Risk Management Plan Guideline for COVID-19 Vaccines

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Foreword

Ethiopia has successfully managed to lead a well-coordinated response plan including vaccination of COVID-19 vaccines to stop the spread of COVID-19 and address the human and economic impacts on the society. The Ethiopian Food and Drug Authority (FDA) has been working to ensure the availability of quality assured COVID-19 vaccines through providing Emergency Use Authorization (EUA) and monitoring of vaccine safety and conducting Adverse Events Following Immunization (AEFI) surveillances. EFDA has been issuing EUA for COVID 19 vaccine manufacturers as per the requirement of EFDA Guideline for EUA of COVID 19 vaccines.

To promote proper use of vaccine and maintain an appropriate risk-benefit balance, Market Authorization Holders (MAHs) and/or applicants should identify the Safety Specification of vaccine a Risk Minimization Plan and develop a Pharmacovigilance Plan based on the identified Safety Specification. When necessary, they should also develop a plan for post-marketing survey/study on efficacy. The Market Authorization holders (MAHs) and applicants for marketing authorization should then prepare RMP by consolidating these plans.

Hence, to further expedite, standardize and support MAHs in the preparation and implementation of RMP, this Risk Management Plan Guideline for COVID-19 Vaccines prepared and issued by the authority. It is believed that this guideline will strengthen the national effort to ensure the availability of quality assured COVID-19 vaccine and strengthen monitoring of vaccine safety. It will undoubtedly support all stakeholders involved in fulfilling regulatory requirements in the use of COVID19 vaccines.

I would like to take this opportunity to express the authority's appreciation to all individuals and respective organizations for successfully developing this guideline. I would also like to encourage MAHs to strictly follow and implement this guideline; and to send their comments to EFDA at: contactefda@efda.gov.et or P. O. Box 5681, Addis Ababa, Ethiopia.

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Acknowledgement

The Ethiopian Food and Drug Authority (EFDA) would like to express its heart felt appreciations to the experts and their respective institutions who were involved in the development of this guideline; *Risk Management Plan (RMP) Guideline for COVID-19 Vaccines* will contribute to the national effort to protect the safety of our population from the adverse effects of COVID19 vaccines. Accordingly, our gratitude is extended to the following experts from EFDA and other organizations who immensely contributed in the preparation of this guideline:

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1. Introduction

1.1. Background

On 30 January 2020, the World Health Organization (WHO) declared a public health emergency of international concern due to the COVID-19 outbreak, which corresponds to the highest level of the WHO grading of emergencies. On 11 March 2020, the Organization's assessment determined that COVID-19 could be characterized as a pandemic.

Coronaviruses are a large family of viruses that can cause diseases in animals and humans. In humans, several coronaviruses are known to cause respiratory infections with symptoms that range from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Severe Cute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), discovered more recently, causes coronavirus disease (COVID-19). SARS-CoV-2 was unknown until the outbreak in Wuhan (China) in December 2019. It has now caused a pandemic that affects most countries around the world. On March 13, 2020, the Federal Ministry of Health of Ethiopia has confirmed a coronavirus disease (COVID-19) case in Addis Ababa, Ethiopia.

One essential strategy to control this pandemic is the rapid development of safe and effective vaccines. Unprecedented efforts are being made to develop large numbers of vaccines simultaneously, in a short time. Global equitable access to vaccines, particularly for protecting health care workers and those most-at-risk is one of the key strategies to mitigate the public health and economic impact of the pandemic.

It is known that vaccines, like other pharmaceutical products, undergo extensive testing and review for safety, immunogenicity, and efficacy in the laboratory, in animals, and in three phases of clinical trials in human subjects before licensure. It is anticipated that, following regulatory authority approval of COVID-19 vaccines, their use will be highly widespread. This can lead to a high volume of reports of suspected adverse events and other safety related issues. Thus, prompt identification and assessment of new information on the benefit-risk balance of these vaccines, timely communication, and strong transparency will be key for protecting public health and ensuring public trust in the vaccines and the regulatory system. To ensure the safety of

vaccine, it is important to consider the ways to manage the risk of vaccines on a consistent basis from the development phase to the post-marketing phase.

The Ethiopian FDA has been working to ensure the availability of quality assured COVID-19 vaccine through providing Emergency Use Authorization (EUA) and monitoring of vaccine safety and conducting Adverse Events Following Immunization (AEFI) surveillance. EFDA is currently issuing emergency use authorization for COVID 19 vaccines manufacturers as per the requirement of EFDA Guideline for Emergency Use Authorization of COVID 19 vaccine. On vaccine safety monitoring, both passive and active surveillance of AEFI has been conducted by EFDA and continuously work with MAHs on post approval safety monitory activities.

To promote proper use of vaccine and maintain an appropriate risk-benefit balance, Market Authorization Holders (MAHs) and/or applicants should identify the Safety Specification of vaccine a Risk Minimization Plan and develop a Pharmacovigilance Plan based on the identified Safety Specification. When necessary, they should also develop a plan for post-marketing survey/study on efficacy. The Market Authorization holders (MAHs) and applicants for marketing authorization should then prepare RMP by consolidating these plans.

1.2. Rationale

The continuous assessment of benefits and risks, as well as effective communication among stakeholders, is the key for protecting and promoting public health, and for strengthening public trust in vaccines and the authorities that oversee the vaccination process.

During the current COVID-19 pandemic, the private sector has played a critical role in the rapid development of vaccines. Furthermore, primary responsibility for vaccine safety and efficacy monitoring rests with use authorization holders. The national regulatory authorities (NRAs) have to make decisions based on limited safety and efficacy data at the time of authorization. Thus, constant monitoring is necessary as soon as the vaccine is authorized, in order to detect and assess possible safety problems associated with the approved vaccines.

Due to the shortness of time to develop COVID-19 and the need to ultimately deploy vaccines present challenges for guaranteeing their safety. Lessons learnt and best practices from past pandemics should be used to guide current procedures for the safety of COVID-19 vaccines.

As with other vaccines, more information about the immunogenicity, effectiveness, and safety of COVID-19 vaccines will only become available during their use in the field. Hence, the risk management plan for COVID-19 vaccines will be an evolving document and should be amended when new significant information, such as a change in the profile of adverse events, results from safety studies, changes in benefit-risk balance, becomes available.

It is required that the plan for pharmacovigilance activities is developed at the time of review for approval and in the post-marketing phase based on the safety specification into which "important identified risks," "important potential risks," and "important missing information" are consolidated, and risk minimization strategies need to be prepared and implemented

2. Scope

This document is applicable to all COVID-19 vaccines that received Emergency Use Authorization (EUA) by the authority and for those COVID-19 vaccines that will get EUA to be used in Ethiopia.

3. Objectives

3.1. General objective

This guideline establishes requirements to guide Use/Market Authorization Holders in the development of the RMPs for COVID-19 vaccines for safety monitoring.

3.2. Specific objectives

This guideline:

- Is intended to present a basic concept for development of the RMP that contains a risk minimization plan to reduce the risk of COVID 19 vaccines.
- Outlines the requirements to be considered by COVID-19 vaccine MAHs when preparing PSURs for submission to regulatory authorities.
- To outline safety specifications for safety monitoring and risk minimization.
- To describe basic requirements on development and implementation of Pharmacovigilance plan with respect to covid-19 vaccine

- To address necessary safety measures that will be taken based on a benefit-risk evaluation performed through post-marketing phases.

4. Components of the RMP

This section lists and describes requirements the components to be considered by market authorization holders during preparation of the RMP for COVID 19 vaccines for authorization.

4.1. Product(s) overview

The current and accurate administrative information on the RMP and an overview of the product(s) should be provided in relation to the ongoing application as it is anticipated to appear in the marketing authorization and includes:

- Active substance(s);
- Pharmacotherapeutic group(s) (ATC code);
- About marketing authorization holder in relation to the submitted RMPs
- Medicinal product(s) to which this RMP refers.
- Brief description of the product focusing on the following points:
  - Chemical class.
  - Summary of mode of action.
  - Important information about its composition (e.g. origin of active substance of biological,
  - Relevant adjutants or residues for vaccines
  - Indications (Proposed indication by applicant for initial application or approved one in case of post authorization)
  - Dosage (Only summarized Information)
  - Pharmaceutical forms and strengths.
  - Approval status in country of origin or other countries with relevant evidences

4.2. Safety Specifications

4.2.1. Epidemiology of the disease and the target population groups

- This section should present updated information on COVID-19 while recognizing uncertainties including specific information from the country or region where the vaccine will be used.

4.2.2. Characteristics of the vaccine

- Characteristics of the vaccine should include such as;
  - Production and formulation platform; degradation of the active substance or antigen; and potential related impacts on safety (for example, mRNA, protein subunit, or vaccine vector).
  - Presence of an adjuvant in line with the associated risk that might affect the vaccine recipient's health.
  - Risks that may be specific to COVID-19 vaccination, such as exacerbated respiratory disease.

4.2.3. Reactogenicity

- If the vaccine group presented greater reactogenicity than the control group during clinical trials (pain, redness, swelling, induration at the injection site, and systemic symptoms like fever, myalgia, or headache), the RMP should include a discussion of this risk, how it may influence the safety profile and necessary risk minimization measures.
- Review of information on the following should be considered: population groups in conditions of vulnerability, such as older people or patients with chronic inflammatory diseases; and differences in reactogenicity between the first and second or subsequent vaccine doses.
- Aspects of vaccine formulation and preparation should be discussed in the analysis of reactogenicity when an increase in associated adverse reactions is suspected. One example is local reactions or abscesses that may be related to effects on the sterility of the product when reconstituting the vaccine.

4.2.4. Preclinical information about specifications

- This section may be available even if the presentation of the RMP has not been completed and in such case, future revision (updated) RMP should include new information from non-clinical studies.

4.2.5. Information from clinical trials:

- General information on the protocols of the trials in progress should be presented in the RMP as part of the application for approval. This includes the number of subjects exposed as of the application date and whether any problems related to vaccine safety have been observed.
- Additional clinical trial data generated post-approval (including for different/additional strains) should be included, as applicable.

4.2.6. Post-authorization experience:

- If the vaccine has been authorized in other countries, the RMP should include any reference information about post-authorization exposures.
- RMP updates post-approval should include data on the use with marketed formulations to put the total safety database in perspective.

4.2.7. Identified and potential risks:

- In applications made through the progressive review mechanism, as is the case with the emergency use authorization (EUA) for COVID-19 vaccines, it is recognized that only limited information from the first stages of the presentation of the RMP will be available while clinical trials are ongoing. A more complete safety specification in the RMP will only be available after preliminary clinical trials results are available (i.e. at the time of the efficacy endpoint analysis) with further data being generated from the same trials post approval.
- It is essential that each decision to classify a (potential) risk of a vaccine is evidence-based and adequately presented and justified in the RMP. Applicants should include a well justified list of important potential risks for which evidence exists and not a comprehensive list of all theoretical risks for vaccines in general. Such theoretical risks could be included in the list of adverse events of special interest (AESI) to be followed up via routine and additional pharmacovigilance activities.

4.2.8. Missing information:

- Based on current evidence and concerns, the following missing information should be added in the RMP (unless clinical trials data - in these populations - is considered comprehensive):
    - Use in pregnancy and while breast-feeding.

- Safety in patients with severe co-morbidities (e.g. Use in immunocompromised subjects; Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune disorders or inflammatory disorders);
- Safety in children and elders (when part of approved indication);
- Long-term safety;
- Interaction with other vaccines and drugs in general.

4.3. Pharmacovigilance plan

- This section should include the planning in the context of the pandemic;
  - Signal detection and review or analysis of individual case safety reports (ICSRs).
  - Data sources for signal detection should be specified; MAHs should perform signal detection using every means available to them. This would include MAHs' own databases, other publicly available or private databases, screening of literature etc.
  - Analysis of adverse events of special interest (AESI) associated with COVID-19; it is advisable to consider the priority list when performing the analysis. The reporting pattern for a vaccination campaign during a pandemic is likely to differ qualitatively from other reporting, which need to be taken into account when performing the analysis;
  - Specific follow-up questionnaire(s) should also be considered by applicants to obtain additional structured information for reports of safety concerns in the RMP and suspected adverse events of special interest (AESI), for example, for monitoring pregnant women who have been vaccinated. It is expected that a summary and analysis of safety considerations will be included in the PSURs.
  - Observations about the background of the following elements: Administration of the vaccine in the pediatric population, vaccination in people with COVID-19, and people that received another vaccine at the same time.

- PSURs including the preliminary and final results of safety-related considerations from the studies in progress. They should also discuss whether there were any early signals during the clinical trials.
- Strategies for vaccine traceability: For example, the use of stickers or cards, or electronic methods such as bar codes or QR codes, with the vaccine name and lot numbers.

- Regarding Spontaneous reporting of suspected safety concerns the following points should be considered:
  - Upon authorization, COVID-19 vaccines will be subject to additional monitoring, which aims at enhancing the reporting of suspected adverse reactions.
  - ICSRs should contain precise information on demographics, vaccine brand, batch number, vaccination and reaction dates, outcome, concomitant drugs etc.
  - The submission of ICSRs with AESIs, or fatal or life-threatening events as immediately as possible

Additional activities:

- As priority, carry out monitoring of the clinical trials in progress.
- Review the safety information reported in the post-authorization studies if there are any in progress.
- Review the safety information reported in medical records, for example, of pregnant women, children, or immunocompromised people who have received the vaccine.
- And also others activities may be considered as applicable.

4.4. Risk minimization measures

- It is agreed that in principle routine risk minimization in the form of the product information could be sufficient to minimize the risks of the product. Hence, MAHs should provide the product information such as;
  - Summary of product characteristics (SmPC), leaflets, complete and standardized labeling of COVI-19 vaccines.
  - Specific strategies should be included for complete and accurate communication about vaccine handling, use and prevention of errors related to vaccines.

- The RMP should also include training and communication strategies to inform health professionals and patients or guardians about the type of vaccine, the risks, and how to prevent or minimize risks.
- In the risk minimization measures, how to manage known events, whether they are potentially serious (for example, anaphylaxis) or non-serious but frequent should be adequately described.

4.5. Periodic safety update reports (PSURs)

- Market Authorization Holders should submit PSURs documents by summarizing and consolidating the updated global information on the safety of COVID-19 vaccines.
  - Market authorization holders should submit simplified PSURs to Ethiopian-FDA at least semi-annually. The PSURs will include information on suspected adverse reactions reported, including adverse events of special interest (AESI), and data of the doses administered, among others.
  - PSURs can be re-evaluated for the need for and periodicity of the presentation based on the evidence requesting and assessing periodic safety reports available during each vaccine's post-authorization period.
- The content of the simplified PSURs should include, at a minimum:
  - Interval and cumulative number of spontaneous reports, overall, by age groups, and in special populations (for example, pregnant women).
  - Interval and cumulative number of ICSRs.
  - Consolidated ICSRs by country or geographic region, and by causal classification
  - Exposure data stratified by country and age groups if any
  - Changes in the reference safety information during the report interval or period.
  - Signals that are ongoing and under evaluation during the report interval or period.
  - Reports of AESI, with relevant numbers and cases, including analyses of observed or expected cases.
  - Reports of fatal cases, with relevant numbers and cases, including the respective analyses.
  - Considerations related to risks and benefits.

4.6. RMP Update submission and Evaluation

4.6.1. Update of Risk Management Plan

- The RMP should be updated depending on the post-marketing situations, and the contents of the RMP should be revised to maintain an appropriate benefit-risk balance of the vaccine. The update of the Risk Management Plan should be performed depending on the situations of individual pharmacovigilance activities and risk minimizing activities included in the Plan.
- The time of reviewing/updating is:
    - When new or significant change in existing additional Pharmacovigilance or risk minimization activity
    - When the content of the Safety Specification needs to be changed; for example, at the time when new safety concerns have been identified after marketing;
    - At a pre-determined milestone in the Risk Management Plan;
    - At the time of periodic reporting ;
    - At the time of renewal of market Authorization.
    - Others as applicable

4.6.2. Evaluation of Risk Management Plan

- The implementation status and the results of individual pharmacovigilance activities, surveys/trials on efficacy, and risk minimization activities should be evaluated appropriately at their respective milestones according to the RMP. At the same time, the benefit-risk balance of the vaccine should also be evaluated and considered based on the information obtained from individual activities conducted according to the RMP.
- The evaluation results of the RMP should be reported at the time of submitting periodic safety update reports (PSURs). If there are changes in the plan, MAHs should preliminarily consult with the EFDA, as necessary. The EFDA checks the contents of the report, and if it considers that some measures should be taken, the authority will give directions to MAHs.

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