



Accessing essential medicines in the South African public healthcare sector via section 21

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Introduction

Like all national medicines regulatory bodies, the South African Health Products Regulatory Authority (SAHPRA), previously the Medicines Control Council of South Africa, is responsible for ensuring that all South Africans access medicines that are safe, efficacious and of good quality.¹ A basic tenet of medicines regulatory practice is to require that all medicines on the domestic market are registered and therefore that their marketing and sale is authorised. There are, however, circumstances where access to an unregistered medicine is needed, requiring an exceptional mechanism to be employed. In South Africa that exceptional mechanism, which allows for the sale of unregistered medicines, is provided by section 21 of the Medicines and Related Substances Act, 1965 (the Medicines Act).

This article describes the circumstances under which the South African public health sector would need to have recourse to section 21, and the required processes that would enable such access.

Access to essential medicines

Access to care (including medicines) is one of the core values of a patient-centred approach to healthcare.² Often, the availability of medicines is used as a sensitive indicator of the performance of health care delivery systems.³ Ensuring access to quality-assured, affordable essential medicines is a key component of delivering universal health coverage.⁴

South Africa's 1996 National Drug Policy⁵ endorsed the World Health Organization (WHO) "essential medicines" concept,⁶ which seeks to ensure that essential medicines, which satisfy priority local health needs, are available at all times in adequate amounts, in appropriate dosage forms, to all who need them. Access to healthcare services is also enshrined in South Africa's Constitution, and specifically in sections 27 and 28 of the Bill of Rights.⁷ While

this is not an unlimited right of access to every possible healthcare service or health product, the state is under a positive obligation to ensure the progressive realisation of the right, within the limits of available resources. Children, though, are guaranteed access to basic health services, without qualification.

One way in which rational and evidence-based restrictions on access to medicines are implemented is through the development of a national Essential Medicines List (EML), which is managed by the ministerially-appointed National Essential Medicines List Committee (NEMLC).⁸ Listing on the EML guides procurement in the public health sector, and is also expected to contribute to the design of the basic care package which will be delivered through National Health Insurance.⁹ The NEMLC is also responsible for the development of standard treatment guidelines (STGs) that guide implementation of the national EML. The EML and STGs have an indirect impact on the provision of care in the private sector, as they set a minimum standard as to which medicines should be accessible.

In general, the national EML does not list products which are not available on the South African market, or not registered by SAHPRA. This does not, however, imply that products can only be selected (and therefore included in STGs) on the basis of the indications approved by SAHPRA. Provided there is sufficient evidence to back such a decision, medicines may be included in the EML for "off-label" uses.

Section 21 – the basics

Section 21 of the Medicines Act, allows SAHPRA to authorise "any person to sell during a specified period to any specified person or institution a specified quantity of any particular medicine ... which is not registered". SAHPRA can also specify how and for what time period the medicine can be used and may withdraw the authorisation, where deemed necessary.

At first glance this would seem not to be applicable to the State, as it does not “sell” medicines in the ordinary meaning of the word. However, the word “sell” is defined very broadly in the Medicines Act and so encompasses the supply of medicine at no cost, as the State does to uninsured patients.

In addition to the Act itself, the application of section 21 is supported by General Regulation 29 issued in terms of the Act,¹⁰ and by SAHPRA guidelines. A revised set of these guidelines was published for comment in April 2019.¹¹

The guidelines describe a number of very different circumstances in which section 21 might apply. These include the need for access to an unregistered medicine for:

- use by an individual patient;
- the conducting of an approved clinical trial;
- post-trial use by a previous participant in a completed clinical trial - only when application cannot be made in accordance with SAHPRA’s “Post Clinical Trial Drug Access” guidelines.

Although many clinical trials are conducted in public sector health facilities, applications for access for this purpose are usually managed by the principal investigator for the study, and do not form part of State procurement processes. Post-trial access should be described and provided for in a trial protocol, in accordance with the requirements of the Declaration of Helsinki.¹²

The procurement of a medicine needed by an individual patient, who cannot be treated with any other medicine available in the country, is possible in the public sector. This is generally referred to as a “named patient” exception to the EML, and requires consideration by the relevant provincial Pharmacy and Therapeutics Committee (PTC). In many jurisdictions, this is referred to as a “compassionate use exemption”.

The draft SAHPRA guideline describes two other circumstances that have relevance in the State. The first entails permission for procurement of bulk stock of an unregistered medicine, for use on a compassionate basis. The guideline explains that “[i]n exceptional circumstances, certain unregistered medicines need to be available urgently and an individually named patient application is not possible”. In that case, an application can be made to procure a specified amount of an unregistered medicine, to be stored in a registered pharmacy. Importantly, the applicant in such cases is proposed to 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”. It is also possible for a manufacturer, importer or wholesaler/distributor (licensed in terms of section 22C of the Medicines Act) to apply to hold bulk stock. This mechanism is used, for example, to enable the timeous access to unregistered antibiotics in the intensive care units of specified health facilities.

The second circumstance referred to in the draft guideline is “state procurement”. This is described as follows: “The State may designate a health care provider as a representative in order to apply for authorisation for the supply or sale of an unregistered

medicine by health establishments. In such circumstances, the co-applicants shall include prescribers, where these are known and the licence holder(s) involved in the supply of the unregistered medicine to health establishments”. The provincial pharmaceutical procurement depots are licensed as wholesalers/distributors in terms of section 22C of the Medicines Act. The circumstances that would justify state procurement in terms of section 21 are not described in any detail.

What the draft guideline has underscored for the first time is that there are always two parties to a request for an unregistered medicine – the prescriber who is caring for an individual patient or who anticipates needing such a medicine for a future patient or patients; and the licensed supplier who will actually bring the product into the country and provide it to a pharmacy for dispensing to the patient. While not specified in the Act itself or the General Regulations, the draft guidelines describe the possible scenarios in which an applicant and co-applicant(s) may be involved. For example, in the individual patient case, the applicant is the prescriber, while the co-applicant is the licensed supplier. In the more complex case of state procurement, the applicant is the designated health care provider, while the co-applicants are the prescribers and licensed suppliers.

Obligations under section 21

Both applicants and co-applicants have clearly defined obligations in terms of the draft guideline issued by SAHPRA. Some of these obligations are also outlined in General Regulation 29.

Firstly, a prescriber of an unregistered medicines must ensure that the patient (or caregiver in the case of a minor) has provided signed, informed consent to the use of the medicine. This is in line with what is specified as the user’s right to full knowledge in terms of section 6 of the National Health Act, 2003.¹³

In terms of sub-regulation 29(3), the prescriber is under an obligation to report any adverse event that occurred during use of the unregistered medicine, and in addition to provide progress reports every six months from the date of first using the medicine and a final report within 30 days after the completion of the use of the medicine. General Regulation 40 requires that all health care providers report “new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine”.

There are also specific obligations placed on licensed suppliers who import any specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substances, as they require a permit from the Director-General of Health in terms of section 22A(11).

Sub-regulation 29(2) also requires an application to be accompanied by a “product brochure containing relevant chemical, pharmaceutical, pre-clinical pharmacological and toxicological data and where applicable, human or animal pharmacological and clinical data”. The draft guideline puts the requirement somewhat differently, calling for either “prescribing information/professional information from the jurisdiction where the medicine may be marketed, preferably a regulatory authority

with which SAHPRA aligns itself”, or “published data to support the application”, or “unpublished reports”, or “data available from medical literature, treatment guidelines, investigator’s brochures, information obtained from the manufacturer, clinical trial reports, consultations with experts”, and finally the “regulatory status of the medicine”. This more nuanced approach is welcome.

State procurement under section 21 - experiences

The most common circumstance that would give rise to a state procurement-type section 21 application is when the contracted supplier is unable to meet demand for an essential medicine, and there are no or insufficient alternative suppliers or alternative medicines available in South Africa. That this should be an option only resorted to *in extremis* is clear: the very essence of an Essential Medicines Programme is to ensure the rational and dependable selection and procurement of essential medicines. To have to resort to bulk importation of unregistered medicines should be an exception, not the norm. However, as the experience of the Affordable Medicines Directorate has demonstrated, global shortages of specific medicines are becoming more common.

The draft SAHPRA guidelines have listed the circumstances under which the Authority will consider the use of section 21 to address a medicine shortage. Firstly, “the medicine is considered to be medically necessary for the treatment, diagnosis or prevention in an area of unmet medical need”. Secondly, “there are no other dosage forms of the medicine on the market that would be considered a reasonable alternative”, and thirdly, “there are no other medicines or therapies that would be considered to be reasonable alternatives”. These are entirely justifiable considerations. Other stipulations appear to be more aspirational and outside of the control of the State when making such an application: “the manufacturer has disclosed the reasons for the shortage or discontinuation of the medicine” and “the manufacturer demonstrates that efforts have been made to avoid and manage the shortage”. Such considerations should not be allowed to hamper access to essential medicines.

Other possible circumstances might involve a public health motivation for a particular medicine, even before it is registered. If, for example, evidence supports the use of a new medicine which is safer and more effective than available medicines for

Table 1: Medicines that have been accessed through S21 approval

Medicine	Indication	EML/VEN status	Supplier	Reason for S21	Comments
Phenobarbital 200 mg/ml injection	Epilepsy	EML/V	No local supplier	No local supplier.	Mainstay of treatment of neonatal seizures.
Benzathine benzylpenicillin 2.4MU	Syphilis	EML/E	No local supplier	Previously registered supplier submitted a technical amendment to MCC/SAHPRA 2017/8 (SAHPRA is currently investigating this matter).	Benzathine benzylpenicillin is the recommended treatment option for syphilis in children and pregnant women (doxycycline may be considered as an alternative in other patient groups).
Medroxyprogesterone acetate (DMPA) 150 mg/ml injection	Contraception	EML/E	Pfizer Laboratories (Pty) Ltd	No national contract awarded – thus stock outs not mitigated. One of two local suppliers discontinued supply.	South Africa relies heavily on injectable progestogen-injectable contraceptives.
Norethisterone enanthate (NET-EN) 200 mg/ml injection	Contraception	EML/E	Bayer (Pty) Ltd sole local supplier	Demand exceeded supply due to supply challenges with DMPA; resulting in active pharmaceutical ingredient supply challenges.	<ul style="list-style-type: none"> NET-EN currently on contract DMPA not currently on contract
Anti-D immunoglobulin 300 mcg/2 ml injection	Prevent Rho(D) alloimmunisation	EML/V	National Bioproducts Institute NPC	Erratic local supply.	Medicine is not currently on national contract – globally there has always been fragility of immunoglobulin supply.
Artesunate injection	Malaria	EML/V	Equity Pharmaceuticals	Compelling evidence of mortality benefit for malaria caused by <i>Plasmodium falciparum</i> .	Application for registration was in process with the MCC when S21 access was applied for; now registered in terms of the Medicines Act.
Flucytosine injection	Cryptococcosis	NON-EML	No local supplier	Evidence of mortality benefit compared to current standard of care for treatment of cryptococcal meningitis.	Advocacy groups and clinicians are motivating for registration, but no application has been received by SAHPRA, to date.

EML: Essential Medicine List; VEN status = categorisation of medicines according to prioritisation; V = vital potential life-saving medicines; E = essential medicines effective against less severe but significant disease; N = necessary medicines for minor or self-limited illnesses.

a serious condition, then an argument could be made for bulk access, or even state procurement. This was the case with the state procurement of intravenous artesunate, even before it was registered by SAHPRA (see Table 1). Finally, where a public health campaign relies on donated medicines provided by a development partner or donor, section 21 approval would be needed to allow for the importation of the medicine, as has been done for mass deworming campaigns.

Where the National Department of Health initiates S21 procurement processes to access an essential medicine in the public sector, estimates are provided by provincial depots. There is then an obligation on the provinces to use the forecasted amount within the period provided by the S21 approval. Failure to do so requires re-initiation of the regulatory process to obtain an additional S21 authorisation, which is counter-productive and impedes streamlined access to the specific medicine.

Conclusion

The public sector faces particular challenges in ensuring continuous access to essential medicines, most notably when unpredictable and unannounced medicine shortages occur. Unlike in other jurisdictions, such as Australia and the United States, holders of certificates of marketing authorisation in South Africa are under no legal obligation to inform the regulator before withdrawing a product from the market or when encountering a predictable

supply disruption. While not perfect, section 21 has allowed for state procurement to bridge gaps in supply and ensure continued access to essential medicines. The new draft guideline attempts to address the very specific challenges experienced by the State in managing bulk procurement of unregistered medicines.

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