revised-signed**.

5. SITUATIONS WHERE EXEMPTION FROM CERTAIN REQUIREMENTS MAY BE CONSIDERED.

5.1 Medicines where limited clinical data and safety 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 process for the development of further supporting evidence (e.g. phase IV studies or patient registries).

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

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

In such circumstances reliance can be applied, if the moiety has been registered in a Recognized Regulatory Authority, with full clinical data, currently still has an active marketing authorization and is under active post-marketing surveillance.

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

In such circumstances peer-reviewed published literature based evidence in support of the safety and efficacy could be considered. Previous registration with MCC or SAHPRA may be considered as evidence of safety and efficacy, unless the innovator was withdrawn due to safety concerns.

In terms of quality, pharmacopoeial requirements, as well as compliance with the minimum requirements stipulated in the Q-BE guideline (Guideline 2.02), when no locally registered reference product would be available for comparison, BE studies and dissolution profiles, using the RRA reference product should be provided.

Refer to the 3.2.R.1 II regarding the choice of reference products.

Exemption for comparative dissolution data with local innovator will be granted if requested.

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

In such circumstances peer-reviewed published 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 PA CTD guideline, could be considered. 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.

Exemption for comparative dissolution data with local innovator will be granted if requested.

5.5 Where the South African innovator product is not available on the market and is only available under specific conditions

For applications for products for which innovator products are not freely available for purchase by the applicant, exemption may be granted for the submission of comparative dissolution data with the local innovator product. BE studies and dissolution profiles, may be submitted using the RRA reference product.

6. VALIDITY

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