Guidance document: Questionnaire on regulatory science issues for the development of emerging infectious disease (EID) vaccines

The purpose of this document to support the completion of the "CEPI Questionnaire on regulatory science issues for development of emerging infectious disease (EID) vaccines". As an important partner with an interest in securing regulatory approval/licensure of EID vaccines, you are invited to provide comment on the regulatory scientific issues for the development of EID vaccines that are most relevant to you.

Please note that **questions are not mandatory** and instead, you are invited to provide comment on those questions that are most pertinent to your organisation.

The information from this questionnaire will support the CEPI Secretariat's understanding of regulatory scientific challenges for the development of rare EID vaccines, from an industry perspective. By completing this, you provide an overview of the current state of regulatory science for EID vaccines; including the needs and opportunities for further development of EID vaccine regulatory science. A report will be developed from the findings of questionnaire, and this will be publicly available to expand knowledge in this area.

The questionnaire focuses on identifying the remaining uncertainties for vaccine development in the absence of an outbreak. To do this we are asking:

- High-level questions related to licensure in the absence of an outbreak, data needs, and stockpiling, and
- More specific information on regulatory scientific challenges.

The scientific challenges are related to Quality & Manufacturing, Safety, and Efficacy under the following seven sections that follow the regulatory approval process:

1. Pre-clinical
2. Clinical trial application (CTA)/Investigational new drug (IND) application
3. Stockpile of investigational vaccines
4. Emergency Use Authorisation or Emergency use assessment and listing EUA/EUAL
5. Licensure/Approval
6. Stockpiled licenced vaccine
7. Post-licensure (pharmacovigilance)

Addressing the regulatory science and clinical development challenges for vaccine development has been highlighted as a priority area for many CEPI stakeholders. In partnership with the World Health Organization (WHO), CEPI can play an important role supporting the different actors and stakeholders.

Summary review ("landscape summary") completed by CEPI. A summary review on vaccine regulatory pathways potentially important for CEPI was drafted together with several stakeholders, with technical experts validating the analysis (now published at cepi.net/resources#Regulatory-affairs). *We recommend that those interested in the various regulatory pathways that are currently available for product development and registration under the auspice of WHO and many of the high-income country regulators refer to the description of these pathways in this document.*

Background information and issues on the CEPI prioritised pathogens Ebola, Lassa, Nipah, MERS

The traditional regulatory paradigm is regulation in the context of a product, and there is normally little interaction with regulatory agencies in the absence of a specific product. Vaccine developers approach regulators at the pre-CTA/pre-IND stage to ensure their proposed pre-clinical package will support human trials (including CMC data) and to get alignment on toxicology study design.

At the stage when developers are taking a vaccine into clinical efficacy and safety studies some of the development tools, such as the animal models used thus far, begin to be critically reviewed and questioned (e.g., is the species relevant, is the challenge strain appropriate). Development of acceptable tools has always occurred concomitant with product development, and consequently, developing these components in a product-independent manner and in the most expeditious and rational manner is quite challenging.

CEPI has prioritised investment in the development of Lassa, MERs and Nipah vaccines, with a special priority to provide support that will facilitate the licensure of Ebola vaccines. The following information is provided below to give you a brief overview of these pathogens and spread of the disease.

Ebola and other filoviruses

WHO R&D efforts during the Ebola epidemic focused on fostering fora for global collaboration on Ebola vaccine R&D. This encompassed reviewing all available Ebola vaccine options, promoting scientific debate on trial designs and providing advice on preferred product characteristics to inform long-term use of Ebola vaccines to control or prevent future outbreaks. WHO actively managed or facilitated parallel implementation of Phase I, II and III trials in affected countries, developed policy guidance on potential vaccine deployment through its GEVIT initiative, and provided technical support for affected countries. WHO has a central role in global scientific advice on regulatory approval – and a mandate to highlight and address challenges.

The following issues are relevant examples to for facilitating the development and regulatory approval of novel Ebola vaccines, and are being addressed by regulators, the WHO and the scientific community:

Results from challenge studies/protection studies conducted in non-Human Primates (NHP) with Ebola vaccine candidates

- Overview of the five Ebola viruses in the genus Ebolavirus and the possibility of cross protection
- Current knowledge on immune markers of protection for Ebola virus disease
- Immunogenicity and survival data in NHP models with various Ebola vaccine candidates

Review of available data from clinical trials

- Can immune correlates of protection from NHP studies be defined for short and long term protection and can immune responses in NHP be bridged to human immunogenicity

Key Characteristics for a Safe and Effective Ebola Vaccine

- Product characterization/CMC information needed
- Potential designs for future clinical trials
- A safety database needed to move to phase 3 clinical trial and using the vaccine in an emergency situation.

Middle East respiratory syndrome coronavirus (MERS-CoV)

MERS Co-V, an emerging infectious disease of growing global importance, has caused severe acute respiratory disease in 1626 people, resulting in 586 deaths (2012-2016). It has a high case fatality of 36%, it is transmissible from human to human, has a growing geographic distribution and a vaguely defined epidemiology. The most recent outbreak was in May 2015 in South Korea. Dromedary camels are the likely intermediate animal reservoir, and research to date indicates bats are the original host. (Modjarrad, 2016) (NIPH Vax opp report 2016).

For MERS issues around how to best develop target product profiles for human and veterinary vaccines that in turn will facilitate planning for the integrated development strategy as well as efficacy trials.

Animal model will also be important for MERS. For the preclinical development of MERS-CoV-specific medical countermeasures, there is need for established animal models that recapitulate the severe disease observed in humans. In addition, animal models are needed for dissection of the underlying mechanisms of pathogenicity of MERS-CoV and the study of cross-species and human-to-human transmission. These models will now need to be utilised for the development of prophylactic and therapeutic medical countermeasures.

Nipah

Nipah virus is a metapneumovirus that is carried by fruit bats. Bangladesh is the major site of human infections, but disease does occur in Malaysia, Singapore, the Philippines and India. There appears to be considerable cross-immunogenicity with the related Hendra virus. Bats can infect pigs, from which virus can pass to humans, or humans can be directly infected. The nature of human-to-human transmission is not clear but requires close contact perhaps mediated by droplets, fomites, intimate contact with body secretions or a combination of these elements. Nipah virus is excreted in saliva, nasopharynx and urine, and human-to-human infection does occur. Human cases typically present with abrupt onset of fever, headache, dizziness, and vomiting. Neurological signs include reduced levels of consciousness, segmental myoclonus, areflexia, hypotonia, and abnormal doll's eye-reflex, which develop in these individuals within a week of fever onset. Encephalitis is a prominent clinical feature and may recur. Respiratory disease is also prominent and the mortality is about 40%. (ref CEPI Task Team 1, Subgroup 1 report; Satterfield 2016)

The African green monkey (AGM), ferret, and hamster models are well established and accurately model human disease. Furthermore, the subunit vaccine based on the G protein (sG) and vesicular stomatitis virus (VSV) vaccines have protected AGMs and ferrets from lethal intranasal and intratracheal Nipah virus challenge.

Identification of an accurate correlate or surrogate of protection might serve as a satisfactory vaccination outcome to facilitate regulatory approval, although true correlates of protection against Nipah viral disease are not completely defined and standardized methods for measuring immune correlates are currently lacking.

The epidemiology and sporadic nature of Nipah virus outbreaks makes large scale, Phase III clinical trials difficult to plan to assure achieving meaningful efficacy results that would support licensure. Most candidate Nipah vaccines are in early stages of development.

Lassa Fever

Lassa fever (LF) virus (LASV) is a member of the Arenavirus family. LASV occurs throughout West Africa and is endemic in Sierra Leone, Liberia, Guinea, and Nigeria. Smaller numbers of cases have been reported Cote d'Ivoire and Burkina Faso, with serological evidence of infection in Togo and Benin. Eastern Sierra Leone has the highest incidence in the world. The main reservoir is the rodent Mastomys natalensis (known as the "multimammate rat"). Transmission of LASV to humans is through direct contact between rodent and humans living in West Africa villages through ingestion or inhalation of virus via Mastomys rodent's urine and droppings. Person to person transmission occurs through close contact with infected blood, tissue, or secretions of Lassa-infected individual, often from patients hospitalized with Lassa fever or in households. Symptoms of LF include fever, malaise, weakness, and headache. In 20% of people, disease may progress to more serious symptoms including hemorrhaging, respiratory distress, vomiting and shock. The case fatality rate is approximately 1%; however, case fatality rates during epidemics can be as high as 50%. The number of LF infections in West Africa ranges from 100,000 to 300,000 annually and approximately 5000 deaths each year but these numbers are believed to be underestimated due to limited systematic disease surveillance. (CEPI Task Team 1, Subgroup 1 report; NIPH Vax opp report 2016)

There are several preclinical LF vaccine candidates currently in development. There are a number of recombinant gene-based vaccines in development including those utilizing alphavirus; vesicular stomatitis (VSV), vaccinia, and chimeric yellow fever live virus vectors as well as a self-assembling vaccine. There is a need to better understand mechanisms and correlates of protection in humans.

Lassa virus (LASV) is endemic in several West African countries and is the etiological agent of Lassa fever. Despite the high annual incidence and significant morbidity and mortality rates, currently there are no approved vaccines to prevent infection or disease in humans. Genetically, LASV demonstrates a high degree of diversity that correlates with geographic distribution.