South African Health Products
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INFORMATION AND GUIDANCE ON APPLICATION FOR REGISTRATION OF CANDIDATE COVID-19 VACCINE

COMMUNICATION TO INDUSTRY

This document is intended to provide guidance to applicants wishing to submit the application for registration of Covid-19 vaccines. This will be a "living document" and will be updated on a regular basis. It is important that applicants adhere to the prescribed requirements in order to avoid delays in the processing and evaluation of applications. This document should be read in conjunction with all other related SAHPRA's revised guidelines and templates, available from SAHPRA's website.

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1. BACKGROUND INFORMATION

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2. The rapid spread of this virus has resulted in the COVID-19 pandemic that has led to a dramatic loss of human life worldwide and presents an unprecedented challenge to public health, food systems and the world of work. The economic and social disruption caused by the pandemic is devastating. In an attempt to tackle this novel virus, many pharmaceutical companies are busy manufacturing and investigating possible candidate vaccines that can be used to limit the spread of Covid-19 virus.

SAHPRA in readiness for the possible registration of Covid-19 vaccines has adopted approaches, which seeks to expedite access to quality, safe and efficacious vaccine to the South African public.

SAHPRA routinely processes the applications for registration of various vaccines, and it may be naturally assumed that the evaluation process for Covid-19 candidate vaccines would follow the same pathway. However, due to the global impact of the Covid-19, the anticipated applications for registration of Covid-19 vaccines need to be expedited and some of the applications received may not fully comply with ZA-CTD requirements, this may present some challenges in terms of how to approach the assessments and what modalities are available to facilitate such assessments.

To that end, SAHPRA's intention with this document is to provide guidance to applicants who wish to submit the applications for registration of Covid-19 vaccine.

2. ABOUT THIS GUIDANCE DOCUMENT

This document provides guidance to vaccine manufacturers or applicants seeking regulatory approval of their vaccine/s that targets the SARS-CoV-2 virus. This document should be read along with other SAHPRA guidance documents concerning information and application requirements for the registration of medicines.

3. EXPEDITED REVIEW

SAHPRA in response to the current health challenges have adopted a priority review approach to applications that relates to Covid-19 management. As such all Covid-19 vaccine applications will undergo priority/expedited review. Note that expedited review includes allocation for review as priority. The review is performed expeditiously whilst not compromising on the quality and/or standard of review.

4. PRE-SUBMISSION MEETING

Applicants intending to make submissions for registration may have different challenges with respect to their applications and these may vary from complying with the administrative requirements in terms of the format extending to what data is available. SAHPRA therefore encourage applicants to schedule a pre-submission meeting with the agency to obtain guidance that is specific to the application concerned.

4.1 How to make a pre-submission appointment?

Contact SAHPRA on the following numbers 012 501 0369/ 0713022135/ 0791117087 and send an e-mail to Covid-vaccines@sahpra.org.za

4.2 What is required for the pre-submission discussion?

Prepare a presentation detailing your product, the technology used, the data available, specific transport/storage and labelling information. Provide information on testing in terms of Lot release and if the applicant intends to follow rolling review submission (see below). Share information on whether the vaccine has been or intends to be submitted to WHO, or other regulators for approval and the time frame for the submissions.

5. LOT RELEASE OF COVID-19 VACCINE BY SOUTH AFRICAN NATIONAL CONTROL LABORATORY

All vaccines registered in South Africa are subject to lot release by the South African National Control Laboratory as prescribed in Regulation 15 of the Medicines and Related Substances Act 101 of 1965 as amended. The extent of the evaluation will, at a minimum include a review of the lot summary protocol. The requirement for independent lot release testing will be based on the NRA/NCL risk assessment and whether reliance can be applied. Applicants must commit to the transfer of technology to the National Control Laboratory if required

6. ROLLING REVIEWS

SAHPRA will allow for the filing of submissions for rolling review. This will allow SAHPRA to review data from early development while later-stage clinical trials are taking place. This strategy will help to expedite the regulatory review process for candidate Covid-19 vaccines. Before filing an application for a rolling review, applicants are to have gathered a certain level of evidence on the safety, quality and efficacy of their vaccine. Applicants should consult with SAHPRA before filing an application for rolling review. To file an application for a rolling review, applicants should at least provide the following:

- Non-clinical and clinical trials phase 2 data that demonstrate promising evidence of safety and efficacy.
- Written confirmation that phase 3 trials have started and there are enough people enrolled to provide evidence of safety and efficacy within a reasonable amount of time (expected to be within 6 months from initial filing)
- Evidence which shows that manufacturing of the candidate vaccine is in compliance with good manufacturing practices (GMP) and that product quality and consistency are well controlled
- A submission plan giving the anticipated timelines for submitting the various components of the application. A preliminary submission plan should be included in the initial filing.

7. CONDITIONAL REGISTRATIONS

SAHPRA may on a risk-based analysis engage with the available data in terms of its acceptability with respect to quality, safety and efficacy. In an effort to avail vaccines for Covid-19 to the public expediently, it may be necessary to consider registration on the basis that the outstanding information be submitted within a prescribed timeline. The conditions will be reflected in a conditional registration.

8. EXPECTED MINIMUM SUBMISSION REQUIREMENTS:

The information presented in Module 1 should be as per SAHPRA 2.01_General Information Guideline and 2.24_Module 1 Guideline. The sub-section below highlights the additional requirements that should be provided when submitting the applications for registration of Covid-19 vaccines.

8.1 Module 1.3.1 and 1.3.2 (PI and PIL)

The format and content of the PI and PIL should be as per SAHPRA latest PI guideline (2.16_Guideline for Professional Information for Human medicines) and PIL guideline (2.14_Guideline for Patient Information Leaflet for Human medicines) and relevant regulations. Applicants may engage with the agency on possible global submission formats.

8.2 Module 1.7: LICENSING

To apply for the registration of COVID-19 vaccine in South Africa, applicant must have an establishment licence to manufacture, package/label, test, import, distribute or wholesale a health product. Applicants without such a licence must apply for one. During the application review process, applicants must

demonstrate compliance with good manufacturing practices (GMP). Depending on several criteria, including where the site is located, applicants can demonstrate GMP compliance through:

- SAHPRA on-site inspection
- A certificate of GMP compliance / an inspection report issued by other regulatory authorities with whom SAHPRA aligns itself with

8.3 Module 1.13: Risk Management Plan (RMP)

All applications for the registration of COVID-19 vaccines should be accompanied by the appropriate risk management plan. Applicants may use an international RMP that will be implemented to address uncertainties in the available data (e.g. elderly response and safety, pregnant women). However, SA specific issues should be considered (e.g. HIV, Tuberculosis and e.t.c).

9. QUALITY DATA REQUIREMENTS (MODULE 2.3.S and 3.2.S)

The candidate COVID-19 vaccines in which the applicant submit application for registration in South Africa must be manufactured under GMP conditions. SAHPRA will require sufficient data to demonstrate that the manufacturing process is well controlled and consistent (i.e manufacturing process validation report). This involves details on the manufacturing process for both the drug substance and drug product as outlined below:

9.1 Active substance information (Modules 2.3.S & 3.2.S)

S.1 General Information

S.2 Manufacture (including information on source of materials, viral seed lot/ cell banks)

S.3 Characterisation

S.4 Control of Drug Substance

S.5 Reference Standards or Materials

S.6 Container Closure System

S.7 Stability

9.2 Final product information (Modules 2.3.P & 3.2.P)

P.1 Description and Composition of the Drug Product

P.2 Pharmaceutical Development

P.3 Manufacture

P.4 Control of Excipients

P.5 Control of Drug Product

P.6 Reference Standards or Materials

P.7 Container Closure System

P.8 Stability (Stability and expiry parameters should indicate vaccine potency whenever possible and be from enough lots to be broadly representative of the product as a whole).

10. MODULE 4: NON-CLINICAL STUDIES (Minimum Non-clinical requirements)

It is noted that, some non-clinical data requirements and the methods used for non-clinical testing may be specific to the type of vaccine being developed. However, certain non-clinical data will be required for all vaccines. Thus, for the development of a COVID-19 vaccine, the non-clinical data package must at minimum include the following:

- Studies that assess the toxicology of the vaccine
- Proof of concept, including antibody and cell mediated immune responses and protection
- Assessment of the theoretical risk of vaccine-associated enhanced respiratory disease (VAERD)

10.1 Assessment of toxicity:

The development and authorization of COVID-19 vaccines must be supported by toxicology studies in relevant animal models. Key animal studies need to be conducted in compliance with the international standards of Good Laboratory Practices (GLP). These studies should address issues pertaining to the general toxicity, local tolerance and other relevant toxicity endpoints. If the candidate Covid-19 vaccine is to be used in pregnant women, then developmental and reproductive toxicity studies must be conducted to better understand the risks.

10.2 Proof of concept assessment:

The non-clinical tests or studies that characterise the ability of the vaccine to elicit a neutralizing immune response against the SARS-CoV-2 virus should be provided. These studies should be performed before proceeding to first-in-human clinical trials. In vivo studies in relevant animal models should evaluate the vaccine's ability to elicit neutralising immune responses using the same dosing regimen and formulation intended for humans (for instance, single-dose or repeat-dose, adjuvanted).

When demonstrating immune responsiveness, consideration should be given to the humoral and cellular immune responses. Non-clinical data should also demonstrate the capacity of the vaccine to protect from SARS-CoV-2 using an appropriate animal challenge model.

10.3 Vaccine-associated enhanced respiratory disease (VAERD)

It is noted that, vaccines developed against some respiratory viruses, including other corona viruses, have been associated with VAERD. This phenomenon occurs when people who are vaccinated and then exposed to the virus develop a worse form of the disease.

At this stage it is acknowledged that, the potential for Candidate vaccines to induce VAERD is theoretical. However, it will be important for the non-clinical vaccine development program to address this theoretical risk. Viral challenge studies intended to demonstrate the capacity of the vaccine to protect against SARS-CoV-2 can provide a suitable model for assessing VAERD. This is the case if studies also include assessments that address enhanced disease such as T-helper cell type 1 and T-helper cell type 2 responsiveness, lung histopathology and immune cell infiltrates

11. MODULE 5: CLINICAL STUDIES

11.1 Assessment of safety data

To assess the safety of a vaccine, SAHPRA requires:

- an adequate number of vaccine recipients
- monitoring for a sufficiently long time

This requirement is needed to detect common and expected adverse reactions, as well as events that are less common but potentially more severe. The safety database for a COVID-19 vaccine should have at least 3,000 study participants who have been vaccinated with the dosing regimen intended for authorization. The data should come from phase 3 randomized placebo-controlled trials that allow for the collection of adverse events in the vaccinated (>3,000 participants) vs. the placebo (>3,000 participants) group. This enables the detection of more common adverse events, which are in the range of at least 1 in 1,000 doses given. The common adverse reactions include: redness and pain at the injection site, sore arm, fever, headaches and malaise. These adverse reactions should be monitored closely for at least 7 days to adequately characterise the frequency of those events.

The uncommon, rare or adverse events that may take longer to manifest should also be monitored closely. The median duration of safety follow-up to support authorisation should be at least 2 to 3 months after all doses in the schedule have been given. Most adverse events are expected to occur within 2 months of vaccination. Given the previous history with vaccines for other respiratory viruses, which have resulted in enhanced disease in people who were vaccinated and subsequently exposed to the virus (VAERD), this risk should be closely monitored for any candidate Covid-19 vaccines. The stability of the immune response following vaccination should also be monitored. A period of 6 months may be required to assess for the potential for VAERD, if data from earlier phase clinical trials suggest that longer-term follow up is needed prior to authorization.

Following authorisation, clinical trial participants should be monitored for as long as feasible. The ideal time is at least 1 to 2 years. This length of time is needed to assess the duration of protection and the potential for enhanced disease. SAHPRA may issue terms and conditions requiring the sponsor to provide longer-term clinical follow-up and post-marketing safety data on adverse events of special interest, such as VAERD, following authorisation.

Internationally, regulators are in agreement on the safety assessment criteria. These criteria include defining: Adverse events of special interest for close monitoring during clinical trials and the size of the safety databases required. SAHPRA will use these criteria when reviewing data submitted during the rolling review.

11.2 Assessing efficacy

SAHPRA requires robust evidence of the vaccine's ability to prevent COVID-19 infection from well-conducted phase 3 clinical trials in humans. Ideally, SAHPRA would like to see as high an efficacy as possible. However, since the virus that causes COVID-19 infection is new, it is not yet known how effective the Covid-a19 vaccines will be. A target threshold of at least 50% efficacy may be considered reasonable for COVID-19 vaccines depending on the risk/benefit ratio.

The clinical trials for Covid-19 vaccine should demonstrate that the vaccine reduces the incidence of a symptomatic SARS-CoV-2 infection by at least 50% in people who are vaccinated, compared to a control group of people who don't receive the vaccine. Enough people should be enrolled so that the trial is sufficiently powered to exclude an efficacy result below 30%. The trial must have a sufficient number of participants with severe COVID-19 infection in the control group to show that the vaccine is effective. This efficacy estimate is

expected regardless of when the data are analysed, including any pre-specified early looks at the data while the clinical trial is under way. SAHPRA may issue terms and conditions requiring the applicant to provide additional data confirming the duration of protection or other pertinent efficacy endpoints.
SAHPRA will review the safety and efficacy of each vaccine on a case-by-case basis. SAHPRA will also consider the availability of other vaccines and treatments, public health needs, the status of the pandemic and the epidemiology of the disease in South Africa.

When comparing a potential vaccine with a COVID-19 vaccine that has already met the efficacy criteria outlined above and been approved by a stringent regulatory authority, a non-inferiority trial design may be used with a non-inferiority margin of less than 10%. This means that the vaccine may show no more than 10% lower efficacy compared to the approved vaccine (lower bound of the confidence interval around the primary relative efficacy point estimate is >-10%).

Critical efficacy results will be summarised in the labelling for the vaccine along with the dosing regimen and the patient populations used to demonstrate efficacy. Efficacy should be shown using the dosing regimen intended for authorisation. The public health officials use this information to develop vaccination programs.

12. APPENDICES (Module 2.3.A & 3.2.R)

A.1 Facilities and Equipment
A.2 Adventitious Agents Safety Evaluation
A.3 Excipients

13. REGIONAL INFORMATION (Module 3.2.R)

14. DISCLAIMER:

The information presented in this document provide a minimum guidance only. As such, SAHPRA reserves the right to ask for additional information before application for registration.