World Health Organization

WHO Target Product Profile for multivalent filovirus vaccines: providing long-term protection to high-risk populations

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Target Audience

The target audience for this document are all those who wish to know WHO's perspective on the desired profile of multivalent filovirus vaccines for prophylactic use. Now that the 2014 to 2016 Public Health Emergency of International Concern (PHEIC) for Ebola Virus has been declared terminated, the unmet public health need for filovirus vaccine development moves beyond monovalent Ebola Zaire vaccines alone.

Acknowledgement

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This Target Product Profile is part of the WHO R&D Blueprint effort, which aims at reducing the time between declaration of a public health emergency of international concern (PHEIC) and the availability of effective diagnostic tests, vaccines, antivirals and other treatments that can save lives and avert a public health crisis (http://www.who.int/csr/research-and-development/en/).

Filovirus diseases are among the prioritized pathogens that need to be urgently addressed under the R&D blueprint. Details of the WHO meeting held in December 2015 on prioritization of pathogens under the WHO R&D Blueprint are found on (http://www.who.int/csr/research-and-development/documents/oslo-meeting-report.pdf?ua=1).

Filovirus Vaccine Target Product Profile

This document considers the following scenario for use of filovirus vaccines:

- **Prophylactic use** to protect high-risk groups whether before or during an outbreak. This target group comprises healthcare workers (HCW) ,frontline workers (FLW) and others at occupational risk, including potentially deployed international workers essential to assist in future outbreaks.

This document does not supersede, but rather complements and expands the existing WHO Ebola Vaccine Target Product Profile. [1] Unlike the 2015 WHO Ebola Zaire (monovalent) vaccine TPP, this TPP provides guidance for prophylactic use only, where the primary objective of vaccination is individual protection and not interruption of transmission (reactive use). Durability of protection is therefore a prominent feature. As part of the WHO R&D strategy, a draft guidance prepared by the Global Ebola Vaccine Implementation Team (GEVIT) has been developed to provide practical guidance on the use of Ebola vaccine in an outbreak response.[2] Readers are referred to the existing WHO Ebola Zaire vaccine TPP for WHOs preferences on monovalent vaccines for reactive use[3]. A reactive vaccination strategy for future outbreaks against other filoviruses may benefit from development of monovalent vaccines against Ebola Sudan, Marburg and Bundibugyo virus. A multivalent filovirus vaccine intended for reactive use would have practical advantages in terms of stockpile management. The preferred and critical attributes of a multivalent filovirus vaccine for reactive use will put less importance on the durability of protection and high initial efficacy compared to time to onset of immunity.

Introduction

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. The main recipients of the vaccine are likely to be populations in previous Ebola-affected countries in Africa and therefore special attention should be given to the affordability of the product and for financing mechanisms to ensure equitable access.

What valencies should be included?

WHO considers that any multivalent filovirus vaccine should be clinically effective against Ebola Zaire, Ebola Sudan, and Marburg Viruses because these three viruses have caused the largest number of outbreaks with fatalities. Additional Ebola valencies could be valuable including Bundibugyo virus which has also caused

[1] http://www.who.int/immunization/research/target-product-profile/WHO_Ebola_vaccine_TPP_version_final.pdf?ua=1
[2] http://www.who.int/csr/resources/publications/ebola/gevit_guidance_may2016.pdf?ua=1
[3] http://www.who.int/immunization/research/target-product-profile/ebolavaccine/en/

outbreaks with fatalities.[4] It is preferable from a public health perspective for multivalent vaccines to be available for prophylactic use, rather than multiple monovalent vaccines.

[4] Burk R et al. FEMS Microbiology Reviews, 2016.

How will efficacy be demonstrated?

It will not be feasible to demonstrate clinical efficacy of multivalent filovirus vaccines in randomised controlled trials prior to future outbreaks. However it is imperative that these vaccines are available for use during future outbreaks. It is therefore envisioned that regulatory authorization will be based on:

A) an assessment of the quality of the vaccine

AND

B) an appropriate clinical safety database supported by non-clinical safety data

AND

C) clinical efficacy will be inferred from 3 sets of data: clinical immunogenicity using a validated and standardized antibody assay, non-clinical immunogenicity and non-clinical efficacy from a standardized non-human primate model using the same (or as close as possible) validated and standardized antibody assay

AND

D) an expectation to generate effectiveness data as far as possible during use in the next outbreak

The detailed pathways and data requirements for licensure will be agreed between manufacturers and regulators, following usual processes.

	Preferred	Critical
Indication for use	For active immunization of persons considered potentially at-risk based on specific risk factors to protect against filovirus disease including that caused by Ebola Zaire, Ebola Sudan and Marburg viruses. Risk groups will include HCW and FLW.	
Target population	HCW, FLW and others with occupational risk	HCW, FLW and other adults with occupational risk, excluding pregnant and lactating women.
Safety/Reactogenicity	Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a highly favorable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination, including in individuals with compromised immune function.	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.
Efficacy	Greater than 90% 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.	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 See section above "How will efficacy be demonstrated?"
Dose regimen	Single-dose regimen preferred without requirement for a	Primary series: No more than 3 doses, and completion of

	Preferred	Critical
	booster.	series within 2 months Booster doses: No more frequent than every 3 years or at time of new outbreak.
Durability of protection	Confers long-lasting protection of 5 years or more following the primary series and can be maintained by booster doses. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.	Confers protection of at least 2 years after primary series and can be maintained by booster doses. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.
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-parenteral route desirable.	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ.
Coverage	Bundibugyo Ebola virus coverage desirable in addition to Ebola Zaire, Ebola Sudan and Marburg viruses.	A multivalent or combination product with minimum coverage of Ebola Zaire, Ebola Sudan and Marburg viruses. Co-administration of a bivalent Ebola Zaire/Sudan virus vaccine with a Marburg virus vaccine acceptable to achieve the minimum 3 valency coverage
Product Stability and Storage	Shelf life of at least 5 years at 2-8°C. The need for a	Shelf life of at least 12 months at 2-8 °C. Shelf-life at least 3

	Preferred	Critical
	preservative is determined and any issues are addressed. Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the vaccine. Vaccines that are not damaged by freezing temperatures (<0°C) are preferred. Vaccines that can be delivered via the Controlled Temperature Chain are preferred[5].	years at -20 °C. The need for a preservative is determined and any issues are addressed.
Co-administration with other vaccines	Preferably a 3-valent Ebola Zaire, Ebola Sudan and Marburg virus vaccine will be given as a stand-alone product not co-administered with other vaccines. The vaccine can be co-administered with other non-filovirus vaccines licensed for the same age and population groups without clinically significant impact on immunogenicity or safety of the filovirus vaccine or the co-administered vaccines.	Co-administration of a bivalent Ebola Zaire/Sudan virus vaccine with a Marburg virus vaccine acceptable to achieve the minimum 3 valency coverage. Three different monovalent vaccines in co-administration will not meet the requirements of this WHO multivalent filovirus TPP.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi-dose (10-20) presentations with a maximal dosage volume	Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (10-20) presentations with a

[5] http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf

	Preferred	Critical
	of 0.5mL. Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy.	maximal dosage volume of 1.0mL Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy. [6] Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
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).	

[6] http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf

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. Licensure 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, March 2015* (http://www.who.int/immunization/policy/committees/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[7]. 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.

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