



Revised working paper following AVAREF meeting February 2019

**Roadmap for introduction and roll-out of Merck rVSV-ZEBOV
Ebola Virus Disease vaccine in African countries**

Regulation of Medicines and Other Health Technologies

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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 specie being the Zaire virus (REF). Over the years, there have been several outbreaks in Zaire, Democratic Republic of Congo, Uganda, Sudan, Gabon and Congo. The last major outbreak occurred in 2014-2015 in countries of West Africa subregion, mainly in Liberia, Guinea and Sierra Leone and to a lesser extent in Nigeria and Mali. This was the largest EVD outbreak to date, and a total of 28,646 Ebola cases were reported in the three most affected countries (Guinea, Liberia and Sierra Leone), with 11,323 deaths. A significant proportion of survivors have both short- and long-term sequelae.

At the time of the outbreak, there was no effective vaccine against the virus and all the vaccine candidates were in very early phases of clinical development. This epidemic has 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 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 generates 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 has exceptionally decided to accept “rolling on submissions” when the manufacturers can submit data sets as they become available. Merck & Co., Inc. submitted data on their rVSVΔG-ZEBOV-GP (V920) vaccine (a Live Attenuated Ebola Vaccine). This vaccine underwent clinical trials (CT) phase I and II in 2014-2015 in Europe and Africa and was consequently used in Guinea in 2015 during vaccination campaigns while going through CT phase III.

The SAGE working group on EVD Vaccines and Vaccination, held on 14–15 March 2017, recommended that the use of the rVSVΔG-ZEBOV-GP candidate vaccine should be deployed under the Expanded Access framework. The recommended delivery strategy is ring vaccination adapted to the social and geographic conditions of the outbreak and affected areas. Pre-emptive vaccination of health care workers was not recommended at that time as evidence was insufficient to support this. In addition, at present, available evidence is insufficient to recommend pre-emptive mass immunization of the general population given partial knowledge on the vaccine immunogenicity, efficacy and safety.

The October 2018 SAGE Meeting reiterated that “should an EVD outbreak due to the Zaire strain occur before a candidate vaccine is licensed, rVSV-ZEBOV vaccine should be promptly deployed within the expanded access framework, with informed consent and in compliance with good clinical practice”¹.

The applicant has chosen to seek regulatory approvals from USFDA and a European centralized marketing authorization as part of its regulatory strategy.

The European Medicines Agency (EMA) has accepted the vaccine under its PRIME (PRiority Medicines) programme, that offers enhanced interactions and early dialogue with developers of promising medicines to optimize development plans and speed up evaluation so that these medicines can reach patients earlier. The vaccine will be reviewed under EMA’s accelerated review provisions.

Given that the vaccine is most likely to be used in Africa, WHO 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.

It should also be noted that US FDA has accepted a “rolling submission” of the Merck EVD vaccine in November 2018.

The African Vaccine Regulatory Forum (AVAREF), initially created by WHO in 2006 as an informal capacity building platform aimed at improving the regulatory oversight of interventional clinical trials being conducted in Africa, has demonstrated its value in strengthening regulatory and ethics reviews, promoting harmonized standards and approaches and accelerating the review of vaccines of high public health value – most recently in relation to vaccines against EVD:

- 15-16 December 2014, Geneva, Switzerland: Joint Review of GSK ChAd3 Phase II Vaccine trial by Ghana, Nigeria, Mali and Cameroon with support from Health Canada, the European Medicines Agency, Swiss medic and the US Food and Drug Administration;
- 3 to 4 February 2015, Arusha, United Republic of Tanzania: Joint Review of the Janssen EVD Zaire Vaccine Clinical Trials Application by Ghana, Kenya, the United Republic of Tanzania and Uganda, with support from Health Canada, the European Medicines Agency, and the US Food and Drug Administration;
- 8 to 10 April 2015, Accra, Ghana: Assisted Review of the Janssen EVD Zaire Vaccine Clinical Trials Application by Sierra Leone with support from Ghana FDA, Health Canada, NAFDAC, the European Medicines Agency, and the US Food and Drug Administration;
- 8-10 June 2015 Accra, Ghana: Joint Review of the Janssen EVD Zaire Vaccine Phase 2 Clinical Trials Application by Uganda, Kenya, Burkina Faso and Côte d’Ivoire with support from Ghana FDA, Health Canada, the European Medicines Agency, and the US Food and Drug Administration, UK MHRA.

Merck has approached the AVAREF Secretariat with a request to consider the feasibility of using the AVAREF platform for facilitating the accelerated registration of the product in the target countries.

¹ <http://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf?ua=1>

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, US FDA, the applicant (Merck) and with the Member States National Regulatory Authorities (NRAs) to facilitate the introduction and roll-out of Merck Ebola Vaccine in Africa; to describe the roles and responsibilities of different stakeholders – WHO (HQ and AFRO), EMA, US FDA etc., as well as using the African Vaccines Regulators Forum (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 EMA or USFDA have 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 Merck 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 - in two potential routes:

- EMA route – following the European Union (EU) Decision after the Centralized procedure. To ensure expedited PQ, representatives from the PQ team will participate in the evaluation process and will confirm programmatic suitability (e.g., stability, presentation, labelling, cold chain considerations, etc.) for targeted African countries;
- US FDA route – following the US FDA approval (including programmatic suitability);
- As the PQ programme will be actively involved in the EMA assessment process, the expectation is that all programmatic aspects will be considered during the review process and the PQ of the vaccine will be issued shortly after EMA/FDA's decision.

2) Facilitating the acceptance of the vaccine in African countries:

Two countries interested in participating in the EMA Centralized Procedure (CP) have nominated experts that will participate in the EMA review. 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, through face-to-face meetings and online platform, with a wider group of African countries (Francophone and Anglophone) 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 (30days²) after EMA 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;
 - Merck has committed to provide the same dossier as is submitted to EMA in accordance with national regulations, in parallel to filing with EMA. Merck will provide an estimate of the time it will take to obtain the Bureau of Industry and Security license and send the unredacted dossiers to the countries.
- b) Sequential route: WHO facilitated registration procedure following either US FDA or EMA approval led process.
- NRAs commit to take a regulatory decision for the product in maximum 90 days through a signed agreement;
 - Merck commits to submit the same dossier as submitted to EMA in accordance with national regulations, in parallel to filing with EMA;
 - 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.

² Consultations with participating countries are necessary to confirm the minimum timelines

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, USFDA 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) once the positive decision is issued by the European Medicines Agency or USFDA, prequalification process will be finalized.

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) Apply the AVAREF platform for information-sharing and facilitated registration of Ebola vaccine application.

European Medicines Agency will:

- a) Involve WHO and country NRA experts in EMA CP for Merck 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.

US FDA will*:

*To be confirmed depending on outcome of above.

To provide technical and scientific support to countries.

Merck will:

- a) Obtain the Bureau of Industry and Security license for participating countries;
- b) Ensure that formal application forms 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.	Collaborate with AVAREF Secretariat (WHO/AFRO) to confirm the priority/interested African countries and seek nomination of the experts to participate in the EMA review as observers: <ul style="list-style-type: none"> - DRC - Central African Republic - Congo, Brazzaville - Rwanda - Tanzania - Angola - South Sudan - <u>Zambia</u> - Uganda Countries of large outbreak: <ul style="list-style-type: none"> - Liberia, - Guinea, - Sierra Leone 	Done	RHT, WHO AFRO	<u>Ghana</u> and Uganda are identified as experts for the EMA procedure.
2.	Confirm with Merck on target countries for submissions	Done	RHT WHO	
3.	Nominated countries' experts for EMA CP process to sign the confidentiality agreements and declarations of interests	By mid- May 2019	WHO AFRO	Should be signed prior to EMA CP starts
4.	Presentation of concept at AVAREF TCC and SC meeting in Addis Ababa	18-22 February 2019 Done	RHT, AFRO	
5.	WHO and AVAREF identify participating countries for WHO facilitated process	May 2019	RHT, AFRO	
6.	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.	Proposed time: July 2019 Proposed location – TBD

7	Nominated countries' experts for WHO to sign the confidentiality agreements and declarations of interests	By mid- May 2019	WHO AFRO	Should be signed prior to receiving dossier
8.	Merck to submit the applications in the countries	Confirmed with Merck	Merck,	Merck should submit the same dossier as was submitted to EMA
9.	Facilitating WHO process with target countries	July 2019	RHT, WHO/ AFRO, EMA or USFDA	
10.	In-country registrations /authorization for use	To be determined	RHT, AFRO, concerned NRAs	Timeline to be committed through signed agreements
11.	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	

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



