Preamble

During the course of the high level WHO meetings on Ebola vaccine development, it was agreed that WHO would develop Ebola vaccine target product profiles to provide guidance on WHO's preferences for Ebola vaccines of two categories (please see below).

The target audience for this document are all those working to improve characteristics of currently tested Ebola vaccines. The document is also aimed at those developing Ebola vaccines that have not yet reached the clinical development phase.

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Ebola Virus Disease (EVD) Vaccine Target Product Profile

This document considers two scenarios for use of an Ebola virus disease (EVD) vaccine, which have different preferred characteristics:

a) **Reactive/emergency use** in the face of an outbreak to prevent EVD in vaccinated individuals as well as interrupt chains of virus transmission to terminate outbreaks. Use will be in populations experiencing an outbreak, in populations geographically close to an outbreak and at high risk for importation of EVD cases from areas experiencing an outbreak:
    - *Durability of protection:* Less critical than rapidly achieving high rates of protection as the emphasis is interrupting transmission and terminating the outbreak.
    - *Stability/storage:* Amenable to stockpiling for future outbreaks of EVD.
    - *Risk/benefit profile:* Acceptability based on the assumption those vaccinated are at high risk of exposure to Ebola virus with relatively high EVD-associated mortality rate.

b) **Prophylactic use** to protect frontline workers (including healthcare workers, deploying international workers and others at particularly high risk of EVD due to their profession such as ancillary staff and those dealing with burials)
    - *Durability of protection:* A more prominent preferred characteristic than for reactive/emergency use
    - *Risk/benefit profile:* assumes that some of those vaccinated may not be as at high risk as the target group for reactive use.

Introduction

This document is intended to serve as guidance for scientists, regulators, and funding agencies, and for industry groups. It is relevant to those groups who wish to obtain WHO policy recommendations for use, and WHO prequalification of their

products to maximise supply volumes for use of EVD vaccines, and meet the public health need related to future EVD outbreaks.

In order to reach the stage of use in countries most affected by Ebola outbreaks, vaccines will need to be prequalified by WHO, and be included within the remit of WHO policy recommendations for use. An essential requirement prior to WHO prequalification is licensure by an NRA considered functional by WHO.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO's case-by-case assessments of EVD vaccines in the future.

None of the characteristics in the tables below dominates over any other. Therefore should a vaccine's profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO's processes.

A generic description of WHO's Vaccine Prequalification process can be found at the end of this document.

Monovalent vs polyvalent vaccines

In the short term (2015) vaccine development efforts may appropriately focus on monovalent Zaire EVD vaccines. From 2016 onwards, WHO will be seeking at least trivalent coverage for Marburg virus and both Zaire and Sudan species of

Ebolavirus when considering Ebolavirus/filovirus vaccines for stockpiling. While less common, Bundibugyo species of Ebolavirus coverage would also be desirable. While other species of filovirus have infected humans, these other species have not caused significant outbreaks with multiple fatalities.

Throughout the table the term EVD is used, but in some cases this refers to an anticipated multivalent vaccine including a component targeting Marburg virus.

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
Indication for use	For immunization of at-risk persons residing in the area of an on-going outbreak to protect against EVD caused by circulating species of filovirus; to be used in conjunction with other control measures to curtail or end an outbreak		For active immunization of persons considered at-risk based on specific risk factors to protect against EVD caused by potential species of filoviruses causing future outbreaks	
Target population	All age-groups and populations[1] at high present risk of EVD caused by circulating species of filovirus	All healthy adults excluding pregnant and lactating women at high present risk of EVD caused by circulating species of filovirus	All age-groups and populations[1] at increased risk of EVD caused by potential species of filoviruses causing future outbreaks	All healthy adults, excluding pregnant and lactating women at increased risk of EVD caused by potential species of filoviruses causing future outbreaks

[1] Where exclusion of special populations is not necessary, this simplifies programmatic use of vaccine.

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination	Safety and reactogenicity consistent with expectations for a licensed vaccine for use in an individual at high present risk for disease with a high mortality rate, providing an overall favourable risk/benefit profile in the context of observed vaccine efficacy	Safety and reactogenicity at least comparable to WHO-recommended routine vaccines in use in low and middle-income countries, providing a highly favorable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination	Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks Safety profile demonstrates primarily mild, transient health effects and rare serious AEs related to vaccination

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
Efficacy	Greater than 80% efficacy in preventing disease in healthy adults, adolescents and children Rapid onset of immunity (preferably less than 2 weeks) If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak	Greater than 50%[2] efficacy in preventing disease in healthy adults Rapid onset of immunity (eg less than 1 month) If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future	Greater than 80% efficacy in preventing disease in healthy children, adolescents and adults If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak	Greater than 70% efficacy in preventing disease in healthy adults If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak to the extent possible

[2] Mathematical modelling indicates that a vaccine with 50% efficacy for 3 months could have a substantial impact if deployed appropriately during an ongoing outbreak. http://www.fondation-merieux.org/documents/en/conference-resources/2015/Ebola-vaccine-where-we-are-how-to-move-forward/challanges-and-potential-impact-of-large-scale-implementation-of-Ebola-vaccines-anton-camacho.pdf

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
		outbreak to the extent possible		
Dose regimen	Single-dose regimen highly preferred	No more than 2 doses, no more than 1 month apart, with some protection after the first dose. Homologous 2 dose schedules preferred over heterologous prime-boost.	Single-dose regimen preferred	Primary series: No more than 2 doses, no more than 1 month apart. Homologous 2 dose schedules preferred over heterologous prime-boost. Booster doses: No more frequent than annually or at time of new outbreak.

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
Durability of protection	Confers at least 1 year of protection. It may be necessary to infer long term protection from immune kinetics.	Confers at least 3 months of protection	Confers long-lasting protection of 5 years or more following the primary series and can be maintained by booster doses. It may be necessary to infer long term protection from immune kinetics.	Confers protection of at least 1 year after primary series and can be maintained by booster doses. It may be necessary to infer protection from immune kinetics.
Route of Administration	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-parenteral	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ.

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
	parenteral route desirable.		route desirable.	
Species coverage	Effective against Zaire and Sudan Ebolavirus and Marburg virus; Bundibugyo Ebolavirus coverage desirable	Monovalent against outbreak species (current: Zaire Ebolavirus)	Effective against Zaire and Sudan Ebolavirus and Marburg virus; Bundibugyo Ebolavirus coverage desirable	Monovalent against outbreak species (current: Zaire Ebolavirus)
Product Stability and Storage	Shelf life of at least 24 months at -20 °C, and demonstration of at least 6 months stability at 2-8 C. The need for a preservative is determined and any issues are addressed VVM: Proof of feasibility and intent to apply a VVM to the	Shelf life of at least 12 months at -80 °C. Demonstrated stability for at least 8 hours at 2-8°C. The need for a preservative is determined and any issues are addressed	Shelf life of at least 24 months at -20 °C and demonstration of at least 6 months stability at 2-8°C. The need for a preservative is determined and any issues are addressed VVM: Proof of feasibility and intent to apply a VVM to the	Shelf life of at least 12 months at -20 °C. Demonstrated stability for at least 8 hours at 2-8°C. The need for a preservative is determined and any issues are addressed

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
	vaccine Vaccines that are not damaged by freezing temperatures (<0°C) are preferred		vaccine Vaccines that are not damaged by freezing temperatures (<0°C) are preferred	
Co-administration with other vaccines	The vaccine will be given as a stand-alone product, not co-administered with other vaccines	The vaccine will be given as a stand-alone product not co-administered with other vaccines.	The vaccine can be co-administered with other vaccines licensed for the same age and population groups without clinically significant impact on immunogenicity or safety of the Ebola vaccine or the co-administered vaccines	The vaccine will be given as a stand-alone product not co-administered with other vaccines.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi-dose (10-20) presentations with a	Vaccine may be provided as a liquid or lyophilized product in mono-	Vaccine is provided as a liquid product in mono-dose or multi-dose (10-20) presentations with a	Vaccine is provided as a liquid or lyophilized product in mono-

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
	maximal dosage volume of 0.5mL Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy	dose or multi-dose (10-20) presentations with a maximal dosage volume of 0.5mL Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy Lyophilized vaccine will need to be accompanied by paired separate vials of the	maximal dosage volume of 0.5mL Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy	dose or multi-dose (10-20) presentations with a maximal dosage volume of 0.5mL Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy Lyophilized vaccine will need to be accompanied by paired separate vials of the

Type of deployment	TPP for Reactive use		TPP for Prophylactic use	
	Preferred	**Critical**	**Preferred**	**Critical**
		appropriate diluent		appropriate diluent
Production (The scale of each vaccine required will depend on the number of available vaccines)	Process and yield scalable to produce at least 5 million doses per year Capacity available to manufacture vaccine expeditiously as possible following scale-up Dosage, regimen and cost of goods amenable to high volume and affordable supply	Capacity available to manufacture vaccine at least 10,000 doses per month immediately with evidence for possibility for further scale-up	Process and yield scalable to produce at least 5 million doses per year Capacity available to manufacture vaccine as expeditiously as possible following scale-up Dosage, regimen and cost of goods amenable to high volume and affordable supply	Capacity available to manufacture vaccine as expeditiously as possible following scale-up
Registration and Prequalification	Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/BS/10.2155).			

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Registration by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/BS/10.2155) available here: http://www.who.int/entity/immunization_standards/vaccine_quality/pq_revised_procedure_final_1may2012.pdf.

The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf)

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.
Recognising the need to encourage early consideration of these issues, WHO has published several documents that describe WHO preferences for vaccine presentations and packaging and programmatic suitability. These documents include:-

- *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification* (WHO/IVB/14.10) (http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/index.html)
- *Vaccine Presentation and Packaging Advisory Group (VPPAG). Generic preferred product profile (gPPP), Version 2.1, August 2009* (http://www.who.int/immunization_delivery/systems_policy/VPPAG_Generic_PPP_and_Workplan.pdf)

Vaccine developers and manufacturers should refer to the current version of these documents to gain an understanding of these parameters and the relevant recommendations to ensure that their target product profile(s) and development program meet WHO preferences. An understanding of these preferences will hopefully ensure not only the development of highly efficacious and safe products that have characteristics desirable for low and middle-income country settings but

also facilitate and enable a successful outcome for vaccine developers from the WHO Programmatic Suitability for Prequalification Process.

Beyond the minimum requirements for consideration of WHO PQ, vaccine developers should be aware of the call from immunization programmes in resource poor settings that innovation related to programmatic suitability aspects such as ease of administration and thermostability will lead to great advances in these areas. Advances that are foreseen in the next decade include, firstly, greater availability of needle-free administration for vaccine delivery in low income countries, and secondly thermostability so greatly improved that vaccines can be stored at ambient temperatures and a refrigerated cold chain will no longer be needed for some vaccines. The economic benefits of ambient temperature storage of a meningitis vaccine have been evaluated[3]. Research and collaboration between academics, vaccine and delivery device developers, together with dialogue and engagement of regulators and WHO to facilitate such advances could be transformative for immunization programmes and is strongly encouraged.

[3] Lydon P et al. *Bulletin of the World Health Organization* 2014;92:86-92. who.int/bulletin/volumes/92/2/13-123471.pdf