Food and Drug Authority of Ethiopia (EFDA)

Guideline for Emergency Use Authorization of COVID-19 Vaccine

Addis Ababa, Ethiopia

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Abbreviation

cGMP	Current Good Manufacturing Practice
CoA	Certificate of Analysis
DART	Developmental and Reproductive Toxicology
DP	Drug Product
DS	Drug Substance
EPSA	Ethiopian Pharmaceutical Supply Agency
ERA	Enhanced Respiratory Disease
EUA	Emergency Use Authorization
HVAC	Heating, Ventilation and Air Conditioning
NGO	Non-Governmental Organization
PPQ	Process performance Qualification
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organization

Introduction

COVID-19 pandemic presents an extraordinary challenge to global health. Currently there are no registered vaccines to prevent COVID-19. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates using different technologies including RNA, DNA, protein, and viral vectored vaccines.

Ethiopian Food and Drug Authority (EFDA) plays a critical role in protecting the public of Ethiopia from unsafe and infective medicinal products used in the health care including those intended for use for emerging infectious diseases (such as COVID-19 pandemic). The Authority is committed to providing timely guidance to support response efforts to this COVID-19 pandemic.

According to article 20(1) of Food and Medicine Administration proclamation number 1112/2019, any medicine shall not be manufactured, imported, exported, and distributed for use with out registration and marketing authorization. However, sub-article 5 of this article indicated that EFDA may in compelling circumstances, grant a permit for the importation or use of unregistered medicine.

As a part of this mandate, the Authority is, therefore, developed this Emergency Use Authorization (EUA) guideline in response to COVID-19 pandemic. The EUA is a risk-based procedure for describing the requirement for assessing and authorizing newly developed vaccines for use primarily during public health emergencies.

This guideline describes EFDA's current requirements regarding the data and information needed to support the issuance of an Emergency Use Authorization (EUA) for an investigational vaccine to prevent COVID-19, including chemistry, manufacturing, and controls information (CMC); nonclinical data and information; and clinical data and information, as well as administrative and regulatory information.

Scope

This guideline is applicable for COVID-19 vaccine application submitted to EFDA for emergency use authorization.

1. General Consideration

These requirements are specific to COVID-19 vaccines, which are complex biological products that are intended to be administered to millions of healthy individuals potentially following interim results from one or mor clinical trial. In this scenario issuance of EUA would require a determination by EFDA that the vaccine's benefits out way its risks based on data from at least one well designed phase III clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.

It is the Authority's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to collect placebo-controlled data in any ongoing trials for as long as feasible and would also work towards submission of application for normal medicine registration as soon as possible.

The Authority's recommendations regarding the safety and effectiveness data and information outlined below are essential to ensure that clinical development of a COVID-19 vaccine has progressed far enough that issuance of an EUA for the vaccine would not interfere with the ability of an ongoing Phase III trial to demonstrate effectiveness of the vaccine to support applicant and to continue safety assessments, including investigating the potential for vaccine-associated enhanced respiratory disease (ERD).

The ability of a sponsor to accrue this information about a COVID-19 vaccine is critical to ongoing assessment of its benefits and risks. The Authority notes that there would need to be an adequate plan for safety data collection among individuals vaccinated under an EUA.

2. Requirements for information and data for COVID-19 Vaccine Application for an EUA

Requirements for Information and Data for COVID-19 Vaccine Application for an EUA

The Authority require well-organized summary of the available scientific evidence regarding the product's quality, safety and effectiveness, risks (including an adverse event profile) and benefits, and any adequate, approved, available alternatives to the product.

The Authority requires that the following information should be submitted in a request for an EUA for a COVID-19 vaccine, as applicable.

2.1. Administrative Information

The following information should be submitted in a request for an EUA for a COVID-19 vaccine:

1. Official cover letter of the applicant
2. Evidence of the product's approval status in other countries including whether the vaccine is approved in a foreign country for the intended purpose and information on the use of the vaccine by either a foreign country or an international organization (e.g., WHO).
3. Application form (as per annex I of this guidance document)
4. Copy of valid Good Manufacturing Practice(GMP) certificate of the manufacturing site(s) of the proposed COVID-19 vaccine form EFDA or WHO listed regulatory authority and/or SRA.

2.2. Product information

A description of the product and its intended use (e.g., identification of the serious or life-threatening disease or condition) for which the product may be effective; where, when, and how the product is anticipated to be used; and/or the population(s) for which the product may be used). The submitted application should address the following details:

- Proposed use(s) under EUA
- Proposed dosing regimen(s) and method(s) of administration for use under EUA
- Rationale for dosing regimen
- Information to support the use, dosing and administration of the vaccine in the following populations, as applicable:
    - ✓ Adults
    - ✓ Pediatric age groups
    - ✓ Other specific populations (e.g., geriatric individuals, pregnant or lactating individuals, immunodeficient individuals);

5. Available safety and effectiveness information for the product;
6. A discussion of risks and benefits, including available information concerning the threat posed by COVID-19 and how that threat would be addressed by the product

under the proposed use under the EUA. The discussion of the risks and benefits in the EUA request should include an assessment of the risks and benefits for the proposed use under the EUA, including a discussion of the following:

- Any steps taken to mitigate risk or optimize benefit
- Any recommended restrictions to ensure safe use
- Any situations under which the product should not be used (i.e., contraindications)
- Important information that should be considered prior to use of the EUA product;

7. The need for the product, including identification of any approved alternative product(s), if any and their availability and adequacy for the proposed use;
8. Product information including proposed package insert; Fact Sheets to be furnished to health care professionals or authorized vaccine administrators, as well as those to be furnished to recipients of the product.
9. Product labelling (secondary and primary) should include the product name strength, proposed storage and shelf life of the product).

2.3. Chemistry, Manufacturing, and Controls

The submission for emergency use authorization of vaccines should follow the CTD format. In the CTD dossier, should indicate in the sections for which no information is available at the time of the initial submission “data or information not available”, “study ongoing” or “not applicable” as the case may be.

Information on chemistry, manufacturing, and controls; a list of each site where the product is manufactured including relevant information about each site and the current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements should be provided.

Characterization of cell banks

Applicant should submit full characterization of cell banks according to the Authority’s Guideline for Registration of Vaccines and WHO Technical Report Series (TRS) 978, and any subsequent updates.

Characterization of master and working seed organism(s)

Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS should be provided

2.3.1. Manufacturing

Name, address, and responsibilities of each manufacturer involved, including contract manufacturers for production and quality control with their specific unit block should be provided.

Evidence should be provided that all DS and DP manufacturing sites, including testing sites, are adequately qualified/validated to ensure that the equipment/process meets all predetermined specifications/intended purposes and the production process is controlled and operates with quality oversight consistent with cGMP requirements. If more than one manufacturing facility is used to produce DS and DP, data should be provided to support the consistency of vaccine quality between manufacturing sites.

A detailed description of the manufacturing process and controls should be provided. Such data shall be sufficient to support drug substance (DS) and drug product (DP) manufacturing to ensure the quality and consistency of the vaccine product that is produced.

Any manufacturing and process control data that will not be available at the time of submission of an EUA request should be discussed and commitment letter for submitting such additional data should be provided.

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 should be provided.

If deemed appropriate, data on clinical batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

if full characterization is not possible at the time of submission, adequate justification must be submitted as to why not, and a plan must be presented to address the data gaps.

Validation of potency tests and other critical assays: If novel test methods have been developed, full description of the test development and qualification must be presented.

2.3.2. Control of Drug Substance and Drug Product

Product data as described below should be provided to support determination regarding the safety and effectiveness of the vaccine:

a. Documentation establishing that critical source materials used in manufacturing is adequately controlled, including history and qualification of cell banks and virus banks, identification of all animal-derived materials used for cell culture and virus growth, and DP excipients.
b. An evaluation and mitigation plan for potential adventitious agents.
c. Data to demonstrate that the DS is sufficiently characterized in order to identify and understand the critical properties that impact performance and stability.
d. A detailed description of the quality control system for all stages of manufacturing, including the testing program for in-process/intermediate product quality and DS and DP quality for release.
e. Analytical methods and qualification/validation data for all quality-indicating assays. Validation data for assays used to evaluate critical vaccine qualities such as purity, identity, and potency are expected.
f. The DS and DP development history and manufacturing changes introduced in Phase 1, 2, 3 and EUA lots, including analytical comparability of DS lots with these changes. Quality release data and supplementary characterization tests to assess the impact of the changes on the DS quality attributes should be provided.
g. A tabular listing of all clinical studies and DP lot numbers used in each study including DS lot genealogy, manufacturing processes used, and the manufacturing site, as well as the Certificates of Analysis (CoAs) for all clinical lots used in clinical studies and information on any lots that were initiated but not accepted for release.
h. Appropriate quality specifications with the justification should be established for all DP lots used under EUA and testing results for the final vaccine lots.
i. A stability plan including safety and stability-indicating tests and available stability data from all developmental, clinical, and commercial lots. If available, accelerated stability data must be included.
j. Aseptic-process information, including the appropriate validation studies.

k. A description of sterile filtration and sterilization processes, as well as validation studies. Dehydrogenation of container-closure systems, if applicable, should also be provided.

l. Storage conditions, including the container-closure integrity, should be validated and this information should be provided.

2.3.3. Process changes

If changes in the manufacturing process are introduce before the assessment is finalized or after the listing, these must be reported to the Authority.

2.4. Safety and Effectiveness Information

The EUA request should include the following safety and effectiveness information, which will inform determination regarding the product's benefit-risk profile:

2.4.1. Bioassays for assessment of clinical endpoints

The diagnostic bioassays that were used to assess study endpoints of clinical studies supportive of the EUA request should be included. The procedures and validation reports for the final assay methods, and a list of all laboratories where the clinical samples have been tested, should be described in support EUA of the vaccine.

2.4.2. Nonclinical

The Authority require non clinical data presentation in CTD format as per structure indicated in module 4 of guideline for registration of medicines of the Authority. Non clinical data should include

a) A list of the nonclinical studies conducted to support vaccine effectiveness and safety (e.g., characterization of markers associated with enhanced disease, biodistribution, shedding, and attenuation) should be provided, along with the timelines for study completion and submission of final study reports for all ongoing nonclinical studies as applicable.

b) A final study report, if available, for a Developmental and Reproductive Toxicology (DART) study, or the timeline for study completion and submission of the final study report, should be provided in order to inform potential emergency use of the vaccine in pregnant women.

2.4.3. Clinical

The presentation clinical data submitted in need of EAU of COVID-19 vaccine should follow module 5 of guidelines for registration of medicines of the Authority and should consider the following points.

a) Only vaccines that have undergone phase IIb and phase III studies and have received authorization from a reference NRA should be submitted for consideration for an EUA for COVID-19 vaccine based on an interim analysis of a clinical endpoint from these phases' efficacy study. Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include not only meeting the prespecified success criteria for the study's primary efficacy endpoint (i.e. a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%) but also additional safety and effectiveness data as described below. The timing of interim analyses planned for a Phase 3 study would thus ideally be aligned with the ability of the analyses to meet these criteria.

b) An EUA request for a COVID-19 vaccine should include all safety data accumulated from phase I and II studies conducted with the vaccine, with focus on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study subjects. The phase I and II data are intended to complement the available data from safety follow-up from ongoing Phase III studies.

c) Data from Phase IIb and Phase III studies 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 (rather than innate) and memory immune responses to the vaccine would be responsible for a protective effect. In addition, To be able to make a favorable benefit-risk determination that would

support an EUA without Phase IIb and phase III data that include the following, which will help the Agency to assess the safety of the vaccine:

- ✓ Local and systemic solicited adverse reactions collected for the protocol-defined duration of follow-up in an adequate number of subjects to characterize reactogenicity in each protocol-defined age cohort participating in the trial;
- ✓ The general safety evaluation report should include
  - adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring at least 14 days after the last dose is administered.
  - subgroup analyses of safety and efficacy endpoints stratified by prior infection status at trial enrolment.
  - Data on sufficient cases of severe COVID-19 among trial participants to support low risk for Enhanced Disease.
- ✓ Sufficient cases of severe COVID-19 among study subjects to support low risk for vaccine-induced ERD (a total of 5 or more severe COVID-19 cases in the placebo group would generally be sufficient to assess whether the severe COVID-19 case split between vaccine vs. placebo groups supports a favorable benefit-risk profile or conversely raises a concern about ERD).

d) Vaccine safety and COVID-19 outcomes in individuals with prior COVID-19 infection, who might have been asymptomatic, are important to examine because screening for prior infection is unlikely to occur prior to administration of COVID-19 vaccines under EUA. An EUA request should therefore include subgroup analyses of safety and efficacy endpoints stratified by prior infection status at study entry, as determined by pre-vaccination serology or medical history.

e) The EUA request should include a plan for active follow-up for safety (including deaths and hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

3. Considerations for Continuing Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

The Authority does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for stopping an ongoing clinical trial.

An EUA request should include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

Reference:

1. Emergency Use Authorization for Vaccines to Prevent COVID-19, Guidance for Industry, U.S FDA, October 2020.
2. Food and Medicines Administration Proclamation, Proclamation No. 1112/2019, Federal Negarit Gazette of the Federal Democratic Republic of Ethiopia.
3. Emergency Use Listing Procedure, Version 8 (draft), World Health Organization, January 2020
4. Guideline for Registration of Vaccines, Ethiopian Food and Drug Authority (former EFMHACA), Feb, 2018, Addis Ababa, Ethiopia

Annex I: Application Form for EUA

Food and Drug Authority of Ethiopia P.O. Box 5681, Addis Ababa, Ethiopia

A. Product Detail

Proprietary name (trade name)			
Approved generic name (s) (use INN if any)			
Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc.)			
Strength(s) per dosage unit			
Dosage form			
Route of administration			
Shelf life (months)			
Storage condition			
Visual description			
Description of container closure			
Packaging and pack size			
Therapeutic category			
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per 5ml, etc.)** ** Add/delete as many rows and columns as needed.	Composition	Strength	Function
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the			

restrictions on sale or distribution, e.g., withdrawn from the market, etc.)	

B. Details of Applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	

C. Details on active pharmaceutical(s) ingredient(s)

Name of manufacturer	
Street number and postal address	
Telephone number	
Fax number	
E-mail	
Name of the drug substance	
Retest period/Shelf Life	

D. Details on local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone number	
Fax number	
E-mail	
Contact person in a company	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANTCOMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true and reflects the total information available.

Signature_____

Name _____

Position in company (print or type) _____

Date: _____