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**SAHPRA reflection document on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2**

**COMMUNICATION TO INDUSTRY**

This document is intended to provide guidance to applicants who already have a SAHPRA registered SARS-CoV-2 vaccine for use in South Africa but wish to submit an application for registration of a variant. 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 guidelines and Covid-19 related guidance documents, available from SAHPRA’s website. This document is adapted, with minor modifications, from EMA reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2.

**Document History**

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## B. DEFINITION OF TERMS

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<b>Parent strain:</b>	The SARS-CoV-2 strain from which the parent vaccine was derived.
<b>Parent vaccine:</b>	The original registered vaccines against SARS-CoV-2.
<b>Variant strain:</b>	The SARS-CoV-2 strain(s) from which the variant vaccine are derived.
<b>Variant vaccine:</b>	Vaccines that are intended to protect against one or more SARS-CoV-2 variants that have emerged.
<b>Vaccine antigen:</b>	The active ingredient in a vaccine against which the immune response is raised. It may be a live attenuated preparation of bacteria, viruses or parasites; inactivated (killed) whole organisms; crude cellular fractions or purified active biological ingredients, including recombinant proteins (i.e., those derived from recombinant DNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; synthetic active biological ingredients; polynucleotides (such as plasmid DNA vaccines); or living vectored cells expressing specific heterologous immunogens. It may also be a combination of the antigens or immunogens listed above.

## 1. INTRODUCTION AND SCOPE

This reflection paper is intended to provide guidance to applicants who already have a SAHPRA registered SARS-CoV-2 vaccine for use in South Africa but wish to submit an application for registration of a variant vaccine that is intended to provide protection against variant strain(s) of SARS-CoV-2. This document outlines the quality, nonclinical and clinical data that would be required to support approval of a variant vaccine, whether monovalent or multivalent.

**N.B:** The requirements stipulated in this document apply only when both of the following criteria are met:

- The parent vaccine has been registered for use in South Africa;
- Except for the difference in the SARS-CoV-2 antigen(s) to be presented to the human immune system following vaccination. The manufacturing process & controls including the manufacturing and testing facilities for the variant vaccine should remain the same to those of the parent vaccine.

There must be a justification for the relevance of the new vaccine antigen(s) included in the variant vaccine intended for use in the South Africa, based on genomic epidemiology of lineages currently circulating. Guidance should come from a global forum to support SARS-CoV-2 lineage selection for vaccines (e.g. by the WHO), as soon as this is established.

The concepts expressed in this document may be subject to further revision as additional evidence is generated and based on the evolving situation.

### 1.1 LEGAL BASIS

Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended and the relevant Regulations.

## 2. DISCUSSION (QUALITY, SAFETY AND EFFICACY)

### 2.1. Quality - Module 3

The requirements for regulatory approval or registration of a variant vaccine will largely depend on the technology underlying the parent vaccine construct (e.g. mRNA vaccine, viral vector, purified protein produced by recombinant DNA technology, inactivated viral vaccine). Thus, the updated Module 3 should address the following:

- There should be an update of the starting materials (e.g. DNA template, virus seed);
- Reliance on the parent vaccine control strategy should be possible with some adaptations to accommodate the new strain-specific requirements;
- Testing of critical quality attributes (e.g. purity, content) should be performed to demonstrate compliance with the registered specifications. Any deviation from or change to the registered specifications (e.g. identity, potency) would require adequate scientific and/or clinical justification;
- Manufacturing consistency should be demonstrated (e.g. by active substance and finished product characterisation, in-process control results, batch analyses);
- In principle, the registered shelf-life conditions/period would be applicable. However, confirmation of the suitability of the active substance and finished product registered shelf-life needs to be demonstrated (e.g. by available real-time stability data, predictive stability models, early stability data under accelerated storage conditions).
- Confirmatory real-time stability data need to be provided post-approval.

If the variant vaccine is to be multivalent, there may be further considerations to assure the quality of the individual active substances at release and up to the end of shelf-life. These considerations would primarily relate to the manufacturing and control of the finished product (e.g. the control of total level of impurities and the validity of the analytical procedures to test vaccines containing different variant strains). The specifications would need to be adapted due to the additional variants. Pharmaceutical development studies and a change to the finished product control strategy in terms of formulation would be required. The requirements for batch analysis data and process validation data are also considered to be higher when moving from a monovalent parent vaccine to a multivalent variant vaccine.

## 2.2. Nonclinical - Module 4

There is no requirement to conduct any further in-vitro or in-vivo nonclinical testing to support the development of variant vaccines. If Holder of Certificate of Registration (HCR) choose to conduct such studies they will be viewed as supportive of the clinical data.

## 2.3. Clinical – Module 5

### 2.3.1. Efficacy of the variant vaccine

The efficacy of a monovalent or a multivalent variant vaccine against the variant strain(s) may be inferred from provision of immunogenicity data (neutralizing antibody response data):

- After primary vaccination with the variant vaccine; and
- After a single dose of the variant vaccine when given to subjects who previously received primary vaccination with the parent vaccine.

The subsections that follow outline recommendations for clinical trials in which the variant vaccine is given for primary vaccination or following primary vaccination with the parent vaccine.

In the following instances:

- The variant vaccine is intended to replace the parent vaccine as the sole marketed vaccine; and/or
  - The variant vaccine will include the parent strain, i.e. it will consist of one or more variant strains plus the parent strain;
- and
- The parent strain is still in circulation in South Africa.

There would be an additional requirement to demonstrate that the variant vaccine elicits an immune response (neutralizing antibody) to the parent strain after primary vaccination that is non-inferior to that elicited by the parent vaccine against the parent strain after primary vaccination.

### **SARS-CoV-2-naïve subjects (i.e. unvaccinated and with no evidence of prior infection)**

It is recommended that, if possible, a trial should be conducted in a SARS-Cov-2-naïve population.

#### ***In the absence of an immune correlate of protection (ICP)***

It is recommended that unvaccinated subjects with no history of COVID-19 disease are randomised to receive primary vaccination with the parent vaccine or with the variant vaccine using the dose schedule approved for the parent vaccine. Trial population may be confined to adults who are not in priority groups for vaccination. The timing of the post-vaccination blood samples for the primary analysis should be based on what is known from data generated with the parent vaccine.

The primary analysis should be conducted in the subset with no serological evidence of prior infection with SARS-CoV-2 found in baseline samples. To immune-bridge from the efficacy previously documented with the parent vaccine to the variant vaccine, neutralizing antibody titres should be measured against the corresponding vaccine strain(s), i.e. in the parent vaccine group against the parent strain and in the variant group against the variant strain(s). The following criteria should be met when comparing the immune response elicited by the variant vaccine against the variant strain to the immune response elicited by the parent vaccine against the parent strain:

- The lower bound of the 95% confidence interval around the difference in seroconversion rates for the (or each) variant vs. the parent strain should not exceed -10%. Seroconversion should be defined as at least a 4-fold increase in titre from pre-vaccination to post-vaccination; since the primary analysis will be in seronegative subjects, a nominal value should be applied to the pre-vaccination samples to calculate the seroconversion rate.
- The lower bound of the 95% confidence interval around the Geometric Mean titre (GMT) ratio should be at least 0.67.

#### **Among the secondary endpoints:**

- The immune response elicited by the parent vaccine against the variant strain(s) and by the variant vaccine against the parent strain should be determined;
- For vaccines with 2-dose primary schedules, the immune responses after the first dose should be compared along the same lines as for the primary analysis.

The reverse cumulative distribution curves should be provided.

If the epidemiology of SARS-CoV-2 indicates that it is no longer in the best interest of subjects to receive primary vaccination with the parent vaccine, an alternative approach to immune bridge from the efficacy previously documented with the parent vaccine to the variant vaccine could be a comparison between immune responses elicited by primary vaccination with the variant vaccine against the variant strain and prior data on the immune response elicited by primary vaccination with the parent vaccine against the parent strain. The primary analysis would then proceed as described above.

To support this alternative approach:

- The assay conditions applied at the time of generating the prior data should not have changed and/or the post-primary samples should be re-assayed for neutralizing antibody against the parent strain;
- The historical data should be obtained from subjects that are matched to the group enrolled into the prospective trial to receive the variant vaccine at least based on age, gender and presence of important underlying comorbidities;
- Residual sera should be available from the matched historical controls so that the immune response elicited by parent vaccine against the variant strain(s) can be determined.

***In the presence of an immune correlate of protection (ICP)***

If there is an ICP which SAHPRA agrees is applicable to the vaccine construct in question, SARS-CoV-2-naïve subjects should receive primary vaccination with the variant vaccine in respect of the dose schedule as per the PI and PIL for the parent vaccine. The percentage of subjects that achieve titres at or above the ICP (i.e. the seroprotection rate) against the variant strain(s) should be determined. The precision of the point estimate for the seroprotection rate should be calculated and expressed with its 95% confidence interval. The lower bound of the confidence interval for concluding that the seroprotection rate is acceptable, should be agreed with SAHPRA or other regulatory authorities that SAHPRA aligns itself with.



## **Subjects previously vaccinated against SARS-CoV-2:**

***In the absence of an immune correlate of protection (ICP)*** The efficacy of the variant vaccine against the variant strain(s) when administered to subjects who received primary vaccination with the parent vaccine may be inferred by conducting a trial in subjects with fully documented prior vaccination with the parent vaccine.

It is recommended that trial subjects should have participated in previous trials with the parent vaccine so that their post-primary neutralizing antibody titres are available. If this is not possible, the post-primary neutralizing antibody titres used in the primary analysis should be drawn from a population that is matched at least based on age, gender and presence of important underlying comorbidities to the population enrolled into the prospective trial to receive a dose of variant vaccine.

The interval between completion of the primary series with the parent vaccine and administration of a dose of the variant vaccine and the window allowed around the interval require consideration and justification.

For the purposes of obtaining the data required to conduct the primary analysis, it would suffice that all subjects enrolled into the trial receive a dose of the variant vaccine.

The primary analysis should be conducted in subjects with no serological evidence of SARS-CoV-2 infection. It should compare the neutralizing antibody GMT elicited by a dose of variant vaccine against the variant strain(s) with the post-primary neutralizing antibody GMT elicited by the parent vaccine against the parent strain. The lower bound of the 95% confidence interval around the GMT ratio should be at least 0.67.

A secondary analysis should compare the neutralizing antibody GMT elicited by the variant vaccine against the variant strain(s) with the post-primary neutralizing antibody GMT elicited by the parent vaccine against the variant strain(s). Other secondary analyses should compare the seroconversion rates elicited by parent and variant vaccines against each of the parent and variant strains.

It is optional that this trial involves randomisation of subjects who completed primary vaccination with the parent vaccine to receive a dose of parent vaccine or variant vaccine. If this design is adopted, the primary analysis to support use of the variant vaccine in subjects who received primary vaccination with the parent vaccine would proceed exactly as outlined above.

In addition to the primary analysis, this optional trial design would allow for a secondary analysis that compares the neutralizing antibody titres against the variant strain(s) elicited by one dose of variant or parent vaccine in subjects who received primary vaccination with parent vaccine. This comparison is of interest since it is possible that the immune response to a further dose of parent vaccine could give substantially higher neutralizing antibody titres against the variant strain(s) compared to the titres against the variant strain(s) obtained after primary vaccination.

If the GMT against a variant strain after a dose of variant vaccine is superior to the GMT against the variant strain after a dose of parent vaccine (lower bound of the 95% confidence interval around the GMT ratio >1) the result would give support to the potential value of administering the variant vaccine rather than the parent vaccine to subjects who received primary vaccination with parent vaccine.

***In the presence of an immune correlate of protection (ICP)***

If there is an ICP which SAHPRA agrees is applicable to the vaccine construct in question, all subjects may receive a dose of variant vaccine as described above. The primary analysis should be based on the sero-protection rate elicited by the variant vaccine against the variant strain(s). The precision of the point estimate for the sero-protection rate should be calculated and expressed with its 95% confidence interval. The lower bound of the confidence interval for concluding that the sero-protection rate is acceptable, should be agreed with SAHPRA.

**2.3.2. Safety of the variant vaccine**

Unless there were safety concerns for the parent vaccine and/or safety concerns emerge from trials with the variant vaccine, the safety data collected during immunogenicity trials with the variant vaccine as outlined above should suffice for approval.

**3. RISK MANAGEMENT PLAN**

All applications for the registration of vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 should be accompanied by the updated risk management plan that addresses how breakthrough infections will be detected, investigated and reported.

**4. 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 can be considered.

**5. REFERENCES:**

EMA (2021). Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 EMA/117973/2021.

**6. AMENDMENT HISTORY**

<b>Version</b>	<b>Date</b>	<b>Reason for amendment</b>