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AVAILABILITY OF MEDICINES FOR USE IN A PUBLIC HEALTH EMERGENCY (PHE)

This guideline provides recommendations to applicants who intend to submit applications for the registration or authorisation of medicines intended to be used in a public health emergency. It represents the current thinking of the South African Health Products Regulatory Authority (the Authority) on approaches to determine the quality, safety, and efficacy of the medicines required in a public health emergency and is not intended as an exclusive approach. The Authority 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 Authority is committed to ensuring that all registered or authorised medicines are of the required safety, quality and efficacy. It is important that applicants also adhere to administrative requirements to avoid delays in the processing and evaluation of applications.

This document should be read in conjunction with all other related guidelines and templates, available from the Authority's website: www.sahpra.org.za.

Document History

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BOITUMELO SEMETE-MAKOKOTLELA
CHIEF EXECUTIVE OFFICER

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Glossary

Abbreviation/ Term	Meaning
API	Active Pharmaceutical Ingredient (also known as Drug Substance)
Applicant:	Organization creating and submitting the eCTD submission. Can either refer to the PHCR or HCR
Application number:	The application number is the official reference number assigned to the dossier or eCTD application by the Authority. It remains with the dossier for its full life cycle and also in archiving.
Dossier:	A collection of documents compiled by an applicant in compliance with South African legislation and guidelines in order to seek registration of a medicine, or any variations thereof. An application may comprise a number of submissions.
CTD	Common Technical Document
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
HCR	Holder of Certificate of Registration
HPA	Health Products Authorisation
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INN	International Non-proprietary Name
IVD	In Vitro Diagnostics
Medicine	Medicine as defined in terms of the Act
NRA	National Regulatory Authority
PEM	Pharmaceutical Evaluation Management
PHE	Public Health Emergency
PI	Professional Information
PIL	Patient Information Leaflet
Q & BE	Quality and Bioequivalence
SADC	Southern African Development Community
WHO	World Health Organisation

1. INTRODUCTION

1.1 Purpose

The purpose of this guideline is to guide how medicines that are not yet available in South Africa may become registered for use by, or authorised for sale during a Public Health Emergency (PHE). Such applications for registrations or authorisations would be received, processed, and decided upon effectively, consistently, 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

The Authority is mandated to assess the safety, quality, and therapeutic efficacy of all medicines in determining whether the availability of a medicine is in the public interest. Before registration of a medicine, access is usually limited to clinical trials. The Authority may, in certain circumstances, and in terms of 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 deem necessary.

PHEs represent a significant concern for their potential domestic and international impact. The unusual and unexpected nature of PHEs may lead to situations where there is no or insufficient effective diagnosis, treatment or prevention of the concerned conditions, diseases or disorders associated with the PHE. The Authority, therefore, needs to consider mechanisms that would allow for the agile, expeditious and appropriate review of medicines required in a PHE.

The Authority seeks to expedite access to safe, good quality and efficacious medicines for the South African public. The processes encompassed in this document guide how applicants may position their applications to best facilitate the review of applications for the registration, or authorisation of the sale, of a qualifying medicine in response to a PHE.

1.3 Objectives

This document is intended to clarify the scenarios for applications for the registration, or authorisation of the sale, of medicines during a PHE in terms of the Act according to the scope of the document described in 1.2 and outlines:

- a) the qualifying criteria for consideration of this pathway.
- b) the application processes that apply to medicines that may address a medical need during a PHE in South Africa.
- c) the responsibilities of applicants; and
- d) the information required to comply with this pathway.

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, as the case may be.*

Section 14(1) of the Act states:

- (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.*

Section 15(1)-(3) of the Act states:

- (1) *Every application for the registration of a medicine, medical device or IVD shall be submitted to the Chief Executive Officer in the prescribed form and shall be accompanied by-*
 - (a) *the prescribed particulars.*
 - (b) *samples of the relevant medicines.*
 - (c) *where practicable, samples of medical devices or IVDs; and*
 - (d) *the prescribed registration fees.*
- (2) *As soon as possible after receipt by the Chief Executive Officer of an application contemplated in subsection (1), he or she shall inform the applicant in writing that the application is being considered.*
- (3)
 - (a) *If after consideration of any such application and after any investigation or enquiry which it may consider necessary the Authority is satisfied that the medicine, medical device or IVD in question-*
 - (i) *is suitable for the purpose for which it is intended.*
 - (ii) *complies with the prescribed requirements; and*
 - (iii) *is safe, efficacious and of good quality and, in the case of a medical device and IVD, performs as intended,*
the Authority shall issue the applicant with a certificate of registration to that effect.

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).*

1.5 Definitions

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

“Authority” means the South African Health Products Regulatory Authority established by section 2 of the Act;

“institution” means any organisation that wishes to sell an unregistered medicine and includes a health establishment as defined in section 1 of the National Health Act, 2003 (Act No. 61 of 2003), or the holder/s 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;

“medicine” means medicine as defined in terms of the Act; and

“public health emergency” means an extraordinary event ¹which, has been determined to:

- (a) constitute a serious health risk to members of the public of the Republic of South Africa; or
- (b) cause or have the potential to cause an outbreak, epidemic or pandemic.

“Rolling Review” means a regulatory tool that is used to speed up the assessment of a promising medicine or vaccine during a public health emergency. Normally, all data on a medicines or vaccine’s quality, efficacy and safety and all required documents must be ready at the start of the evaluation in a formal application for marketing authorisation. In the case of a rolling review, the Authority reviews data as it becomes available from ongoing studies.

2. BACKGROUND INFORMATION

A PHE may lead to an unprecedented challenge to public health, resources and way of living, economic and social disruptions as well as possible loss of human life. To mitigate the effects of any disease or health risk, the impact of which is sudden, unexpected and is not readily addressed by the existing therapeutic means, may potentially rely upon the availability of novel medicines or medicines not yet legally available in the country.

Due to the potential global impact of a PHE, the anticipated applications for registration in terms of section 15 of the Act or authorisation of the sale of an unregistered medicine in terms of section 21 of the Act need to be appropriately motivated, contextually applicable and guided.

The Authority’s legislated mandate is to consider the safety, quality and efficacy of any medicine when deciding whether or not to make a medicine available for use in the country. All three elements must be ensured so that members of the public realise the inherent therapeutic or preventative benefits of a medicine but also that such medicines do not cause any harm because of their quality deficiencies or inherent safety concerns. The Authority would consider a non-routine approach for the authorisation and approval of such medicines or medical devices taking into consideration the risk versus the benefit in the case of a PHE.

This guideline should be read together with other relevant guidelines determined by the Authority concerning information and application requirements for the authorisation for sale or registration of medicines as may be appropriate.

Despite the guidance provided herein, the Authority may request any other information as may be required by the Authority in terms of regulation 16(3)(g) (with respect to applications submitted for the registration of a medicine) or regulation 29(2)(g) (with respect to applications for the authorisation of the sale of an unregistered medicine) of the General Regulations.

3. POSSIBLE SCENARIOS FOR MEDICINES INTENDED FOR A PHE

In either of the possible scenarios provided in 3.1 and 3.2 below:

- The medicine must be a novel medicine or medicine not yet registered in the country and is not readily addressed by the existing therapeutic means.
- The medicine may be already registered, for a purpose other than addressing the PHE.

¹ A public health emergency may be determined by a number of factors, including but not limited to, a Public Health Emergency of International Concern (PHEIC) declared by the World Health Organization, an emergency declared by the National Department of Health, or an event which results in the declaration of a state of disaster, in terms of the Disaster Management Act (Act 57 of 2002).

- the medicine in question must be verified to be manufactured in compliance with Good Manufacturing Practices (GMP); as accepted by the Authority
- in the case that the applicant is the original manufacturer of the medicine, a commitment to:
 - provide SAHPRA with all necessary information related to the safety, quality, and efficacy of the medicine, and all research and development relevant to the medicine; and
 - complete the necessary research and development steps to comply with the requirements for registration.
- in the case of a medicine to be imported by an entity or person other than the original manufacturer the applicant must:
 - have demonstrable contractual agreements in place, without any hindrance or limitation, that empowers it to have access to and provide all necessary information required by the Authority relating to the safety, quality, and efficacy of the medicine and all research and development relevant to the medicine; and
 - include an undertaking from the original developer and manufacturer to complete and make available all the necessary information as well as the research and development steps to comply with the requirements for registration.
- based on the outcome of a risk-based analysis concerning the safety, quality, and efficacy of the medicine in question, registration of that medicine or authorisation for sale as an unregistered medicine may be undertaken, with conditions that require the submission of outstanding information within a timeframe stipulated by the Authority; and
- in the case of applications for registration of a medicine in terms of section 15 of the Act:
 - motivations for a priority review should take account of the context of the defined PHE and its clinical and social impact; and
 - motivations for a rolling review, should include reference to the following minimum available evidence:
 - non-clinical and early clinical phase data that demonstrate promising evidence of safety and efficacy;
 - written confirmation that phase 2/3 trials have started and there are sufficient participants expected to be enrolled to provide reliable evidence of safety and efficacy within an appropriate and reasonable amount of time;
 - quality information, including minimum development data, chemistry, manufacturing and compliance; and
 - a plan stipulating the proposed timelines for submitting the various components of the application.

3.1 Medicines that have been authorised for use by Medicines Regulatory Authorities (MRAs) recognised by the SAHPRA

The Authority may consider the authorisation of an unregistered medicine for sale in terms of section 21 of the Act if the medicine has been authorised or registered for use under comparable circumstances by any MRA recognised by the Authority (see **SAHPRA Guideline SAHPGL-HPA-07: General Information Guideline**).

In such instances, applicants must consult **SAHPGL-CEM-S21-01: Access to Unregistered Medicines** (scenario 2.5.1) and submit an application in terms of section 21 of the Act.

In line with the commitment to continue the necessary research and development of the medicine, the applicant must, within a period stipulated by the Authority (on a case-by-case basis), after the submission of an application in terms of section 21 of the Act, apply for registration of the medicine in question in terms of section 15 of the Act (see **sections 4 and 5 below**) including suitable motivation for the application to be considered for (a) priority review; and/or (b) rolling review. The application for submission in terms of section 15 of the Act should be within 30 working days of submission in terms of

section 21. The expected timeline for registration is 90 working days, excluding the time taken by the applicant to provide responses to queries. This timeframe may be affected by the availability of data, based on the rolling submission.

In the event of a successful application for registration, any active authorisation for the sale of the unregistered medicine will be withdrawn. The registration of the medicine may be subject to conditions in terms of section 15(6)(a) of the Act.

3.2 Medicines that have not been authorised for use by Medicines Regulatory Authorities (MRAs) recognised by SAHPRA

In the case of novel medicines which have not been authorised for use by an MRA recognised by the Authority (see **SAHPRA Guideline SAHPGL-HPA-07: General Information Guideline**) and which are intended to be used for the management of a PHE, an application for registration in terms of section 15 of the Act must be made to the Authority.

Applicants must ensure that applications meet minimum requirements for submission as stipulated by the Authority.

If required, applicants may submit, together with the application, motivation for the application to be considered for (a) priority review; and/or (b) rolling review. The type of review of such application will be determined after the screening phase with reference to the motivation and the completeness of the information/dossier submitted.

Based on the context of the PHE, the need for the medicine in question and the progress of the review of the application for registration, a positive risk-benefit analysis for its use may be achieved. In such instances, the availability of the medicine to the public may be best facilitated by way of authorisation in terms of section 21 of the Act before all the requirements for registration are met. Applicants must consult **SAHPGL-CEM-S21-01: Access to Unregistered Medicines** (scenario 2.5.2) and submit an application in terms of section 21 of the Act.

In the event of the medicine being registered in terms of section 15, any active authorisation for the sale of the unregistered medicine will be withdrawn. The registration of the medicine may be subject to conditions in terms of section 15(6)(a) of the Act.

4. PRE-SUBMISSION MEETING

Applicants intending to make submissions for section 21 approval for a PHE and for registration in terms of section 15 may face different challenges regarding their applications and their ability to comply with all administrative requirements.

A pre-submission meeting provides an opportunity for applicants to explain the nature of these challenges and to develop a preliminary review of the data required. The Authority requires applicants to request a pre-submission meeting to obtain guidance, in accordance with the requirements outlined in section 3 above.

4.1 How to make a pre-submission appointment?

Send an email to PHE@sahpra.org.za and section21@sahpra.org.za together with a summary of the information requested in 4.2, requesting an appointment and undertaking to supply all information stipulated in 4.2 in detail prior to the meeting. The applicant should indicate in the meeting requests details of the proposed attendees and agenda.

The subject of the email should include "PHE PRE-SUBMISSION APPOINTMENT REQUEST".

4.2 What is required for the pre-submission discussion?

The following information must be supplied in writing at least five (5) working days prior to the intended meeting date and must be presented during the pre-submission meeting:

- information on authorisation or registration status with other regulators and whether the medicine has been or is intended to be submitted to WHO or other regulators;
- all details of the medicine including, but not limited to, the technology used, the data available, specific transport/storage, and labelling information;
- evidence which shows that manufacturing of the medicine is in compliance with GMP as accepted by the Authority and that product quality and consistency are well controlled;
- For Biologicals, if a variant is involved applicant to include any data available on the efficacy to the prevalent variant; Risk Management plan and pharmacovigilance activities.
- information on testing for lot release, where applicable, in terms of General Regulation 15; (see **SAHPGL-PEM-BIO-01_v4_Guideline for Lot Release of Human Vaccine**)
- requested type of review (e.g. priority and/or rolling) and the motivation thereof.

The applicant will be required to submit formal applications for consideration by the Authority subsequent to the pre-submission meeting.

5. APPLICATION PROCESS

5.1 General

- An application may be submitted in accordance with the applicable scenario, as outlined in section 3.
- Applicants are requested to adhere to the following file naming convention when submitting a PHE application on the FTP: Application number-PHE-BAU(N)-Sequence number.
- The application may be subject to any recommendations for further submissions made by the Authority during the pre-submission meeting.
- In terms of section 1(3) of the Medicines Act, whether or not the registration or availability of a medicine is in the public interest, regard shall be had to the safety, quality and therapeutic efficacy of a medicine as would be assessed from the application submitted.

5.2 Timeframes

- Application for medicines in terms of point 3.1 will undergo consideration for section 21 authorisation following review of available information and will be completed in a period of 30 working days, excluding days taken to provide additional information required to support access via section 21. These applications should be followed by the rolling review submission within 20 working days.
- In relation to a section 15 application, the expected timeline for registration is 90 working days excluding the time taken by the applicant to provide responses to queries. This timeframe may be affected by the availability of data, based on the rolling submission.
- Application for medicines in terms of section point 3.2 will undergo consideration for section 21 authorisation following review of available information and will be completed in a period of 30 working days, excluding days taken to provide additional information required to support access via section 21.
- For more information on Priority Review of New Medicines timeframes, see **communication Request for Priority Review of New Medicines and Variations Applications, document No: HPA03**

5.3 Fees

- The fees payable for section 21 authorisation of the use of medicines in a PHE will be as published in the Government Gazette.
- The fees for section 15 applications for registration will be the same as those published in the Government Gazette for such applications.

6. DATA REQUIREMENTS

This section outlines some of the critical information, including general, technical and formal data requirements, to be provided for medicines (including finished pharmaceutical products and vaccines) required during a PHE. Critically, the minimum clinical and non-clinical data are required for authorisation, even in emergency situations. Recommendations cannot be made for the use of the product if the safety is not yet established. The minimum safety data must be provided, and efficacy and further clinical data must be planned to be developed.

The benefit-risk outcome will be determined at each stage of a rolling data submission, based on the data available at the time. A favourable risk/benefit profile will be required in order to grant approval. Risk/benefit ratio assessment will be adjusted as new information is submitted for review. Based on the outcome of a risk-based analysis concerning the safety, quality and efficacy of the medicine in question, registration of that medicine or authorisation for sale as an unregistered medicine may be granted, with conditions that require the submission of outstanding information within a timeframe stipulated by the Authority.

6.1 General requirements

General aspects on what is required:

- The procedure is applicable to applications which are submitted for use in addressing, treating or preventing PHE situations, where a public health emergency is declared and confirmed.
- Applications should be submitted as outlined in section 3.
- Where available comprehensive data should be provided, which refers to a complete application with all quality, safety and efficacy information. Comprehensive data may only be available for some applications; such as for products which are used for other indications and have been repurposed for use in the PHE, therefore these will be determined on a case-by-case basis.
- For novel products, only limited information may be available at early stages of submission and comprehensive data will be available at a later stage and should be submitted once available. Data that are not available at time of application and authorisation, should be discussed by the applicant and the Authority in pre-submission meetings.
- For products which are approved by other regulatory authorities, reliance approaches may be used for obtaining authorisation or approval, however, all data which is available and submitted to the relying authority, should be submitted to SAHPRA with the application. For reliance processes to be used, full scientific assessment reports may be required, based on country-specific requirements for reliance. The reliance processes followed are as described in SAHPRA reliance guidelines, and may include WHO-SRA approved, WHO Collaborative registration process and the Zazibona process applications.
- Any application made in terms of section 15 of the Act, will undergo review and will not undergo standard screening, such that data may be submitted on a rolling submission schedule. Registration may be granted with conditions. The registration process should be completed within 90 working days, excluding days taken to provide additional information required to support the registration of the product.
- New information that becomes available which affects the safety, quality and efficacy, at any time outside the rolling submission schedule may be submitted after notifying the authority. The rolling , review submission schedule should be updated to reflect the changes.

- The Authority will ensure priority review of any application based on the need for a medicine for use in a PHE. The priority review process may include waiver of requirements of standard screening validation, review allocation on a priority basis, and the scheduling of *ad hoc* or specific advisory committee meetings. The Authority may rely on the decisions of other regulatory agencies it aligns with, as well as recognise test reports and lot release certifications from such sources.

6.2 Formal requirements:

A submission for section 21 approval or section 15 registration of medicines and vaccines for a PHE should follow the ZA CTD format, unless the ICH CTD format has been permitted after pre-submission discussion. In the CTD dossier, sections for which no information is available at the time of the initial submission should be indicated as “data or information not available”, “study ongoing” or “not applicable”, as the case may be. An indication should be given by the applicant of the timeline for submission of the missing data.

Note that regional working groups may be considered in order to facilitate faster response in an emergency situation, by enabling authorisation by the NRAs in the region based on joint assessments or pooling of resources.

6.3 Risk management plan

Risk management plans should be provided for all section 21 and section 15 applications for PHE, but the extent of the information provided at the time of submission might not be complete, as the product may still be under development and data collection may be ongoing. Post-marketing data would not be expected to be available at the time of application unless if the product is registered and used elsewhere. The applicant should discuss the plans for the collection and analysis of information on the safety and effectiveness of the product world-wide in the pre-submission meeting. Data should be collected during the period when the availability through authorisation would be in effect and for a reasonable time following such period. A plan for submission of missing data is to be provided.

6.4 Technical requirements for pharmaceutical and biological products(for vaccines requirements see 6.5)

Minimum available evidence:

1. non-clinical and early clinical phase data that demonstrate promising evidence of safety and efficacy;
2. written confirmation that phase 2/3 trials have commenced and that sufficient participants are expected to be enrolled to determine evidence of safety and efficacy within an appropriate and reasonable amount of time; and
3. a plan stipulating the proposed timelines for submitting the various components of the application. If not available at the time of submission the applicant should make a commitment to provide the plan as soon as possible.

Non-clinical and clinical data:

1. All relevant *in vitro* and *in vivo* pharmacodynamic (PD) data (e.g. on microbiologic/virologic activity, including any modelling performed; the relevance of the applied cell types/line(s) for the target disease) should be justified.
2. Data on efficacy and safety in *in vitro* tests and in animal model(s) under well-controlled and documented conditions. The preferred model depends on the disease and may vary according to the medicine’s mechanism of action. The applicant must justify the choice of animal model.
 - a. Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.

- b. All available evidence of the medicine's activity *in vitro* and in other animals, together with pharmacokinetics and efficacy in humans, also against other diseases should be submitted.
3. A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be safe and effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be safe and efficacious in the relevant animal model.
4. If human pharmacokinetic trials or studies in other indications at the exposure level proposed for treatment of the PHE disease have been conducted, assessment of safety using standard parameters (e.g. adverse events, clinical laboratory monitoring) will be done. This safety evaluation may be supplemented by any other non-clinical and clinical data at different exposure levels.
5. If available, clinical data demonstrating safety and efficacy at the proposed dose for PHE field use should be submitted.
6. For products that are repurposed, literature data on the safety of the product should be provided, however if dosage differs for the PHE disease, safety data for this dose should be provided.
7. For previously approved products, data requirements will be the same as new registration applications, as the product is known. Since the safety profile is known, non-clinical data does not have to be submitted, however clinical data to support the new indication must be included.

Chemistry, manufacturing and control data:

1. Information on the active ingredient(s) (All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls) and finished product, including characterisation (including known and potential impurities), composition, preparation, controls (specifications, analytical methods and their validation) [Refer to Quality and Bioequivalence guidelines, https://www.sahpra.org.za/wp-content/uploads/2022/01/SAHPGL-PEM-02_Quality-and-Bioequivalence-Guideline25.pdf and for Biologicals refer to the QSE guideline <https://www.sahpra.org.za/document/general-guidance-document-on-qse-for-biological-medicines/>.
2. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the quality and safety/efficacy profile of the product.
3. Stability data for a minimum of 1 month accelerated and 3 months long term stability studies. Stability data obtained from the proposed container closure system and the final formulation. Applicants can choose to follow the requirements of SADC, ICH or EMA's Stability Guideline, on condition that this is clearly stated in the Stability Protocol. This does not apply to products applied for through reliance on the Zazibona collaborative process for evaluation. In this case, the SADC Stability Guideline must be adhered to.
4. Evidence of GMP compliance of manufacturing, packing and testing sites in terms of GMP Approval Guidance in SAHGPL-INSP-02 Guideline on Good Manufacturing Practice for Medicines. SAHPRA may or may not need to perform its own assessment of GMP compliance.
5. The finished product is correctly processed and checked, according to the defined procedures.
6. Submission of Regional requirements Module 3.2.R should be met. In the baseline submission, inclusion of 3.2.R.1 Pharmaceutical and Biological availability; and 3.2.R.7 Production documentation is mandatory. Refer to the SAHPGL-PEM-02 Quality-and-Bioequivalence-Guideline_.
7. A letter of commitment provided by the applicant to assure the compliance with standards and regulations is expected when ultimate information and data are still missing for an EUA approval
- 8.

Regional requirements:

Specific labelling requirements:

1. At a minimum, South African basic labelling requirements should be met before authorisation. This can be revised as more data is provided.

2. Minimum requirements for the following to be in English or one official national language, depending on the end user:
 - i. Summary of product characteristics (information for health care provider) or Professional information.
 - ii. Patient information leaflet
 - iii. Primary and secondary labelling
 - iv. Any other instructional materials provided to the user.
 - v. A plan to ensure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When a novel product is authorised, the labelling should clearly indicate that that product is for public health emergency use only. Exemption of labelling could be considered, such as acceptance of labelling in English for products that are meant for professional use, such as vaccines. Additional region specific clinical requirement/implications based on public health issues specific to the country should be met.

Technical requirements vaccines:

Clinical and non-clinical:

Minimum clinical and non-clinical data is required for authorisation, even in emergency situations. Recommendation cannot be made for the use of the product if the safety is not yet established. Even in the cases of the above scenarios, the minimum safety data must be provided, and efficacy and further clinical data must be planned.

Minimum available evidence:

1. non-clinical and early clinical phase data that demonstrate promising evidence of safety and efficacy;
2. written confirmation that phase 2/3 trials have started and that sufficient participants are expected to be enrolled to determine evidence of safety and efficacy within an appropriate and reasonable amount of time; and
3. a plan stipulating the proposed timelines for submitting the various components of the application. If not available at the time of submission the applicant should make a commitment to provide the plan as soon as possible.

Non-clinical data:

1. Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy – if available- in the most appropriate animal model. The applicant must justify the choice of animal model.
2. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and a plan and timeline for submitting those data.

Clinical data:

1. Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency.
2. Preliminary data showing some efficacy– if available. If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, the Authority will consider whether the

preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use authorisation can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a reliable surrogate endpoint.

3. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review if applicable.

Note: products developed under the animal rule will also be considered for review.

Chemistry, manufacturing, and control data:

1. Full characterisation of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates.
2. Full characterisation of master and working seed organism(s), based on reference to the most appropriate WHO TRS.
3. Process validation (based on quality risk assessment for the development stage) and demonstration of consistency of production at the production scale used for the lots to be distributed. If deemed appropriate by the Authority, data on clinical trial batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered. Note: if full characterisation is not possible at the time of submission, adequate justification must be submitted and a plan must be presented to address the data gaps. If novel methods for validation of potency tests and other critical assays have been developed, full description of the test development and qualification must be presented.
4. Justified specifications for starting material, intermediates, and final products.
5. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included.
6. Evidence of GMP compliance of manufacturing, packing and testing sites in terms of GMP Approval Guidance in [SAHGPL-INSP-02 Guideline on Good Manufacturing Practice for Medicines](#). SAHPRA may or may not need to perform its own assessment of GMP compliance.
7. At the time of submission, it is likely that the manufacturing process will not have been finalised and that numerous changes will have to be made after the first emergency authorisation. These changes should be submitted as updates.

Regional requirements:

Specific labelling requirements:

1. At a minimum, basic South African labelling requirements should be met before authorisation. This can be revised as more data is provided.
2. Minimum requirements for the following to be in English or one official national language, depending on the end user:
 - i. Summary of product characteristics (information for health care provider) or Professional information.
 - ii. Patient information leaflet
 - iii. Primary and secondary labelling
 - iv. Any other instructional materials provided to the user.
 - v. A plan to ensure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When a novel product is authorised, the labelling should clearly indicate that that product is for public health emergency use only. Exemption of labelling could be considered, such as acceptance of labelling in English for products that are meant for professional use, such as vaccines. Additional region-specific clinical requirement/implications based on public health issues specific to the country should be met.

7. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces guideline, 2.64_Availability of medicines for use in a PHE_Aug21. It will be reviewed on this timeframe or as and when required.

8. AMENDMENT HISTORY

Table 3: Update History

Version	Date	Reason for amendment
Version 1	1 August 2021	New guideline for implementation
Version 2	1 June 2022	Update to include: timelines and requirements for small molecules; stakeholder comments and update to guideline numbering as per SAHPRA QMS
Version 3	1 August 2023	Update to be inline with current processes and guidelines. Inclusion of glossary as per SAHPRA QMS