



Working paper

**Roadmap for introduction and roll-out of Janssen VAC52150 (Ad26.ZEBOV,
MVA-BN®-Filo)
Ebola Virus Disease vaccine in African countries**

Regulation and Prequalification Department

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1. Background and Introduction

Ebola Virus Disease (EVD) is caused by one of five species of Ebola viruses, namely, Zaire, Sudan, Tai Forest, Bundibugyo and Reston, with the most fatal species being the Zaire virus (REF). Over the years, there have been several outbreaks in Zaire, Democratic Republic of Congo, Uganda, Sudan, Gabon and Congo. Epidemics have demonstrated the need for a WHO emergency response covering different angles from development and policy recommendations through SAGE and regulatory issues. The regulatory preparedness activities for vaccines include facilitating joint review through the African Vaccine Regulatory Forum (AVAREF) platform of clinical trials of vaccines, development of norms and standards and development of the emergency use assessment and listing procedure (EUAL) for candidate vaccines for use in the context of a public health emergency, as an extraordinary procedure to expedite the availability of vaccines needed in public health emergency situations.

The EUAL process is intended to generate WHO recommendations that provide advice to procurement agencies and Member States (MS) on the acceptability of a specific vaccine in the context of a public health emergency. These recommendations are based on: 1) a minimum set of available quality, safety, and efficacy data; 2) a plan for further evaluation of safety and effectiveness; and 3) a plan for subsequent prequalification (PQ) of the product.

In order to facilitate potential submissions as well as the assessment process under the EUAL procedure, WHO decided to accept “rolling submissions” when the manufacturers can submit data sets as they become available. Janssen Vaccines and Prevention B. V. (Janssen) filed an EUAL application on their two-dose regimen (Ad26.ZEBOV, MVA-BN®-Filo vaccine) in a rolling submission in 2015 and 2016. The latest update to EUAL has been submitted in December 2018.

In March 2019, Janssen announced its intention to submit an application for marketing authorisation (MAA) to the European Medicines Agency, followed by WHO prequalification and requested WHO to collaborate with EMA and with concerned African regulators to facilitate authorization based on reliance principles in the event of a positive scientific opinion from EMA.

Ebola 2018/2019 crisis

At present, the Democratic Republic of the Congo (DRC) is grappling with the world’s second largest Ebola epidemic on record, with more than 2000 lives lost and more than 3000 confirmed infections since the outbreak was declared on 1 August 2018. The outbreak is occurring in North Kivu, South Kivu and Ituri provinces. Two studies have been planned to evaluate the vaccine regimen in health care workers in the DRC and in Mbarara, Uganda. An international consortium proposed a large-scale study in the DRC aiming to deliver the vaccine regimen and to evaluate field effectiveness during the ongoing outbreak. This study commenced in the DRC in Goma on 14 November 2019. Janssen has committed to provide up to 500,000 vaccine regimens in support of this trial.

Current status

Janssen submitted two MAAs to EMA for each vaccine of the two-dose regimen on 6 November 2019. The review will happen under accelerated timelines (EMA granted accelerated review in Sept 2019). The vaccine regimen includes Ad26.ZEBOV as the first dose, which is based on Janssen's AdVac® technology, and MVA-BN-Filo as the second dose, which is based on Bavarian Nordic's MVA-BN® technology and is administered approximately eight weeks later. The MAAs are supported by data from Phases 1, 2 and 3 clinical studies evaluating the safety and immunogenicity of the vaccine regimen in adults and children, preclinical studies, and immunobridging analyses. To date, more than 6,500 volunteers across the U.S., Europe and Africa have participated in over 10 clinical studies of the Janssen vaccine.

The vaccine will be reviewed under the European Medicines Agency's (EMA) centralized procedure. Due to the public health interest of this MAA, in the context of this procedure, Janssen has requested the involvement of WHO with a view towards possible prequalification on the basis of the EMA evaluation and has asked WHO to facilitate authorization of the vaccine in several African countries based on reliance principles.

WHO, through AVAREF has sought the involvement of both relevant African NRAs in the EMA review process and WHO PQ to expedite the prequalification of this vaccine and in-country registrations.

2. Purpose

The main purpose of this document is to describe how WHO, working across multiple departments and the three levels of the organization, will coordinate collaboration with EMA, the applicant (Janssen) and with the Member States National Regulatory Authorities (NRAs) to facilitate the introduction and roll-out of Janssen Ebola Vaccine in Africa; to describe the roles and responsibilities of different stakeholders – WHO (HQ and AFRO) and EMA, as well as using the AVAREF as a platform for the development of recommendations of the candidate vaccine for its registration or authorization for use in the target countries.

3. Operating Principles

It is expected that, once the European Commission (EC) has issued a positive decision, WHO would be able to pursue the prequalification (following the abbreviated procedure). WHO proposes the below described process to facilitate the prequalification of the Janssen EVD vaccine and the registration or authorization for use in several countries at risk in the African region:

1) Prequalification process:

The vaccine PQ will follow the abbreviated procedure established following approval by Stringent regulatory authorities. As the PQ programme will be actively involved in the EMA assessment process, the expectation is that the programmatic suitability for African countries (e.g., stability, presentation,

labelling, cold chain considerations, etc.) will be considered during the review process and the PQ of the vaccine will be issued shortly after EC decision.

2) Facilitating the decision-making on the acceptance of the vaccine in African countries:

AVAREF has been asked to nominate two countries interested in participating in the EMA Centralized Procedure (CP). These experts will have access to the dossiers and expert deliberations during the EMA assessment process.

Based on the EMA timelines, WHO, in parallel, will facilitate a process for assisting NRAs in their decision-making process, with a wider group of African countries (Francophone and Anglophone) through the AVAREF platform which are not directly part of the EMA process.

The WHO facilitated process may include some of the regulatory experts from target countries involved with previous trials. For logistical and visa reasons, these discussions will take place in Africa or in Geneva. Timings and locations will be scheduled in accordance with EMA timelines- WHO's priority in this context is to expedite the availability of a safe, effective and quality assured vaccine, facilitate a regulatory decision by the participating countries and ease deployment of the vaccine with a high public health need.

In country registrations/authorizations for use in target African countries

- a) "Simultaneous route" - direct in-country registration based on the country experts' involvement in the EMA CP
- No sequential steps;
 - Countries commit to take a regulatory decision within agreed timelines (30 working days¹) after the EC grants a positive opinion and shares the assessment report with the participating countries. Signed agreements need to be established;
 - Full engagement of NRA experts in the process;
 - Janssen has committed to provide the same dossier as is submitted to EMA, in parallel to filing with EMA. Country specific requirements will be provided on NRAs' requests.
- b) Sequential route: WHO facilitated registration procedure following EMA approval led process.
- NRAs commit to take a regulatory decision for the product in maximum 90 days after EC decision through a signed agreement;

¹ Consultations with participating countries are necessary to confirm the minimum timelines

- Janssen commits to submit the same dossier as submitted to EMA in accordance with national regulations, in parallel to filing with EMA². Country specific requirements will be provided on NRAs' requests.
- The participating African regulators will be actively involved in the regulatory process ensuring that the countries will take their own regulatory decision.

The AVAREF Secretariat will have an important role in identifying the experts from the target countries to participate in the EMA CP, as well as in the WHO facilitated process and to facilitate subsequent registration/authorization for use of the vaccine in the target countries.

4. Roles and responsibilities

In the context of this roadmap, different parties will collaborate very closely, but each would have their roles and responsibilities specified as follows:

WHO HQ will:

- a) Provide overall coordination of different parties' efforts;
- b) Collaborate with EMA, and with AVAREF Secretariat (WHO/AFRO) to nominate WHO and country experts;
- c) Facilitate the participation of the nominated experts in the EMA CP (either in-person or remotely);
- d) Implement the WHO facilitated process through face-to-face meeting and existing electronic platform to support in-country registration/authorization for use of EVD vaccine in target countries;
- e) Finalize the prequalification process once the positive decision is issued by the EC.

WHO AFRO will:

- a) Collaborate with WHO HQ and the NRAs of target countries to identify the country experts for participation in the EMA review and (if considered useful);
- b) Collaborate with WHO HQ in the implementation of the WHO facilitated process
- c) Facilitate registration for use of the vaccine in the target countries.

European Medicines Agency will:

- a) Involve WHO and country NRA experts in EMA CP for Janssen EVD Vaccine;
- b) Support the registration/authorization process by sharing the assessment report once it is available with the participating countries and provide expert advice when and if it is needed.

² *timing of the submission of specific documents to be agreed with NRAs as it depends on an availability of the information

Janssen will:

- a) Ensure that formal application forms including Country Specific Information are submitted to the countries, with the unredacted dossier.

5. Process and timelines

WHO will support the target countries to accelerate the regulatory decision making process for the EVD vaccine. To achieve these expectations the following steps and respective timelines should be considered to be maintained:

	Activity	Timelines	Responsible	Comments
1.	<p>Collaboration with AVAREF Secretariat (WHO/AFRO):</p> <ul style="list-style-type: none"> ▪ to confirm the priority/interested African countries ▪ to seek nomination of the experts to participate in the EMA review as observers 		RHT & AFRO	<p>Rwanda and Uganda agreed to participate in the EMA led process.</p> <p>Both countries will be invited to the WHO facilitated process F2F meeting as resource persons</p>
2	<p>WHO and AVAREF identify participating countries for WHO facilitated process</p> <ul style="list-style-type: none"> ▪ To seek nomination of the NRAs from the countries below in the WHO facilitated process: <ul style="list-style-type: none"> - Angola - Burundi - Central African Republic - Congo, Brazzaville - DRC - Tanzania - South Sudan - Zambia - Mali - Ivory Coast - Nigeria 	<p>ASAP, to ensure timely discussions regarding countries specific requirements, ideally prior to the dossier submission</p>		

	<ul style="list-style-type: none"> - Senegal - Sudan - Gabon - Ghana - Uganda - Rwanda - Liberia, - Guinea, - Sierra Leone 			
3.	Nominated countries' experts for EMA CP and WHO facilitated process to sign the confidentiality agreements and declarations of interests (DOIs)	Not later than 2 months prior to the planned MAA submission	RHT & AFRO	Confidentiality agreements and DOIs should be signed prior to EMA CP starts For WHO: should be signed prior to receiving dossier
4	Agree on the date(s) of the WHO facilitated process with participating African countries (Francophone and Anglophone).	Timings and locations will be scheduled and communicated relative to the review timetable confirmed by EMA	RHT & AFRO	Janssen is expected to participate partially in the meeting (open sessions)
5	Janssen to submit the applications in the countries		Janssen	Janssen should submit the same dossier as was submitted to EMA and meet country-specific requirements
6	Facilitating WHO process with target countries		RHT, AFRO, EMA	
7	In-country registrations /authorization for use	Timeline to be committed through signed agreements. Proposed timing 30 working days	RHT, AFRO, concerned NRAs	Timeline to be committed through signed agreements
8	Post-market surveillance (PMS) activities (introduction and post-introduction monitoring) initiated and maintained in the countries	To be defined as part of the review. To be introduced following the registration/authorization for use	SAV, AFRO, concerned NRAs	To be handled via Reliance process

Annex 1: AMRH Medical Products Regulatory Systems Strengthening and Harmonization Governance Framework

