Medicines Control Authority of Zimbabwe

GUIDANCE ON SUBMISSION OF COVID-19 VACCINE APPLICATIONS FOR EMERGENCY USE AUTHORISATION AND REGISTRATION

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1. BACKGROUND INFORMATION

Coronavirus disease (Covid-19), caused by the coronavirus, SARS- CoV-2, was declared a public health emergency of global concern by the World Health Organisation (WHO) on 30 January 2020. The infectious viral disease rapidly spread across the globe leading to dramatic loss of human life. It disrupted public health systems, food systems, tourism, travel, trade, work, and educational systems. Whilst temporary public interventions such as lockdowns, social distancing, hand-sanitization, among others, managed to slow down the rate of transmission, more permanent and cost-efficient ways of containment and stopping the epidemic are being sought. To that end partners in the global health community, led by the WHO, collaborating with health research institutions, provided guidance to pharmaceutical industry, for production and testing of candidate Covid-19 diagnostics, vaccines, and therapeutics

MCAZ, in anticipation of submission of applications for Emergency Use Authorisation (EUA), Expedited Review Process (ERP) and Registration of Covid-19 vaccines, developed this guideline for applicants wishing to provide safe, efficacious, good quality vaccines to the Zimbabwean public. MCAZ has an established regulatory process for vaccines and other medicines. However, in view of the public health emergency posed by the ongoing Covid-19 pandemic, expeditious assessments will be conducted to ensure that the public has timely access to Covid-19 vaccines that have a positive benefit-risk balance.

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 WHO vaccines guidance (https://www.who.int/biologicals/BS2287_Clinical_guidelines_final_LINE_NOs_20_July_2016.pdf) and MCAZ CTD Guidance (https://www.mcaz.co.zw/index.php/downloads/file/74-mcaz-ctd-guidelines).

3. PRE-SUBMISSION ENQUIRIES

MCAZ encourages applicants intending to submit Emergency Use Authorisation (EUA) applications and those intending to submit applications for expedited review for full registration of Covid-19 vaccines to contact the Authority to obtain guidance which is specific to the application concerned. Pre-submission meetings help clarify administrative requirements in terms of the format, acceptability of minimum data available and any product-specific challenges faced by applicants. Prospective applicants may contact MCAZ by sending an email to covid@mcaz.co.zw

4. EMERGENCY USE AUTHORISATION

MCAZ may on a risk-based analysis of the quality, safety and efficacy data, place the vaccine under emergency use authorization (EUA). EUA is time-limited authorization for a vaccine that has accumulated considerable safety, quality and efficacy data but is still undergoing further clinical studies and process optimization. The authorization is **valid for a period of 12 months** provided it maintains a positive benefit-risk ratio in terms safety and efficacy or when the **public health emergency ends**, whichever is shorter. Please note that EUA may be issued with conditions attached with respect to the distribution imposed by MCAZ and the Ministry of Health and Child Care. The following are the minimum requirements that any manufacturer of Covid-19 vaccines should meet to enable the authority to grant EUA

i. Manufacturing facilities, processes and controls

- Evidence must be submitted that the facilities conform to current Good Manufacturing Practices (cGMP) for the production of vaccines (see section 8.2)
- Information of cell banks and virus banks (information on virus strain), identification of all animal-derived materials used for cell culture and virus growth, and excipients.
- Specifications for active substance and finished product

- Stability of the finished product (including proposed storage conditions in the intended container closure system)

ii. Phase 1 and 2 clinical trials data

All efficacy and does-related data accumulated from phase 1 and 2 studies conducted with the vaccine.

iii. Phase 3 Clinical Trials data (see also section 10)

These data should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile, including: adverse events; cases of severe Covid-19 disease among study subjects; and cases of Covid-19 occurring during the timeframe when adaptive and memory immune responses to the vaccine would be responsible for a protective effect.

v. Labelling

- Package insert
- Carton and vial labels

vi) Target Timelines for Emergency Use Authorisation:

The **Target Timelines** for completion of emergence use authorization (EUA) review and feedback to the applicant and to the Ministry of Health and Child Care in **48 hours.** The timelines apply after MCAZ and the applicant have held a pre-submission meeting, agreed on the data package to be submitted and the data package specified above, has been received by MCAZ.

5. EXPEDITED REVIEW FOR FULL REGISTRATION

This priority pathway is for Covid-19 vaccines that have a full safety, quality and efficacy data (including Phases I, II and III clinical trial data) package data that has been reviewed by the National Regulatory Authority in the country of origin and has received full marketing authorization, over and above any prior EUA. The pathway is also available for Covid-19 vaccines that have received full WHO Prequalification and full registration by WHO-listed Regulatory Authorities, maturity level 3. Please note that once full registration is attained the vaccine will have a wider and less restricted distribution in public and private sector than EUA approved vaccines.

5.1 MODULE 1 REQUIREMENTS

The information presented in Module 1 should be as per MCAZ CTD Guidance (https://www.mcaz.co.zw/index.php/downloads/file/74-mcaz-ctd-guidelines). The sub-section below highlights the additional requirements that should be provided when submitting the applications for registration of Covid-19 vaccines.

5.1.1 Package insert, carton and vial labels)

5.1.2 Module 1: Manufacturing Licence and GMP Certification

To apply for the registration of Covid-19 vaccine in Zimbabwe, the applicant must have an establishment licence to manufacture, package/label, test, import, distribute or wholesale a health product. During the application review process, applicants must demonstrate compliance with current Good Manufacturing Practices (cGMP).

Depending on several criteria, including where the site is located, applicants can demonstrate GMP compliance through:

- MCAZ remote/ on-site inspection

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

Further details on GMP requirements are detailed in the MCAZ GMP Guidance document obtainable on the mcaz website https://www.mcaz.co.zw and can also be requested on gmp@mcaz.co.zw

5.1.3 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. However, Zimbabwe specific issues should be considered (e.g. HIV, tuberculosis, malaria etc.).

5.2. QUALITY DATA REQUIREMENTS (CTD MODULE 3)

5.2.1 Active Substance information (Modules 3.2.S)

S.1 General Information

S.2 Manufacture
- history and qualification of cell banks, history and qualification of virus banks, and identification of all animal derived materials used for cell culture and virus growth
- batch records
- manufacturing process validation

S.3 Characterisation

S.4 Control of Active Substance
- quality-control release tests
- specifications

S.5 Reference Standards or Materials

S.6 Container Closure System

S.7 Stability

Post marketing commitments to provide full shelf life data may be acceptable with appropriate justification.

5.2.2 Finished product information (Modules 3.2.P)

P.1 Description and Composition of the Biological Product

P.2 Pharmaceutical Development

P.3 Manufacture
- manufacturing process validation
- media fill study data

P.4 Control of Excipients

P.5 Control of Biological Product
- quality-control release tests
- specifications

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.
- Post marketing commitments to provide full shelf-life data may be acceptable with appropriate justification.

5.4.3 APPENDICES

Adventitious Agents Safety Evaluation (Module 3.2.A)

5.4.4 REGIONAL INFORMATION (Module 3.2.R)
Batch production records

5.3. NON-CLINICAL DATA REQUIREMENTS (CTD MODULE 4)
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)

5.3.1 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.

5.3.2 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.

5.3.3 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 SARSCoV-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

5.4 CLINICAL DATA REQUIREMENTS (CTD MODULE 5)

5.4.1 Assessment of safety data
To assess the safety of a vaccine, MCAZ 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 (at least 3,000 participants) vs. the placebo (at least 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. 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. 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. MCAZ 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.

5.4.2 Assessing efficacy

MCAZ requires robust evidence of the vaccine's ability to prevent Covid-19 infection from well-conducted phase 3 clinical trials in humans. 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 regardless of when the data are analysed, including any pre-specified early looks at the data while the clinical trial is under way.

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%).

5.5 TIMELINES FOR EXPEDITED REVIEW

As agreed by stakeholders that developed the Zimbabwe Covid-19 National Deployment and Vaccination Strategy the **target timeline** for the issue MCAZ decision is **5 days.** In order to achieve the timelines the following facilitative conditions must be considered:

- Holding a pre-submission meeting / enquiry and agreeing on data and format for submission

- The vaccine is fully registered in country origin and other well-regulated markets
- Or the vaccine is prequalified by WHO
- Applicants arranging for submission of product evaluation reports and GMP inspection reports from the NRA in the country of origin, WHO Prequalification and other WHO Listed Agencies

5.6 VALIDITY OF FULLY REGISTERED COVID-19 VACCINES

Unlike EUA Covid-19 vaccines, fully registered Covid-19 vaccines get a registration certificate that is not limited to the public health emergency or 12 months. Fully registered products can be retained on the MCAZ register year after year, as long as the applicant updates the registration through variations, period safety updates reports (PSUR) and pays annual retention fees

6. LOT RELEASE OF COVID-19 VACCINE BY MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Lot Release System applies to all imported prior to distribution whether they come as unregistered Section 75 products, Emergency Use Authorisation or after full Registration.

The extent of the evaluation will be based on review of lot summary protocol as a minimum. The Authority applies reliance on testing of vaccines by recognizing lot release certificates from the National Regulatory Agency/ National Control Laboratory (NRA/NCL) of the country where the vaccine is manufactured.

The following documents will be required with the shipment of vaccines:

i. Summary Lot Protocol for the batch or lot being imported to Zimbabwe
ii. Lot release certificate by the competent national regulatory / quality control laboratory in the country of production
iii. Samples, labels and package inserts

It is advised that the summary lot protocol, labels and package inserts are sent to the Authority before shipment of the vaccine to allow review of the documentation prior to arrival of the vaccine for speedy release of the vaccine.

References

Zimbabwe COVID-19 National Deployment and Vaccination Strategy
WHO Emergency Use Listing of Vaccines for Public Health Emergencies, December 2020
WHO vaccines guidance
(https://www.who.int/biologicals/BS2287_Clinical_guidelines_final_LINE_NOs_20_July_2016.pdf)
South African Products Heallth Regulatory. Authority Information and Guidance for registration of candidate Covid-19 vaccines