Developing a **Target Product Profile** for a **Preventive HIV Vaccine**

SECOND EDITION

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Table of Contents

What This Workbook Does and How to Use It

The first part of the workbook describes the purpose of a target product profile (TPP) and how to develop one. The goal is to inform scientists, funders, advocates, and other stakeholders about the concept of a TPP and to stimulate discussion in the field about what a TPP for a preventive HIV vaccine may look like.

The second part of the workbook contains descriptions of eleven TPP attributes that have the most relevance to a preventive HIV vaccine. The reader is encouraged to go through each section and answer questions in the provided space. Points for considerations are meant to highlight potential challenges or caveats in answering the questions. Each section includes examples of targets from two sample TPPs as well as excerpts from a product insert of a licensed vaccine showing how TPP attributes and corresponding evidence are eventually used to support claims in marketing labels.

A sample TPP for a preventive HIV vaccine is included in the Appendix.

What Is a TPP and Why Do You Need It

The TPP is a strategic planning document used to guide the vaccine development process from the earliest stages. It embodies the notion of beginning with a goal in mind and specifies, among other desired attributes, labeling concepts and claims. Each of the desired attributes has an "optimal target" and a "minimal target." For example, an optimal target for dosage schedule would be one vaccination that lasts a lifetime; a minimally acceptable target may be a series of vaccinations over a certain time period. In the early stages, some required information may not be available or may be estimates. The TPP should include a summary of the status of completed or planned studies that support the targets. As development proceeds, each of the estimated targets are refined based on manufacturing, nonclinical, and clinical results. Typically, the stated targets do not change unless the intended use of the product or standard of care changes, or in response to regulatory guidance. The final version of the TPP often serves as the precursor to the annotated product label.

For the R&D team, a TPP defines common goals and ensures that various departments are aligned during all stages of development on desired outcomes, product characteristics, and measures of success. A well-crafted TPP guides the design, conduct, and analysis of clinical trials. It allows the development team to focus on the desired characteristics of the vaccine and to ensure that the proposed clinical trials can support eventual label claims. Another major role of the TPP is to help create a product optimally suited for its intended use and market by differentiating it from the current standard of care. This helps to make the business case for product development. Emerging data on the product are benchmarked against the established TPP attributes to determine whether continued development is justified.

Although submitting the TPP to regulators is voluntary, sections of the TPP can be submitted as part of a Briefing Document for a meeting and may facilitate feedback on critical aspects of the development process. The US Food and Drug Administration (FDA) published a Draft Guidance on the use of a TPP.

Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool March 2007.

Funders may develop their own versions of a TPP to articulate to potential developers what vaccine candidates they are willing to support or what vaccine attributes are most important to them.

Developing and Modifying a TPP

The TPP is usually developed by a cross-functional team that includes experts in preclinical, safety assessment, process development, product analytics, manufacturing, regulatory, clinical, marketing or commercial, statistics, policy/access/delivery, and intellectual property areas. A TPP should be developed as soon as a candidate vaccine has been identified as a viable product for clinical trials.

Depending on the familiarity of team members with the TPP concept, creating the first version of the TPP can take 1 to 3 months. Because the TPP is an evolving document, some areas may initially have gaps. Identifying these gaps may trigger additional studies, appropriate market research, or engagement with key opinion leaders or experts to fine-tune the TPP. As product development continues and its attendant data mature, the quantity and quality of data supporting specific targets should improve, and the TPP targets become more specific and quantitative. Supporting data and ongoing or planned studies can be noted in an Annotations section of the TPP (see the Appendix). The TPP is updated as new information (e.g., at stage gate reviews) becomes available, although key agreed-upon targets typically remain unchanged.

Target Product Profile for a Preventive HIV Vaccine

There are no strict rules regarding the information included in the TPP, but the sections usually follow those in the final product label/information. The following attributes are most relevant to the development of preventive HIV vaccines.

1. Indication
2. Target population
3. Components
4. Product presentation
5. Route and method of administration
6. Dose and schedule
7. Efficacy
8. Duration of protection
9. Safety and tolerability
10. Co-administration
11. Shelf life and storage

The following sections provide questions to answer and issues to consider for each attribute. Answers to these questions are meant to capture greater detail and the rationale that supports the Optimal Target and the Minimal Target at the specific stage of development program. Creating a TPP is an iterative process because answers to one section may affect other sections and raise additional questions. If the required evidence to support the claim is not available, consider what kinds of studies are needed to generate the necessary data.

About Examples

Each section contains examples of the targets, which were drawn from TPPs developed by the World Health Organization (WHO) to guide the development of vaccines for the Zika virus and for the Ebola virus. In addition, to illustrate how a TPP attribute evolves and becomes much more specific in the course of development, each section includes an excerpt from a product insert for GARDASIL®, a vaccine developed and licensed by Merck for human papillomavirus.

The documents used to generate these examples have been downloaded from the WHO and Merck websites on 15 September, 2016:

http://www.who.int/immunization/research/meetings_workshops/WHO_Zika_vaccine_TPP.pdf

http://www.who.int/immunization/research/target-product-profile/WHO_Ebola_vaccine_TPP_version_final.pdf

http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf

The full versions of these documents can also be found on the Enterprise website at:

http://www.vaccineenterprise.org/timely-topics/target-product-profile

A sample TPP for a preventive HIV vaccine, located in the Appendix at the end of this booklet, provides additional examples of targets for a hypothetical vaccine candidate.

1. Indications

As part of development, you may choose to begin with a single indication. If so, the TPP should delineate this indication, and additional indications can be added later. If there are multiple clinical indications, these should be clearly separated. As development progresses, the indication language should match that of the desired actual product label, especially during late development.

ANSWER:

- What is the intended indication for the vaccine? In addition to prevention of HIV infection, are there other objectives that you would like your vaccine to achieve? For example, control of viral load or prevention of transmission from an infected person?
- Is the prevention of disease, without preventing infection acceptable?

CONSIDER:

- Will your clinical development program support each claim proposed for the initial Biologics License Application (BLA)?
- What will be required to advance from the target population in your initial efficacy trial to more global use of the vaccine? What types of population bridging studies will you propose to demonstrate that data from the efficacy trial population are relevant to non-efficacy trial populations?
- What indication(s) will be targeted in the initial BLA submission versus subsequent BLA supplement(s)?

EVIDENCE REQUIRED:

- Clinical studies to demonstrate desired clinical benefit

EXAMPLES- INDICATIONS:

Zika Vaccine TPP - For the prevention of Zika virus-associated clinical illness of any severity.

Ebola Vaccine TPP - For active immunization of persons considered at-risk based on specific risk factors to protect against Ebola Virus Disease (EVD) caused by potential species of filoviruses causing future outbreaks.

GARDASIL Product Insert – "GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine: Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18; and Genital warts (condyloma acuminata) caused by HPV types 6 and 11. GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine: Anal cancer caused by HPV types 16 and 18; and Genital warts (condyloma acuminata) caused by HPV types 6 and 11."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

2. Target Population

Defining the target population for initial licensure is key to defining the clinical development plan. Each distinct target population must be supported with adequate evidence of safety and efficacy. Ideally, the target populations should be justified with epidemiology, public health impact, and health economic models.

ANSWER:

- What is the intended primary target population: high-risk adolescents and adults, the general adult population, children? Are any special populations being targeted?
- What age range will the vaccine development program support? At what age should vaccination ideally begin? Is there an age beyond which someone should not be vaccinated? Note: it is useful to distinguish plans for initial licensure from supplements.
- What, if any, is the intended target country/countries?

CONSIDER:

- Are you targeting a general adult population living in a highly endemic country or specific at-risk groups?
- What data are used to select this population and/or age range?
- Does the choice of target population depend on HIV prevalence and/or incidence? How will decreases in prevalence/incidence affect your target population?
- Regulatory agencies consider age groups separately (neonates, infants, children, adolescents, adults, older adults) and generally require clinical evidence of safety and efficacy for each group.

EVIDENCE REQUIRED:

- Clinical safety and efficacy in all target age groups

EXAMPLES- TARGET POPULATION:

Zika Vaccine TPP - Women of child bearing age (including adolescent and pre-adolescent girls 9 years of age or older), and boys/men of reproductive age (9 years or older). Potential exclusions: pre-existing neurologic or autoimmune disorders, immuno-suppressed individuals.

Ebola Vaccine TPP

Minimal: All healthy adults, excluding pregnant and lactating women, at increased risk of EVD caused by potential species of filoviruses causing future outbreaks.

Optimal: All age-groups and populations at increased risk of EVD caused by potential species of filoviruses causing future outbreaks.

GARDASIL Product Insert - "GARDASIL® is a vaccine indicated in girls and women 9 through 26 years of age," Also "GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

3. Components

All active and inactive components must be listed and justified. This includes information on targeted viral genes and clades and on the physical and chemical form of the components.

ANSWER:

- What is the active component of the vaccine?
- Does the vaccine contain adjuvant(s)?
- What is the target concentration or dose?
- What are the inactive or other components (buffers, salts, stabilizers) in the vaccine? Does the vaccine require a preservative?
- If the vaccine has heterologous prime-boost, what is used for priming and what is used for boosting?

CONSIDER:

- What data support the need for each component? For example, will you justify the inclusion of the adjuvant with clinical safety and immunogenicity data?
- Carefully evaluate all components of the vaccine (and all materials used in the preparation of the vaccine) for materials of animal origin.
- If possible, select inactive components that are commonly used in other pharmaceutical preparations and generally considered safe.

EVIDENCE REQUIRED:

- Product and process descriptions supported with characterization data

EXAMPLES- COMPONENTS:

Zika and Ebola Vaccine TPPs – There are no specified components for Zika or Ebola vaccine candidate, because these TPPs have been developed by the World Health Organization, which does not promote any specific vaccine candidate.

GARDASIL Product Insert - "GARDASIL, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

4. Product Presentation

ANSWER:

- How will the vaccine be presented (single-dose vials, multi-dose vials, prefilled single dose syringes, powder for reconstitution, capsule, tablet, dropper)?
- How will it be packaged (vials, syringes, cartridges, single containers, multiple containers)?
- Does the vaccine regimen contain a single or multiple components? If multiple, can they be combined in a single vial and administered in a single visit or do they need to be administered separately or at different times?
- What is the volume of delivery?

CONSIDER:

- In the United States and European Union, prefilled syringes are generally preferred presentations.
- Are there needle-free options that can be considered, such as intranasal or oral administration?
- What are the technical feasibility and costs of alternative delivery options?
- Can heterologous prime-boost components be avoided, given the large barriers to implementing such a product?
- Do you anticipate that the product will change during clinical development?
- Can multi-dose vials (or containers of choice) be targeted, or must the vaccine be packaged as single-dose containers?
- Will there be market demand for multiple presentations (e.g., single-dose vs multi-dose presentations?)

EXAMPLES- PRODUCT PRESENTATION:

Zika Vaccine TPP

Minimal: Vaccine is provided as a lyophilized product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5mL for i.m. administration. 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 appropriate diluent.

Optimal: Vaccine is provided as a lyophilized product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5mL for i.m. or s.c. administration. Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy.

Ebola Vaccine TPP

Minimal: Vaccine is provided as a liquid or lyophilized product in mono-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 appropriate diluent.

Optimal: Vaccine is provided as a liquid product in mono-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.

GARDASIL Product Insert – "GARDASIL is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

5. Route and Method of Administration

ANSWER:

- What is the route and method of administration?
- What is the rationale for the choice of route of administration?
- Are any special devices needed to administer the vaccine?

CONSIDER:

- Will different routes or methods of administration be offered depending on the target population? What is the impact on the clinical and manufacturing programs of multiple routes of administration?
- Is route of administration affected by local conditions?
- Is the route of administration chosen based on the type of response to be elicited?
- What alternate delivery technologies, such as microneedle patches or other needle-free options, can be considered for those who are needle-averse?
- What data will be needed to support the use of a delivery device? Will the delivery device change during clinical development?

EVIDENCE REQUIRED:

- Route and method of administration justified in Phase 1 and 2 clinical immunogenicity studies and confirmed in Phase 3 studies

EXAMPLES- ROUTE AND METHOD OF ADMINISTRATION:

Zika Vaccine TPP - Injectable (IM or SC) using standard volumes for injection.

Ebola Vaccine TPP

Minimal: Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for Pre-Qualification (PQ).

Optimal: 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.

GARDASIL Product Insert – "GARDASIL is a 0.5 mL suspension for intramuscular injection."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

6. Dosage and Schedule

ANSWER:

- What dose level is desirable, keeping in mind the need to balance maximum benefit with minimal adverse events and reactogenicity, cost of goods, number of doses/lot, and manufacturing feasibility?
- How many doses will be required? Over what period of time?
- Is dose level/number of doses/schedule the same for all populations, or does it depend on patient characteristics (e.g., age, weight)?

CONSIDER:

- What regimen is needed to initially generate an effective immune response? What boosting schedule might be needed for durability? (Note: A “boost” that is not part of the initial schedule/claim for duration of protection may be addressed following licensure.)
- What is technically feasible to produce, and is that dosage level commercially viable?
- What data are needed to support the proposed dosage schedule?
- What immunologic testing will be performed to determine whether a booster is required?
- If different populations require different dosage strengths, will this be achieved by different product fills or by one fill that is used in part or in multiples?
- Administering multiple doses over a long period can be counter-productive if the goal is to reach specific target populations. The tougher a population is to reach, the easier the schedule needs to be for a successful program.

EVIDENCE REQUIRED:

- Dose and schedule justified by Phase 1 and 2 clinical immunogenicity studies and confirmed in Phase 3 studies

EXAMPLES- DOSAGE AND SCHEDULE:

Zika Vaccine TPP

Minimal: Primary series: No more than 2 doses, no more than 1 month apart. Homologous 2 dose schedules preferred over heterologous prime-boost.

Optimal: Single dose primary series.

Ebola Vaccine TPP

Minimal: 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.

Optimal: Single-dose regimen preferred.

GARDASIL Product Insert – "0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

7. Efficacy

The ability of a vaccine candidate to prevent HIV infection can only be established in a large-scale efficacy trial. At early stages of development, it is more appropriate to state the hypothesis for the mechanism of action and the relevant immune measurements.

If a vaccine has more than one indication, efficacy targets should be listed separately for each indication.

ANSWER:

- What immune response is expected and what is the targeted minimum percentage of positive responders required to move this product into late stage clinical development?
- What is the targeted efficacy level? Consider point estimate for efficacy and the lower bound of the two-sided 95% confidence interval.
- What studies will be performed or required to evaluate vaccine efficacy?
- Are immunologic studies of the vaccine's effects available? If not, what is required?

CONSIDER:

- What factors may affect vaccine efficacy? Would efficacy be expected to vary based on demographic factors?
- Has efficacy been assessed in all applicable patient populations?
- What measurement instruments or validated assays will be used to support efficacy, especially to support the primary and secondary efficacy case definition(s)?
- For non-clinical efficacy studies, what are the strengths and caveats of the chosen animal model? Can the model give credible information to predict clinical performance?
- What validated assays will be available to assess immunogenicity?
- Has a correlate of protection that can be used for bridging and other purposes been identified and validated? What needs to be done to identify and validate one (or more)?

EVIDENCE REQUIRED – EARLY PHASES:

- Phase 1 and 2 immunogenicity studies

EVIDENCE REQUIRED – LATE PHASES:

- Clinical studies powered to demonstrate statistical evidence of efficacy

EXAMPLES- EFFICACY:

Zika Vaccine TPP

Minimal: If a surrogate of immunity is established through animal models or cohort studies, a reasonable assumption is a ZIKV specific neutralising antibody titre, to be specified, in >70% of vaccinated population.

Optimal: Demonstration of prevention of virologically confirmed ZIKV illness, in accordance with proposed PAHO definition 14 in 80% of the population or higher. Evidence of prevention of viremia.

Ebola Vaccine TPP

Minimal: 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.

Optimal: 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

GARDASIL Product Insert – "In 4 studies of Girls and Women 16 through 26 Years of Age Prophylactic Efficacy against HPV Types 6, 11, 16, and 18 was 93.8-100%. In a study of Boys and Men 16 through 26 Years of Age Prophylactic Efficacy against HPV types 6 and 11 was 89.3-100%. In a study of Boys and Men 16 through 26 Years of Age in the MSM group, prophylactic efficacy against HPV types 6, 11, 16, and 18 was 60.4-100%."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

8. Duration of Protection

Because vaccine efficacy often wanes over time, there is a trade-off between efficacy and duration targets: higher efficacy maintained for a shorter period of time can be preferred to lower efficacy over a longer time period. Depending on the epidemiology in a given target population, different combinations of duration and efficacy can be acceptable to public health agencies.

ANSWER:

- For how long will your vaccine maintain the target level of efficacy?
- Will the vaccine require boosting later in life? How often?

CONSIDER:

- What data are available to indicate the duration of protection?
- Are there similar vaccines for which duration of protection is known?
- Are there demographic factors (e.g., age) that affect durability? If so, what additional studies may be needed to address the frequency of (or age for) boosters?

EVIDENCE REQUIRED:

- Long term follow up in immunogenicity and/or efficacy studies

EXAMPLES- DURATION OF PROTECTION:

Zika Vaccine TPP

Minimal: Confers protection of at least 1 year after primary series and can be maintained by booster doses. If a booster is required, it should be no more than once annually, or at the time of a new outbreak.

Optimal: Confers long- lasting protection of more than 1 year after administering the primary series and can be maintained by a single booster dose.

Ebola Vaccine TPP

Minimal: 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.

Optimal: 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.

GARDASIL Product Insert – "The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. The peak anti-HPV geometric mean titers for HPV types 6, 11, 16, and 18 occurred at Month 7. Anti26 HPV GMTs for HPV types 6, 11, 16, and 18 were similar between measurements at Month 24 and Month 60 in Study 2." And "The protection of GARDASIL against HPV-related disease continues to be studied over time in populations including adolescents (boys and girls) and women who were enrolled in the Phase 3 studies."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

9. Safety and Tolerability

There may be precedents of contraindication for a specific product class or for similar vaccines in other disease areas. This information can be used to inform the types of reactions that you may expect and be useful for clinical trial design.

ANSWER:

- What is the overall acceptable safety profile of the vaccine based on the entire safety database? Are there known side effects for similar vaccines?
- What are the preclinical toxicology data for this vaccine or its components?
- Are there specific events that might be acceptable, if rare, or events that, even if rare, would be unacceptable?
- Could there be special safety considerations for specific populations? For example, during pregnancy and breast-feeding, or for people who are HIV-positive?

CONSIDER:

- Are there components in the vaccine that would be expected to raise the reactogenicity above what is common for vaccines?
- Are expected side effects mild and quickly resolved? If not, are treatments for side effects readily available and highly effective?
- Are there conditions that may indicate someone should not receive this vaccine? If an at-risk person needs to receive the vaccine, what information will their medical team need to mitigate that risk?
- Does this vaccine need to be safe for pregnant or breast-feeding women? How will the vaccine affect an infant born to a woman who was vaccinated while pregnant? Are any non-teratogenic effects in women of childbearing age acceptable? Do any components of the vaccine pass through breast milk?
- Can your vaccine be administered to HIV-infected people? ART-naïve and on treatment? Does viral load matter? Might any co-infections affect the safety of the vaccine?
- Will the product be initially licensed for all populations or will the first Phase 3 trial be in a restricted population? If the latter, what information must be collected in those studies to inform how to expand to other populations? (e.g., to pregnancy)
- Are there conditions that may increase the risk of HIV infection in vaccinated people?
- Does the risk of harm change due to age, sex, or current disease state?

EVIDENCE REQUIRED – EARLY PHASES:

- Phase 1 and 2 studies to demonstrate adequate safety prior to large trials

EVIDENCE REQUIRED – LATE PHASES:

- Clinical studies powered to detect serious allergic reactions in less than 1 in 10,000
- Reproductive toxicology studies.
- Pregnancy register

EXAMPLES- SAFETY AND TOLERABILITY:

Zika Vaccine TPP

Minimal: Tolerable reactogenicity and acceptable safety profile where vaccine benefits outweigh safety risks; platform technologies should have extensive safety data from relevant applications, and at least observational data on the inadvertent or other use during pregnancy are desirable.

Optimal: Safety and reactogenicity at least comparable to WHO recommended routine vaccines, providing a highly favourable risk benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination.

Ebola Vaccine TPP

Minimal: 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.

Optimal: Safety and reactogenicity at least comparable to WHO-recommended routine vaccines in use in low and middle-income countries, providing a highly favourable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination.

GARDASIL Product Insert – "Across the clinical studies studies, 258 individuals (GARDASIL N = 128 or 0.8%; placebo N = 130 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals reported a serious systemic adverse reaction."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

10. Co-administration

Co-administration studies are usually explored when proof of concept is established, but consideration of these questions may inform inclusion criteria for efficacy studies.

ANSWER:

- Could co-administration affect the efficacy of other scheduled or non-scheduled licensed vaccines such as pediatric vaccines (DPT, hepatitis B, polio, hemophilus), adolescent vaccines (HPV), seasonal vaccines (influenza), or travelers' vaccines (yellow fever, hepatitis A, typhoid, cholera). If co-administration is desired, clinical studies must be performed to support the claim.
- Is there a potential for clinically significant interactions between the vaccine and prescription or over-the-counter drugs, certain classes of drugs, or foods?

CONSIDER:

- Are there groups of people who should be excluded from clinical studies until further information is obtained? For example, people who have recently received a live viral vaccine, who are on immunosuppressive drugs, or who have recently received immune globulins or blood transfusions.

EVIDENCE REQUIRED:

- Clinical immunogenicity studies with vaccines potentially co-administered with HIV vaccine

EXAMPLES- CO-ADMINISTRATION:

Zika Vaccine TPP

Minimal: The vaccine will be given as a stand-alone product not co-administered with other vaccines.

Optimal: 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 Zika vaccine or the co-administered vaccines.

Ebola Vaccine TPP

Minimal: The vaccine will be given as a stand-alone product not co-administered with other vaccines.

Optimal: 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.

GARDASIL Product Insert – "GARDASIL may be administered concomitantly with RECOMBIVAX HB® or with Menactra and Adacel. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

11. Shelf Life and Storage

ANSWER:

- What are the expected storage duration and temperature requirements for the vaccine?
- Will short-term storage at elevated temperatures (ambient in the target countries) be detrimental to the vaccine? What if these are expected or needed during manufacturing, shipping, or storage?
- Is the vaccine stable during shipment and transport?
- Does the vaccine require a preservative?

CONSIDER:

- What studies will be required to demonstrate stability for each presentation?
- What studies will be required to demonstrate short-term stability during administration or transport of product outside the recommended storage temperature? For example, if the product presentation is in vials, but syringes need to be loaded, transported, and administered, what studies support this clinical practice?
- What are the local environmental and cold-chain conditions in each country to ensure appropriate deployment under cold-chain conditions?

EVIDENCE REQUIRED:

- Stability studies conducted according to regulatory guidelines.

EXAMPLES- SHELF-LIFE AND STORAGE:

Zika Vaccine TPP

Minimal: Shelf life of at least 6 months at -20°C. Demonstrated stability for at least 6 hours at 2- 8°C. The need for a preservative is determined and any issues are addressed.

Optimal: Shelf life of at least 24 months at - 20°C, or preferentially above, 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 vaccine vial monitor (VVM) to the primary container.

Ebola Vaccine TPP

Minimal: 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.

Optimal: 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. 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.

GARDASIL Product Insert – "GARDASIL should be administered as soon as possible after being removed from refrigeration. GARDASIL can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours."

MINIMAL TARGET:

EVIDENCE REQUIRED:

OPTIMAL TARGET:

EVIDENCE REQUIRED:

APPENDIX: Example of a TPP for a Preventive HIV Vaccine

This example is based on a hypothetical candidate vaccine that elicits broadly neutralizing antibodies against HIV-1 subtype C viruses and primarily provides sterilizing protection, although may have clinical benefits in breakthrough infections. The objective for this example is to illustrate how a TPP may look like at a particular point in the research and development process, including the uncertainty in some targets common to early development stages. The TPP would be accompanied by a number of supporting documents providing additional data and the rationale for various targets, as well as plans for clinical development and manufacturing process development.

The example is provided for educational purposes only and should not be taken as a guidance for development of preventive HIV vaccines in general.

THE CANDIDATE VACCINE:

- The team developed and optimized a soluble native-like trimeric Env subunit protein (subtype C) that is expected to focus the antibody response on the several bNAb targets. The protein is adjuvanted with a newly-discovered IL-99, which is hypothesized to stimulate affinity maturation, as well as increase the magnitude and the duration of the antibody response.
- The candidate has been tested in the rhesus model. It was administered intramuscularly in three doses at 0, 6, 12 week schedule. It showed good safety (no adverse events), immunogenicity (neutralization of 60% of viruses in a Tier 2 panel, including some subtypes A and B viruses), and protection against a heterologous subtype C low-dose intrarectal SHIV challenge (80% reduction of per-challenge risk of infection).
- For NHP studies, the protein was manufactured at small scale by stable transfection of CHO cells and tested for structural stability by binding of bNAbs recognizing quaternary epitopes. Human IL-99 was also produced in CHO cells, it is sufficiently similar to rhesus IL-99 to have similar biological activity in macaques. The Env and IL-99 were mixed immediately before each vaccination.

Characteristic	Optimal Target	Minimal Target	Evidence required
Indication	Prevention of HIV-1 subtype C infections and delay of disease in cases of breakthrough infections in adolescents (>16 years old) and adults	Prevention of HIV-1 subtype C infections in adolescents (>16 years old) and adults	Clinical studies to demonstrate prevention of infection; long-term follow-up to demonstrate delay of disease
Target population	Adults and pre-sexual activity adolescents in areas with high incidence of HIV-1 subtype C infection	Adults in southern Africa at high risk for HIV-1 subtype C infection through heterosexual transmission	Efficacy studies in high risk adults; bridging studies for adolescents
Components	Soluble native-like trimeric Env subunit protein (HIV-1, subtype C). IL-99 peptide	Soluble native-like trimeric Env subunit protein (HIV-1, subtype C). IL-99 peptide	Data demonstrating native-like trimeric form of Env; immunogenicity data demonstrating benefits IL-99 as an adjuvant; mixing studies demonstrating Env structure and adjuvant activity remain intact
Product presentation	Single dose 2 ml glass vial containing lyophilized product.	Two single dose 2 ml glass vials, one with subunit, one with adjuvant that can be mixed together at bedside.	Release testing demonstrating purity, stability, potency; studies demonstrating equivalency of lyophilized product
Route and method of administration	Intramuscular injection	Intramuscular injection	Clinical studies demonstrating safety and efficacy
Dosage and schedule	1 dose, 10 ug/dose, 0.1 ml	3 doses administered at 0, 2, 6 months, 100 ug/dose, 1ml	Phase 1 and 2 clinical immunogenicity studies and confirmed in Phase 3 efficacy studies
Efficacy	80% prevention of infection for HIV-1 subtype C and 50% in subtype A,E infections 3 year delay in time to reduction of CD4 cell counts to 500 cells/mcl	50% prevention of infection for HIV-1 subtype C matched infections	Efficacy studies powered to demonstrate statistical evidence of efficacy in prevention of infection; follow-up cohorts to demonstrate delay of disease
Duration of protection	10 years	1 year after initial vaccination with yearly booster immunizations	Long term follow-up in immunogenicity and/or efficacy studies
Safety and tolerability	Similar to other licensed vaccines in the target population	Up to moderate short-term reactogenicity. Cannot be used during pregnancy	Clinical studies powered to detect serious adverse events in less than 1 in 1,000; reproductive toxicology studies
Co-administration	No restrictions; can be co-administered with HPV vaccines	No interference with standard vaccines in the population.	Clinical immunogenicity studies with vaccines potentially co-administered with HIV vaccine
Shelf life and storage	5 years Refrigeration between 2°C and 8°C; cannot be frozen. Stable at up to 25°C for up to 72 hours	1 year Refrigeration between 2°C and 8°C; cannot be frozen	Stability studies demonstrating preservation of structure

About the Global HIV Vaccine Enterprise

The Global HIV Vaccine Enterprise (the Enterprise) is a unique collaboration of the world's leading HIV vaccine research funding, policymaking, advocacy and stakeholder organizations dedicated to working together to advance HIV vaccine research and development.

Recognizing that no single institution, country or individual can develop an HIV vaccine in isolation, the Enterprise promotes and facilitates coordination, collaboration, knowledge sharing and resource optimization.

A small Secretariat supports the Enterprise, helping to catalyze the activities of this collaboration and implement programming to move its mission forward.

For more information on the Global HIV Vaccine Enterprise, please visit: www.vaccineenterprise.org

About Timely Topics in HIV Vaccines

This Guide was developed as part of the *Timely Topics in HIV Vaccines* a strategy series launched in 2012, convening experts as rapidly as possible to analyze, address, and respond to unresolved and emerging priority issues in the field to help accelerate HIV vaccine research and development. Through an open call for proposals, the Enterprise is working to identify the most important strategic needs of the field and sponsoring think tanks, meetings, forums and other events to tackle these issues.

For more Timely Topics, visit:
www.vaccineenterprise.org/content/timely-topics-hiv-vaccines

Global HIV Vaccine Enterprise

TIMELY TOPICS in HIV Vaccines

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