Coalition for Epidemic Preparedness Innovations

CEPI | New vaccines for a safer world

Meeting report

Photo: Daniel Berehuliak, New York Times

CEPI – Ebola vaccines regulatory science meeting

22 March,

National Academy of Sciences, 2101 Constitution Avenue, NW, Washington, DC

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Introduction

Historic progress in vaccine development for Ebola was made in 2014-16. The portfolio is now strong with multiple platforms having proof of concept in animals, and 9 vaccine candidates having progressed into Phase I clinical trials, with 5 of these continuing into Phase II and 1 into Phase III. Vaccine industry, academia, government laboratories and clinical trial centres worked incredibly hard to reach this achievement. These efforts are now about to be translated into improved preparedness for future outbreaks. WHO R&D efforts during the Ebola epidemic focused on fostering global collaboration and information sharing on Ebola vaccine R&D. This encompassed reviewing all available Ebola vaccine options, promoting scientific debate on trial designs, fostering dialogue on regulatory considerations and potential vaccine implementation policies, and providing advice on preferred product characteristics to inform long-term use of Ebola vaccines to control or prevent future outbreaks.

Regulatory agencies in the Ebola outbreak regions provided unprecedented global support to vaccine developers to facilitate regulatory assessment of clinical trial applications. This included consultations for expediting vaccine development and availability, in particular on clinical trial designs and subsequent regulatory pathways while keeping safety as a main concern. FDA, EMA, MHRA, Health Canada and Swissmedic are examples of agencies that provided timely and rapid regulatory guidance during this crisis, ensuring the best scientific advice was available to support safe, sound and speedy product development. AVAREF provided authorities with experience of pre-licensure vaccine trials to support those in the most affected countries that had less experience with clinical trials.

Coalition for Epidemic Preparedness Innovations (CEPI) engagement and work with development of Ebola vacccines

The Coalition for Epidemic Preparedness Innovations (CEPI) was formed as a consequence of the WHO-initiated R&D Blueprint in 2015. Despite the progress made in Ebola vaccine development in the past two years, no Ebola vaccine is yet licensed, accepted or available for use through a WHO pre-qualification process. CEPI therefore performed a gap and options analysis of Ebola vaccines, and the consulted stakeholders (WHO, MSF, Industry observers, members of CEPI SAC), indicated a strong need for focusing on regulatory assessment and approval facilitation for Ebola vaccines in the current absence of an Ebola outbreak. CEPI will support WHO in its role to coordinate global regulatory scientific advice to facilitate further development and eventual approval of Ebola vaccines. The CEPI Interim Board asked CEPI to address the regulatory science gaps by co-convening a meeting with key stakeholders in Ebola vaccine development. Stakeholders had highlighted the need for regulatory advice and knowledge sharing to address regulatory scientific issues important for regulatory approval.

The objectives of the meeting agreed with the organising committee were:
To clarify the current gaps in scientific knowledge and data needed to support licensure of Ebola vaccines via pathways other than traditional approval, i.e., approval in the absence of clinical efficacy data. Thus, CEPI initiated a process to allow regulators and Ebola vaccine developers to discuss data needed to support approval using non-traditional approval pathways and to arrive at a joint action plan to fill the gaps in regulatory science.

- To develop a common understanding and shared solutions to enable the timely licensure of vaccines needed to provide desired public health protection against filovirus infections targeted by CEPI.
- To present, discuss and identify immunological assessment bridging responses to Ebola vaccines between non-human primates and humans
- To outline a research agenda and draft an action plan to improve the understanding of vaccine-induced markers of protective immunity against Ebola disease

Organizing committee

Daniel Brasseur	Former CPMP/CHMP, Chair CEPI Regulatory Working Group
Benoit Callendret	Compound Development Team Leader Filovirus Vaccines, Janssen Vaccines & Prevention B.V.
Marco Cavaleri	Head of Anti-infectives and Vaccines, EMA
Emer Cooke	Head, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products, World Health Organization
Gary Disbrow	Director, Division of Chemical, Biological, Radiological, and Nuclear Countermeasures, BARDA
Mark Feinberg	President & CEO, International AIDS Vaccine Initiative; Chair of CEPI SAC
Marion Gruber	Director, Office of Vaccines Research and Review, FDA
Karianne Johansen	Senior Advisor, CEPI Secretariat
Marguerite Koutsoukos	Director, Vaccine Development Leader, GSK
Murray Lumpkin	Deputy Director Integrated Development, the Bill & Melinda Gates Foundation
Peter Marks	Director of the Center for Biologics Evaluation and Research, FDA
Line Matthiessen	Head of Unit DG Research and Innovation, Directorate for Health, European Commission
Elmar Nimmersgern	Deputy Head of Unit, Innovative and Personalised Medicine, DG RTD, European Commission
Gunnstein Norheim	Senior Scientist, CEPI Secretariat
Melissa Tice	Executive Director Biologics Regulatory, Merck
David Wood	Coordinator, Technologies Standards and Norms, World Health Organization

This report has been drafted by the CEPI Secretariat and reviewed by the organising committee of the meeting. The purpose of this meeting report is to provide a summary of the meeting in a transparent way to assist and inform the future regulatory scientific work and research areas on Ebola vaccines.

We wish to thank the organising committee for their valuable contribution to making this meeting happen in such a collaborative manner. We wish to particularly thank the National Academy of Sciences and Victor Dzau for kindly hosting the meeting and Margaret Hamburg from the National Academy of Science, Chair of CEPI JCG, for moderating the meeting. Finally, we want to thank Mark Feinberg, the Chair of CEPI SAC, for being the driving force behind this initiative and for his contributions to planning the meeting.

Agenda

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Meeting chair and moderator: Peggy Hamburg, NAS

Time	Topic	Presenter
07:00-8:00	**REGISTRATION AND BREAKFAST**	
08:00-08:05	Welcome address	**Victor Dzau**, NAM
08:05-08:15	Introduction – Framing the key questions for the meeting	**Mark Feinberg**, CEPI (SAC)
	Session 1 **Setting the stage – Available pre-clinical and clinical data**	
08:15-08:30	Brief review of the history of the Ebola virus outbreaks and overview of the five viruses in the genus Ebolavirus and the possibility of cross protection	**Sina Bavari**, USAMRIID
08:30-10:35	Presentation of background, data from animal models and human clinical trials, including immunogenicity data (35 minutes for each of the three vaccine sponsors with phase 2 or 3 clinical data) 8:30-9:05 **Speaker** from JnJ 9:05-9:40 **Jayanthi Wolf**, Merck 9:40-10:15 **François Roman**, GSK 10:15-10:35 **Helen Mao**, Tinanjin CanSino	
10:35-10:50	**BREAK**	
	Session 2 Chair: Peggy Hamburg **Assess the strength of the evidence from the immune response and animal models**	
10:50-11:00	WHO Reference Reagents for Standardisation of EBOV Antibody Assays	**Dianna Wilkinson**, NIBSC
11:00-11:10	Standardisation of assays and state of progress	**Nicole Kilgore**, JVAP
11:10-11:30	Overview of non-human primate (NHP) models of Ebola virus disease	**Amy Shurtleff**, USAMRIID
11:30-11:50	Bridging the gap between immune responses in non-human primates and those seen in humans - "Correlates of Protection by Ebola Vaccines as Predictors of Efficacy"	**Stanley Plotkin**, VaxConsult

11:50-13:00	**LUNCH**	
13:00-14:00	**Panel/group discussion:** **Dianna Wilkinson**, NIBSC; **Nicole Kilgore**, JVAP; **Amy Shurtleff**, USAMRIID; **Stanley Plotkin**, VaxConsult; **Peter Marks**, FDA; **Marco Cavaleri**, EMA; **Nancy Sullivan**, NIH; **Ed Nuzum**, NIH Discussion topics to include: • Can immune correlates of protection from NHP studies be defined and can immune responses in NHP be bridged to human immunogenicity • Which studies should be initated to address the gaps in bridging immunogenicity in NHPs and humans	
	Session 3 Chair: Marco Cavaleri **Licensure Pathways**	
14:00-14.15	Overview of US licensure pathways	**Marion Gruber**, FDA
14:15-14.30	EMA perspective on licensure	**Marco Cavaleri**, EMA
14:30-14:45	Emergency use and assessment listing (EUAL)	**Emer Cooke**, WHO
14:45-15:00	Perspective of African regulators	**Dicky Akanmori**, AVAREF
15:00-15:30	**BREAK**	
15:30-16:10	**Panel/group discussion:** **Marion Gruber**, FDA; **David Wood**, WHO; **Dicky Akanmori**, AVAREF; **Ozzie Berger**, GSK; **Johan van Hoof**, JnJ; **Ercem Atillasoy**, Merck Discussion topics to include: • Paths toward licensure of additional vaccines following the licensure of the first vaccine and • How to apply clinical data derived from monovalent vaccines to support the demonstration of safety and efficacy of multivalent vaccines	
	Session 4 Chair: David Wood **Key Characteristics for a Safe and Effective Ebola Vaccine**	
16:10-16:30	Potential designs for future clinical trials/postlicensure studies	**Ira Longini**, UFL
16:30-17.15	**Group discussion** Gaps in regulatory science/ Summarizing the remaining work to be done	**Peggy Hamburg**, NAS

Meeting summary

Executive Summary

The Ebola vaccines in advanced clinical development were reviewed at this meeting, along with the challenges that need to be addressed to ensure successful development and approval of safe and effective Ebola vaccines. Given the different modes of action of each of the candidate vaccines, their different characteristics, and the varying degrees of data to date on vaccine performance, extrapolation of efficacy and safety determinations from one candidate to another is not currently supported. The efficacy, safety, and manufacturing quality data needed to support regulatory approval have to be accrued separately for each candidate, and programmatic use determinations made separately. Immunological assessment methods bridging responses to Ebola vaccines between NHP animal studies to humans have been developed; however, successful bridging to predict the actual clinical benefit in humans has proven difficult and remains to be formally achieved as the level of antibody responses between the two species was different.

A number of areas of regulatory science were identified as requiring further work. Chief among these areas is **refining the non-human primate (NHP) animal model**. This is particularly the case with respect to its relevance to human Ebola disease (i.e., to aid in "immunobridging") and could include the **exploration of adaptive trial designs and/or changes to current protocols**, especially as to whether there might be clinical endpoints other than mortality that could be used to assess efficacy of a vaccine candidate in the NHP model. Other areas include: 1) **standardization of laboratory assays used in investigation of Ebola vaccines**, 2) **understanding potential immune correlates of protection**.

There was agreement that advance preparations should begin, in coordination with WHO and AVAREF, for regulatory review of vaccine candidates in countries where the next outbreak might occur. Advance consensus on clinical trial designs that might be used in the event of an outbreak was also agreed to be a critical part of the response that would facilitate evaluation of vaccine candidates. In addition, establishment of robust post-vaccination surveillance mechanisms for study participants would contribute considerably to the evaluation of vaccines. By developing appropriate assays, performing the appropriate animal studies, conducting and evaluating well-designed clinical trials, and taking advantage of all existing regulatory pathways, the availability of safe and effective Ebola vaccines will be possible.

Overall summary and conclusions from the meeting

For the leading Ebola vaccine candidates, efforts and data have been presented, including immunological assessment methods bridging vaccine-induced immune responses (IR) between NHP and humans. Methods to bridge immunological data between human and NHP studies have been developed; however, successful bridging to predict the actual clinical benefit of the vaccines in humans is difficult and, if possible, remains to be formally achieved as the level of antibody responses in humans versus NHP have been very different.

Given their potentially different modes of action of each candidate vaccine, their different characteristics, and the data to date on performance, extrapolation of safety, immunogenicity, and efficacy from one vaccine candidate to another is not currently supported. Thus, efficacy, safety, and manufacturing quality data needed to support regulatory approval need to be accrued for each vaccine candidate and programmatic use determinations, especially with respect to correlates of protection in NHP and/or humans.

Specific areas of regulatory science remain to be explored further with respect to these current candidate vaccines. These specific areas are highlighted below.

Further work per topic area should be defined in smaller task forces with developers and scientists to define the research agenda that CEPI could contribute to addressing.

To finish the job on Ebola it is imperative to determine what is practical and/or feasible regarding efforts to address outstanding regulatory science questions. If not all of these can be addressed, they should be prioritized based on potential impact on the ability to interpret Ebola NHP vaccine candidate trials vis-à-vis human implications.

Areas of regulatory science that need further exploration

Refining the NHP animal model with respect to its relevance to human Ebola/Filovirus disease (i.e., to have a model that could better mimic what happens in humans to support "immunobridging").

For Ebola vaccine development extensive NHP data have been generated with current challenge models that seem to be more stringent than EVD in humans. However, at this advanced stage of vaccine development, a complete redesign of the NHP model is not practical, and therefore data acquired using the existing NHP model need to be an acceptable part of the dossier considered for potential licensure. While the feasibility and priority of issues listed below has to be determined for Ebola, aspects could be considered for the development of other Filovirus vaccines (including multivalent formulations) that haven't yet progressed as far.

Issues to be addressed include:

- The magnitude of challenge doses administered to NHPs.
- The route of viral exposure to NHPs (IM versus intranasal or other routes of exposure more relevant to the human route of exposure), as apparently the current IM route was chosen because the protocol was developed when concern was infection by inadvertent laboratory needle stick.
- The source of virus administered to NHPs.
- The source of animals used in the NHP testing protocols.
- Adaptive trial designs and/or changes to current protocols.
- Determination of clinical endpoints other than mortality that could be used to assess efficacy of a vaccine candidate in the NHP model.
- Further quantitation of duration of protection conferred on the NHPs by a candidate vaccine.
- Cross protection, if any, against Ebola virus strains/species other than just the one used in the candidate vaccine.
- Tissues other than blood as a possible source of viral detection in infected NHPs

Regulatory science issues with respect to assays.
Standardization of laboratory assays such as ELISA and PRNT is needed. PRNT in particular has given inconsistent results. This issue highlights the need for the development and standardization of alternative live virus neutralization assays, in particular, those that could be run in BSL2 laboratories (e.g., with pseudotyped virus). Further development and standardization of additional antibody-based assays would be useful to enhance understanding of antibody function (other than neutralization, e.g., ADCC), avidity, affinity and specificity. In addition, standardized cellular immunological assays should also be considered. These data could inform efforts to identify mechanisms of protection.

Other areas identified as needing further investigation included:

- Further standardization of plaque assays for challenge virus stocks.
- Determination of acceptable strategies for assay use to determine NHP and human immune responses for bridging

- Standardization of immunological assessment methods used for bridging Ebola vaccine-induced responses in NHP to humans

Correlates of Protection /Surrogate Endpoints reasonably likely to predict clinical benefit.
For the purposes of this report, a correlate of protection (CoP) is an immune marker responsible for and statistically associated with protection. A surrogate endpoint (SE) is an immune marker that is not directly involved in protection, but is reasonably likely to predict protection or other clinical benefit. While a CoP is preferred, under certain circumstances an SE can be used for inferring protection when a CoP is not available.

There was a consensus to evaluate each vaccine separately, since animal studies have indicated that the mechanisms of protection may be different for each vaccine. Furthermore, the vaccine candidates may differ in which indications are appropriate:

- Acute use to quench an outbreak
- Prophylactic use for long-term protection in an endemic or high-risk population
- Emergency preparedness use in first responders

SE need to be established for each vaccine that reflect their putative mode of protection for a given indication. Clarification is also needed regarding against what exactly the SE predicts "protection," e.g., viremia or clinical disease.

Other approaches discussed as possible alternatives to current NHP approach
Approaches discussed included alternative designs for NHP immunization challenge studies (e.g., different doses or routes of challenge), passive protection studies in NHP using transfer of specific immune components, and surrogate human challenge studies using pseudotyped virus.

Regulatory Issues
The session on licensure pathways discussed the need to prepare now, in coordination with WHO and AVAREF, for regulatory review of vaccine candidates in countries where the next outbreak is likely to occur. Advance agreement on the design of clinical trials that could be used in an outbreak was seen as a critical part of the preparedness effort. Advance agreement on the parameters for a potential clinical trial by regulatory authorities in countries most likely to be affected was also mentioned as important, since more definitive information related to the specific outbreak could be added at the time of the outbreak to complete the previously drafted clinical trial protocol.

Another area of importance will be to develop and agree on plans regarding post-deployment follow-up to gather further safety and efficacy information from the field if investigational candidate vaccines are deployed in low-income countries that currently do not have systems for such surveillance in place.

After the first vaccine candidate has been licensed for use -- either fully licensed or licensed through a conditional mechanism -- post-licensure follow-up to further study its safety and effectiveness will be needed. There is need for agreement on clinical trial designs for assessing the safety and effectiveness of further monovalent investigational vaccine candidates after the first monovalent vaccine candidate has been licensed for use, as well as clarify requirements for clinical development of multivalent vaccine candidates.

Contingency Planning as highlighted by one of the African regulatory agencies.
This meeting focused primarily on what still needs to be done to get an Ebola vaccine licensed. At the same time, we need to focus on what we would do if there were an outbreak prior to the licensing of

a vaccine – i.e., if we had to use our current tools (at their current state of development) and our current state of knowledge about those tools:

- Clinical trial designs?
- Use in first responders?
- Use in ring trials or other trial designs to try to stop the outbreak?
- Availability/delivery/storage issues?
- Different approaches with different candidates, if more than one had to be used?

Upcoming SAGE meeting should address some of these issues.
Based on SAGE recommendations, CEPI should determine if there are areas that need further regulatory science engagement to address this contingency, while continuing to press forward with developing the information needed for the candidate Ebola vaccines.

Post-note after the meeting:
The SAGE recommendations can be found here.

The path forward

Based on discussions during this meeting, within the CEPI secretariat, and with the organizing committee, the future research areas can be grouped into the following themes: NHP models, CoP/SE, and assays. A further refinement of specific research questions that CEPI should focus on will be taken forward in smaller task forces. Small task forces will be established to focus respectively on each of the main themes. The CEPI Secretariat is currently working on the composition of these groups, as well as their mandates and timelines.

It should be emphasized that CEPI's ultimate goal with this exercise is to facilitate the path to licensure for candidate Ebola vaccines by identifying areas where CEPI could contribute to closing important scientific gaps. This process is not intended to interfere with ongoing conversations between the companies developing these vaccines and regulatory bodies, but rather to complement these efforts, where needed. Addressing these research questions could be useful for future generations of these vaccines, new vaccines against other Ebola species or other filoviruses, and multivalent formulations. To what extent they should be addressed for the current generation of vaccines will need to be determined on an individual basis, and for each defined indication, through dialogues between companies and regulators.