CEPI

Summary review on vaccine regulatory pathways important for CEPI




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CEPI's response *(adapted from CEPI Preliminary Business Plan)*

The global response to the 2014 Ebola viral disease (Ebola) outbreak in West Africa highlighted the consequence of limited investment in medical countermeasures for epidemic infectious diseases that are characterized by limited market potential (EIDs), resulting in loss of human lives, devastation of national economies, and a humanitarian crisis. Recognizing the urgent need for a new approach to EID vaccine development, leading figures from governments, foundations, industry and civil society proposed a coalition for proactive R&D during the Annual Meeting of the World Economic Forum in Davos in January 2016. Since then, representatives from industry, governments, foundations, regulators, intergovernmental organisations, such as WHO and civil society organisations, have been closely collaborating to create a Coalition for Epidemic Preparedness Innovations (CEPI). CEPI has been separate from (but complementary to and strongly informed by) the WHO-led process to develop an R&D Blueprint for emergencies.

During its initiation phase (January 2016 – June 2016), CEPI has consisted of a stakeholder group and a project management group that set up expert task teams to consider issues such as pathogen prioritisation, clinical development, manufacturing capacity and regulatory pathways, potential models for partnership, funding needs, resource mobilization and shared risk/reward arrangements between sectors.

This summary review on vaccine regulatory pathways important for CEPI was initiated under Task Team 1, specifically the sub-groups looking at clinical development and regulatory affairs. The purpose of this summary is to provide an overview of the current regulatory standards available for EIDs in an emergency. This summary is available on the CEPI website www.cepi.net and will be a reference for future work related to vaccine and regulatory pathways important for CEPI. A working group focused on regulatory affairs will develop a work plan and coordinate further work with the CEPI Scientific Advisory Committee (SAC) and Joint Coordination Group (JCG).

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Introduction and overview

The applicability of current regulatory standards and pathways, guidelines and requirements influencing the development of EID vaccines that can be applied in an emergency are fragmented. There is a global need for increased clarity and predictability in regulatory pathways and processes to ensure fast and efficient development and access to vaccines. This is required for "proof of principle" studies, for data required for emergency use during an outbreak and for stockpiles for preparedness in the absence of an ongoing outbreak. Such efforts can immediately be advanced by early engagement with regulatory authorities in the development of candidate vaccines or in the utilization of existing candidate vaccines for further clinical trials to evaluate efficacy and safety. Regulatory authorities in vaccine producing countries have a particularly important role to play, as well as regulators and ethics committees in countries where vaccines are most likely to be investigated, and ultimately used. Similarly, WHO has a critical role to play in the assessment of these vaccines and in making recommendations for the use of vaccines under both emergency and routine circumstances. Finally, while beyond the scope of this paper, we must acknowledge that procurement agencies and national utilization decision-makers will play major roles in the path to patient access under these circumstances.

Evidence clearly shows that rigorously designed clinical trials can be conducted with fidelity during an epidemic.[1,2] However, the designs of these trials must be agreed to the extent possible well before an outbreak, so that precious time is not lost debating clinical trial design as the outbreak spreads.

1. Background

The purpose of this summary review is to describe the current state of global approval processes for clinical trials and marketing authorization for vaccines and the current state of regulatory pathways, and relevant processes, for emergencies. This summary review will be an important tool to further engage and work with regulatory partners on collaborative efforts to provide advice and negotiate on regulatory and ethical pathways for vaccines for and during epidemics.

National Regulatory Authorities (NRAs) and local health research ethics committees are responsible for overseeing and authorising clinical trials that are to be conducted in their jurisdiction, and NRAs are responsible for licensing vaccines and monitoring safety after introduction. Different NRAs have different levels of experience in the assessment of clinical trial applications (CTAs) and the procedures for the oversight of clinical trials varies considerably between jurisdictions, especially with respect to roles and responsibilities of NRAs and national/local ethics committees. In both emergency and non-emergency situations, less well-resourced NRAs may work through WHO pathways to support approval of clinical trials and/or of vaccine registration.

There are some main categories of marketing authorisation application (MAA) approval pathways for vaccines at the U.S. Food and Drug Administration (USFDA) and the European Medicines Agency (EMA), these are:

- Standard regulatory procedures for vaccine approval
- Frameworks for accelerated assessment of data and accelerated development in non-emergency situations
- Procedures for vaccine approval and emergency use assessment, or expanded access strategies in public health emergency situations

Standard regulatory procedures for vaccine approval

Standard approval pathways are appropriate and preferred in most situations; however in the situation of a Public Health Emergency of International concern (PHEIC)[3] the level of evidence required to authorize a product may be reduced through the willingness of the larger community to tolerate a greater level of uncertainty about the vaccine as a result of the severity of the emergency and the lack of alternative therapies. In some emergency circumstances, standard development approaches might be inapplicable, for example, during a public health emergency where meeting certain clinical trial requirements may not be feasible.

Accelerated assessment of data and accelerated development in non-emergency situations

In non-emergency situations, some regulatory agencies have developed tools like conditional approval (EMA) and accelerated approval (USFDA) for early access to certain vaccines when these products are believed to meet an otherwise unmet serious and life-threatening medical situation. Most often, these authorisations are based on an established effect on a surrogate endpoint that is believed to be reasonably predictive of clinical benefit accompanied by substantial safety data to support a favourable risk/benefit assessment. Such conditional approval and accelerated approval are then subject to specific obligations, on the basis of less comprehensive data. In addition, new studies are expected to be provided after the conditional- and accelerated approval to verify the anticipated effect relying on the surrogate endpoint on which the conditional- and accelerated approval was based. Such approvals may be withdrawn if additional studies and/or emerging safety or efficacy data do not support use.

Likewise, some agencies have developed specific procedures for using animal data alone to support an efficacy claim, when efficacy testing in humans is either not possible or would be unethical. Such "animal rule" authorizations usually also require substantial human safety data which may not be able to be gathered from individuals drawn from the communities for which the vaccine is intended. Vaccines approved under the animal rule require further efficacy evaluation as well as safety monitoring under conditions of use if/when the product is used in specific populations in the future.

Procedures for vaccine approval in public health emergency situations

In emergency situations, some national and regional regulatory authorities (NRAs) and the World Health Organisation (WHO) have developed specific emergency evaluation pathways and procedures that may allow for time-limited emergency use authorization of products based on a risk/benefit assessment of more limited available data, which are usually less than those required for a full authorisation under non-emergency situations. These time-limited emergency authorizations often require formal declarations of PHEIC under the International Health Regulations (2005)[3], or a specific public health emergency in that jurisdiction, and are based on the community's greater level of tolerance of the unknown with regard to product efficacy, safety, and quality given the exigencies of the public health emergency.

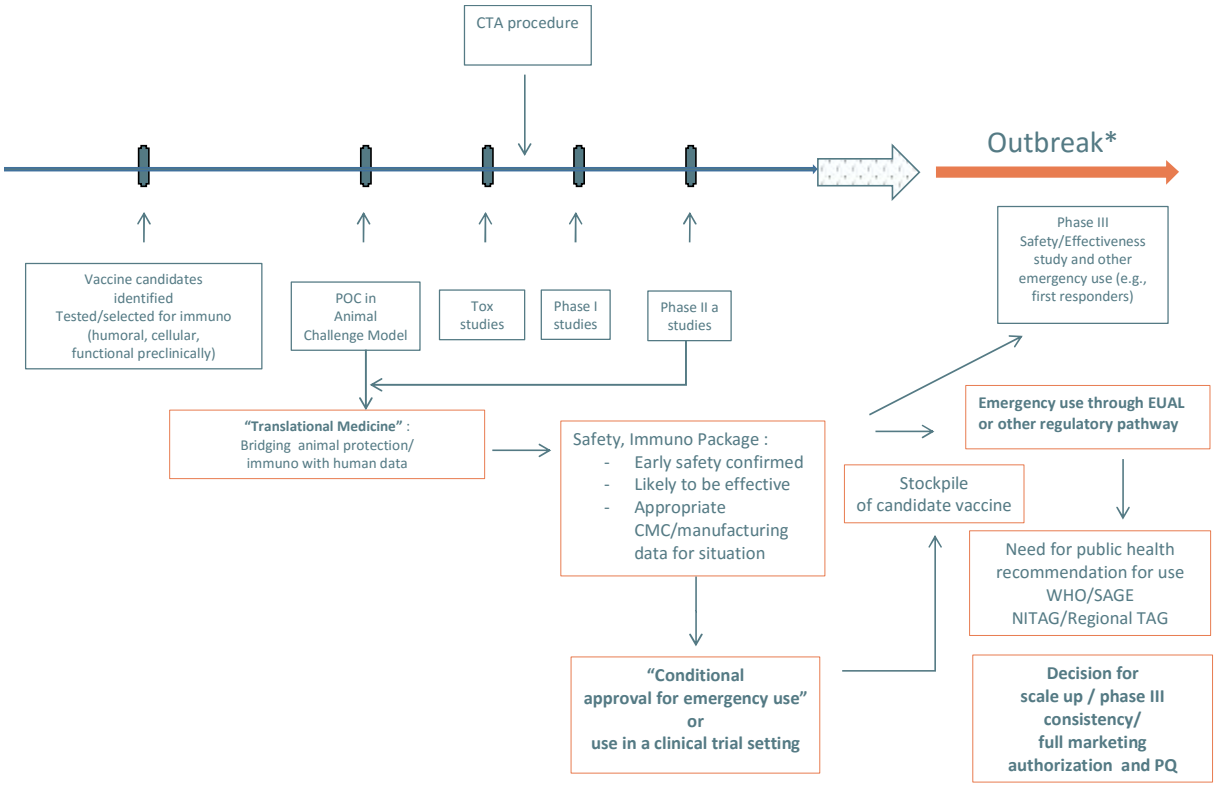
Clinical trial approval/Investigational new drug application

It is important to consider that even in emergencies, non-emergency pathways for using or studying products may be applied flexibly under an investigational new drug application (IND) or comparable regulatory vehicle. Regulators have a key role to play in reviewing all available data to optimize what can be learned from emergency use to better characterize the product's risk/benefit. Regulatory authorities and ethics committees must protect subjects rights even under emergency provisions and ensure that subjects are informed about what is known and unknown about a product and are not exposed to undue risks from its use.

With the Coalition for Epidemic Preparedness Innovations (CEPI) focusing on the development of vaccines for a limited number of prioritised pathogens that are considered to be for 'high and unmet public health need', it is anticipated that different regulatory frameworks and bodies may be applicable. There are several regulatory procedures in addition to the emergency procedures that are relevant for a public health emergency situation, which may have a role in the development pathway of these vaccines.

The initial development pathway for candidate vaccines for use in potential emergencies funded by CEPI will be up to "proof of principle" and ready for phase III whenever possible in the absence of an on-going outbreak. There will then be requirements for stockpiling product at this stage, until effectiveness studies and characterisation of safety in larger populations ideally can be obtained during an outbreak (see figure 1). Such studies need to be planned and implemented with full consideration of pragmatic limitations and ethical issues that will arise in the field and during an emergency. The flow chart highlights key clinical development and regulatory stages in the end-to-end continuum of development of vaccines and can be used to build milestones into CEPI activities to facilitate development in the regulatory and manufacturing areas.

Figure 1. One possibility of key clinical development and regulatory stages in the end-to-end development of vaccines.



*If an outbreak occurs before product development reaches phase 2a decisions would likely be on a case-by-case basis

Figure 1 includes one possible approach to achieving conditional approval or authorisation status for emergency use, based on clinical data on safety and immunogenicity to ensure availability of stockpiles, ready to be used mobilised for studies and where supported by risk/benefit analysis, potential to be used at the time of outbreak (e.g., in first responders or others a high risk). The development, and to the extent feasible, pre-positioning of standardised and agreed clinical trial protocols with appropriate of pre-approvals for different types of pathogens would be useful to facilitate rapid and efficient initiation of clinical trials during an epidemic outbreak. The use of EUAL is today a time-limited emergency authorizations which requires formal declarations of PHEIC under the International Health Regulations (2005)[3]. The process to develop these clinical trial protocols during an epidemic outbreak should involve regulatory scientific advice with relevant developed and developing country regulators and ethics committees, to facilitate global consensus on study design and on the pre-clinical and clinical data required to support phase III studies for a selected candidate vaccine. While recognising that each outbreak and each pathogen will be different, it should therefore not be excluded for some pathogens to extend the scope to generate additional safety, immunogenicity and additional efficacy data to further inform Phase III trial design when possible.

National Regulatory Agencies (NRAs)

Over the last ten years there has been an increase in the establishment and capacitation of NRAs in developing countries, often with the support of WHO and assistance from more highly resourced NRAs. The evaluation of vaccines for possible approval by NRAs is based on the evaluation of pre-clinical data, of demonstrated safety and effectiveness, and approval of consistent, high quality manufacturing processes and facilities. Processes used by these NRAs can differ. Many less well-resourced NRAs depend on WHO's prequalification process[4] which enables WHO to work with a

WHO-recognised NRA in a manufacturing country to ensure Good Manufacturing Practice (GMP) standards and proper clinical evaluation. Some well-resourced NRAs conduct full licensure/authorisation procedures, including inspection of manufacturing facilities. Other less resourced NRAs may use an abbreviated assessment procedure, which references the work of a trusted regulatory agency to inform their own regulatory decisions, thus avoiding repetition of manufacturing inspections and/or of duplication of complete scientific assessments. Some agencies have developed conditional/accelerated authorisation processes for use in non-emergency circumstances when a community is faced with a serious and life-threatening outbreak for which there are limited medical tools.

Enhancing NRA decision making through collaboration and harmonization

Circumstances in an emergency situation are time critical, often with fear and alarm about an evolving disease outbreak. In this pressurised situation, NRAs must consider issues related to conduct of clinical trials and may be asked to consider access or even broad authorisation/approval of vaccine use outside of such trials. This must be done in a manner that balances complex issues and priorities, while promoting access that may benefit patients, and also protects patients and optimises the generation of data that will be useful in vaccine assessment and public health decisions in order to ultimately benefit the individuals and establish how best to respond to the present and potential future outbreaks. Noting the variable level of resources among NRAs, collaboration and technical assistance through either more open discussion or other arrangements with more resourced regulatory authorities, such as the USFDA, EMA, Swissmedic, and Health Canada, can provide critical technical assistance to less resourced NRAs. This kind of collaboration (which has sometimes been coordinated through WHO) leverages the expertise and resources of well-resourced NRA's to help to ensure access to and review of key data so that vaccines meet required safety, efficacy, and quality standards. Further, the involvement, preferably as early as possible, of the NRAs and local research ethics committees from countries where vaccines may be investigated and/or used, provides critical cultural, public health and programmatic perspectives, which strengthen risk/benefit assessments, communication strategies and the likelihood of successful implementation of clinical studies. Such collaborations with more resourced NRAs were utilized with Sierra Leone, Liberia and Guinea, in partnership with WHO and with the African Vaccine Regulatory Forum (AVAREF), in the context of candidate vaccine clinical trial application (CTA) review and CTA evaluation during the West Africa Ebola outbreak.

WHO Prequalification[4]

With respect to assessment for market authorization and access, the WHO vaccine prequalification (PQ) process plays an important role. Working with an NRA that takes responsibility for the on-going oversight of the vaccine (usually in the manufacturing country) and that WHO believes is qualified to do so, the WHO vaccine PQ process assures the safety, efficacy and the quality of a vaccine, distributed by UNICEF and other United Nations (UN) and global multilateral agencies. Approximately 66 % of the world's vaccines are prequalified by WHO. Likewise, many NRAs have

chosen to rely on the assessments of the WHO vaccine PQ program to help inform their own national vaccine registration decisions.

The principles of WHO vaccine prequalification are:

- Reliance on an NRA that the WHO has judged to be "functional for certain vaccine related regulatory functions, especially post-approval" (usually in the manufacturing country).
- Assurance of production process and quality control (QC) methods that meet international standards.
- Production consistency ensured through international good manufacturing practices (GMP) compliance.
- Testing for compliance with specifications.
- Monitoring of complaints from the field.
- Assurance of data to support product safety, efficacy, and country program suitability.

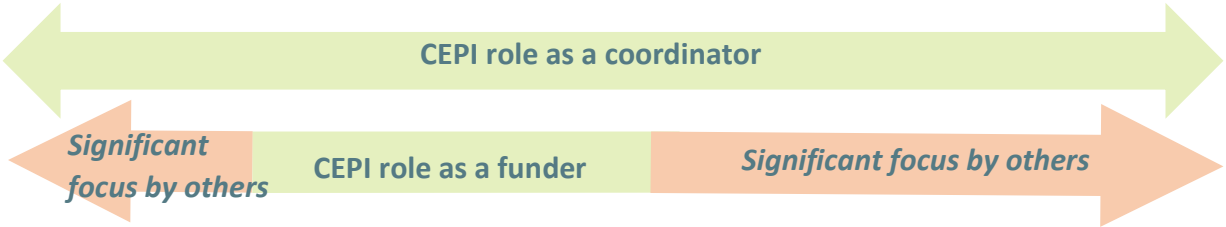
Clear, accountable and predictable regulatory procedures are required

Clear, accountable and predictable regulatory procedures and data requirements are required to ensure that vaccine development for use in emergencies occurs in an efficient, yet scientifically valid and safe, manner. This is important for CTA assessment/authorization and for marketing application assessment/authorization in relation to requirements for clinical data in humans in the absence of an on-going outbreak, as well as for effectiveness studies and, to the extent feasible collection of safety data, during an outbreak.

2. The scope of CEPI in the end-to end spectrum of vaccine development

As noted previously, there is not one single pathway for regulatory approval for vaccine CTAs and MAAs. The leading well-resourced regulatory authorities, such as USFDA, EMA and EU NRAs, Swissmedic, the Australian Therapeutic Good Administration (TGA), the Japanese PMDA, and Health Canada, each have their own, somewhat similar, pathways. In addition, WHO plays an important role in both the clinical trials application authorization in LICs and the vaccine prequalification processes and also in defining norms, promoting harmonization, and supporting smaller NRAs with limited technical capacity. Figure 2 outlines the planned scope of CEPI involvement in the end-to end spectrum of development of vaccines against specific pathogens chosen by CEPI. This is in addition to working in partnership with the different stakeholders and existing initiatives.

Figure 2: The role of CEPI within clinical development pathway



	1 Discovery	2 Development/ Licensure	3 Manufacturing	4 Delivery/Stockpiling
Current Stakeholders	• Academia • Governments • WT/NIH • GLOPID-R • Industry • Regulators • Biotech	• Industry • National Governments • Regulators • Bill and Melinda Gates Foundation • BARDA/DTRA etc. • WHO • Biotech • PDPs	• Industry • BARDA • CMOs • Regulators • National • Governments • WHO	• GAVI • UNICEF • PAHO • National Governments • WHO • Industry • Pandemic Emergency Facility (World Bank)

Most initial CTA (EU or IND US) authorisations for clinical trials and MAA applications for approval of novel vaccines are managed by EMA, EU NRAs and/or USFDA. These agencies are also frequently engaged by governments/NRAs/or study sponsors/vaccine developers in the vaccine development, evaluation and regulatory process in the case of epidemics in regions and countries not overseen by the EMA or USFDA, where there are examples of one, or both, of these agencies engaged in review and oversight of early (i.e., Phase I and IIa) clinical testing of candidate vaccines within their own jurisdictions. In this situation WHO will work with USFDA/EMA, and local NRAs to secure vaccine CTA and/or MAA review and approval [either accelerated or emergency (temporary)] to ensure there is appropriate testing and access in the region.[4]

Some well-established NRAs have various regulatory pathways in place that, in the event of a PHEIC, could permit expedited review of MAA submissions as well as, where deemed appropriate, the emergency use of investigational (or unapproved) vaccines with limited safety and efficacy data. It is important to note that expedited review of submissions does not imply a less thorough evaluation of the data submitted. It refers firstly to the compressed timelines for undertaking the review. In addition, expedited review may also include assessments of the use of surrogate endpoints, mainly immunogenicity, that are thought to be reasonably predictive of clinical benefit. In such situations, a sponsor will need to demonstrate and confirm the clinical benefit with follow-up studies post licensure/approval (this is described in detail in Section 3). The choice of regulatory options will depend on the specific disease, including whether there are likely correlates of protection, and the availability of data on the vaccine under consideration and the exigencies of the public health emergency, as well as the intended extent of vaccine distribution under such an option.

In the current regulatory structure for approval of vaccines, several possibilities are available to be applied in an emergency situation under the EMA, the USFDA and through WHO to encourage and expedite the development and approval of novel vaccines to meet an unmet need. These include already established measures, including early access options and faster regulatory assessments. Examples of these processes are:

Table 1: Short summary of accelerated and emergency use assessment procedures related to Marketing Authorization Application assessment

	Expedited regulatory procedures and frameworks	Emergency Use regulatory procedures
USFDA[5]	- Priority review - Accelerated approval - Fast track - Breakthrough therapy - Animal Rule - Expanded access - Treatment IND	- (in addition to the expedited procedures) - Emergency IND - Emergency Use Authorization (EUA)
EMA[6]	- Accelerated assessment - Conditional marketing authorization - Compassionate use opinion - Approval under exceptional circumstances - Priority Medicines (PRIME) - Article 58 (enables the EMA to give a scientific opinion with the WHO; it could also be conditional or exceptional circumstances)	- EMA's accelerated approval pathways: - Conditional marketing authorization - accelerated assessment with rolling reviews - Marketing authorization under exceptional circumstances (such as orphan conditions). - Article 58 (enables the EMA to give a scientific opinion with the WHO – can be used in an emergency situation)
WHO[7]	Abbreviated assessment (reliance on the work products of stringent NRAs to inform the WHO PQ decision, rather than repeating them)	Emergency Use Assessment and Listing procedure (EUAL).

In addition to Table 1, a detailed overview of the global standard procedures and already existing accelerated procedures and emergency procedures are presented in Appendix 1 (tables 1 & 2). The Appendix can be found through this web link.

To complement processes used by EMA and USFDA, WHO has established an Emergency Use Assessment and Listing procedure (EUAL), Appendix 1 (table 3).[7] The purpose of this special procedure is to provide guidance regarding the safety, efficacy, and quality of vaccines for use under emergency situations to interested UN procurement agencies and national regulatory authorities

(NRAs) of relevant WHO Member States. The EUAL vaccine procedure was developed for use in the case of a PHEIC declared by WHO under International Health Regulations 2005, when the community may be more willing to tolerate less certainty about the efficacy and safety of a vaccine, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options.[7]

3. Clinical development of vaccines of particular importance for CEPI

The clinical development pathway for a vaccine to protect against a pathogen causing a PHEIC depends on its indication and target population. Thus, the study population, laboratory and clinical evaluations, trial designs and endpoints chosen are specifically tailored to the product and the emergency situation it is trying to address.

In general, the clinical immunogenicity, safety and effectiveness of a vaccine are evaluated in various phases. In the CEPI model, it is proposed that Phase I and II data are generated before an emergency occurs. While Phase III randomised, placebo-controlled clinical trials typically provide the most definitive confirmatory evidence of vaccine efficacy it may be difficult to conduct such studies of conditionally approved (EMA) or emergency use authorized (FDA) vaccines in the midst of an outbreak, whether related to perceptions that a potentially beneficial product is being withheld from some participants, or for logistical/pragmatic reasons. Although, in the Ebola outbreak this was done with the approval of the affected country NRAs and ethics committees (1,2). In some emergency circumstances, and where appropriate to disease epidemiology, alternate study designs/types of controls (e.g. adaptive study designs, cluster randomization) may be considered to characterise or confirm field efficacy. A full discussion of the issues in study design, including when alternate approaches may provide useful data, as well as the potential risks of not obtaining data from RCTs, is critical, but beyond the scope of this paper.

Under traditional development pathways, a demonstration of vaccine effectiveness is based on a clinical disease endpoint or alternatively, an accepted correlate of protection (e.g. antibody response data previously linked to thresholds of protection). As described above it is critical that scientific, logistic and ethical issues in clinical trial designs to be used for specific CEPI vaccine candidates are thoroughly discussed, and plans developed and agreed upon, including by regulators. This should be ensured as early as possible prior to the emergency both to ensure adequate consultation of all appropriate stakeholders that informs decision making and to prevent delays in implementation of the trial as quickly as possible once the emergency commences.

In the case of an emerging infectious disease, there is usually no known accepted correlate of protection. Thus, a demonstration of effectiveness based on clinical disease endpoints would typically be required for traditional vaccine approval when a proven or likely correlate of protection is not available.

Some of the accelerated emergency use regulatory approaches listed above in Table 1 are pathways to emergency licensure that might not always require a demonstration of effectiveness in a clinical disease endpoint trial or an accepted correlate of protection. In these cases, emergency licensure/approval could be based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response) that is *reasonably likely* to predict clinical benefit. The surrogate endpoint used to evaluate effectiveness could be derived from animal and/or human studies. Adequate and well-controlled studies would be required post-licensure to verify, and describe the clinical benefit of the vaccine and possibly try to verify the surrogate.

Approval under the "animal rule," as by USFDA, can be considered for products for certain serious or life-threatening conditions when definitive human efficacy studies are not ethical or feasible and when other efficacy standards (e.g. the accelerated approval provisions) cannot be used.[8] This regulation permits USFDA to license vaccines based on adequate and well-controlled animal studies using well-characterized and relevant models when the results of those animal studies establish that the vaccine is *reasonably likely* to produce clinical benefit in humans, provided that safety of the vaccine in humans, including the intended population(s) for use, has been adequately evaluated.

As noted, there are regulatory requirements under this provision including criteria for the animal model(s) and the need for data or information, in animals and humans, to allow selection of an effective dose in humans. In this situation, post-marketing studies are required to verify the vaccine's clinical benefit and immunogenicity and to further assess safety as well as duration of the protection and monitoring the need for booster dose. They must also be conducted at a time when such studies are feasible and ethical.

The role of WHO in developing guidance for the regulation of vaccine development and approval

WHO identifies and consolidates current consensus opinions on key regulatory issues, and communicates them to national authorities and manufacturers through guidance documents addressing both general issues and specific products. Through this mechanism, NRAs are informed of the scientific background needed to assess critical issues, and advised on which regulatory approaches and methodologies have been found to be optimal for insuring the global supply of uniformly high quality and efficacious biological medicinal products. The guidelines provide more general regulatory expectations for pre-qualification of vaccines. In some areas WHO has developed more disease specific clinical guidelines (Table 2).

Table 2: Examples of WHO guidelines on clinical evaluations of vaccines

	Examples of key standard clinical guidelines	Examples of some relevant disease specific clinical guidelines
WHO	- WHO Guidelines on clinical evaluations of vaccines: regulatory expectations 2004 - WHO Guidelines on clinical evaluations of vaccines: regulatory expectations 2015 - WHO Guidelines on nonclinical evaluations of vaccines 2005 - WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines.	- WHO Guidelines on the quality, safety and efficacy of Ebola vaccines (Proposed new guidelines) 2016. - WHO Guidelines on the quality, safety and efficacy of Dengue tetravalent vaccines (live, attenuated) 2011 - WHO Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines - WHO Guidelines on the quality, safety and efficacy of pandemic flu vaccines

For further reading on the publications related to Table 2, the Technical Report Series (TRS), WHO immunization norms and standards, such as clinical guidelines and the emergency use guidelines procedures can be found on the WHO Immunisation standards website.[9] Existing guidelines for clinical development from regulatory agencies such as USFDA and EMA are also available. The EUAL procedure, established by WHO, lists minimum data requirements for emergency use listing and offers guidance to NRAs and manufacturers of these vaccines in the context of use during a PHEIC.[7]

In terms of epidemic/pandemic preparedness, discussions within CEPI and WHO Blueprint workshops have focused on trial designs for priority diseases, approaches to assess each design in terms of methodological robustness and feasibility, and a process leading to the development of generic annotated protocols for priority diseases.

A collaborative research preparedness exercise around the WHO R&D Blueprint priority pathogens has been proposed.[10] The objective of this preparedness work is to perform a prospective assessment of different vaccine efficacy designs under different scenarios. In addition, experts have proposed that White Papers should be developed to discuss methodological issues relevant to the design of trials in the context of epidemics (e.g. optimal approaches for interim analyses).[i]

4. Overview of important topics for discussion for CTA and MAA regulatory pathways with respect to emergency circumstances

The following important topics for further discussion between regulators and developers to obtain safe and expedient development and approval of vaccines in emergency situations have been identified in the literature and verified through consultations with CEPI partners and through the

[i] As raised in consultations between CEPI stakeholder meetings April-October 2016.

work of members of task team 1, subgroup 2 and 4. The topics are categorised by sector (below) and in Table 3 for those related to clinical development pathways.

Important topics by sector

- NRAs (in general)
    - Some developing country NRAs have limited human resources and/or technical capacity to evaluate vaccines, and particularly to evaluate novel vaccine constructs, or novel clinical trial designs to establish efficacy.
    - Additional support is necessary for some NRAs, before and during an emergency, to optimally act and respond to an epidemic.
    - Both resources and technical capacity for vaccine clinical trial and licensure assessment is challenging in some countries.
    - The guidance from regulatory agencies is often perceived as “binding”, without a clear pathway to appeal or discuss further recommendations. This may reduce opportunities for discussions to develop/refine approaches tailored to specific outbreaks or emergencies.
    - In the case of novel vaccines for emergencies, at the time of the first outbreak there may be no known correlates of protection.
    - NRAs may not have clarified what would be required for emergency licensure in the absence of a clinical endpoint efficacy study.
    - NRAs may not have clarified what would be required for authorisation in the absence of a clinical endpoint efficacy study.
    - Legal pathways to licensure and/or for emergency access are not fully developed in many countries and may not cover all contingencies including emergencies.

        - USFDA and EMA (specifically)
    - Parallel scientific advice between USFDA and EMA is valuable and in emergency situations, this should be considered one of the best procedures to use.
    - The requirements for licensure/approval and pathways may in some areas differ between the agencies. These differences may arise from different laws and regulations i.e. animal rule. Understanding the reasons for these differences, and how to try to align, is often difficult for less experienced developers.
    - Better understanding of non-USFDA/EMA regulatory requirements that need to be evaluated by individual countries, especially those related to differences in geography, underlying disease burden in the community, and differences in health care and transport systems realities between HICs and LICs.

- Multilateral organizations
  - WHO
    - Lack of understanding on how WHO provides support to countries, regional regulatory groups, and how they work with USFDA and EMA.

- Vaccine manufacturers/sponsors
  - Differences in scientific, legal, patent/market exclusivity, reimbursement, liability, and other factors between the US and EU means that MNCs may not file with both US FDA and EMA.
  - Both perceived and real risks of unanticipated adverse events and liability issues are increased when a vaccine has not been through licensure and is widely used based on less complete data than normally available.
  - Data sharing and transparency limitations slow coordinated development and approval processes.
  - Alternative procedures like the animal rule can still be very difficult and complicated.
  - Unclear degree of process validation related to chemistry, manufacturing and controls (CMC) and what needs to be done by when. (i.e. principles to ensure that the vaccines from the onset is designed to meet patients' needs and efficacy requirements, critical sources of variability are identified and controlled, critical quality attributes are met, continuous monitoring, evaluation and update of the product quality).
  - Uncertainty with production of consistent batches (and demonstration of 'clinical consistency). The batches prepared for stockpiling might be the only batches that will be produced for years (decades?).
  - Challenges with assay validation for release tests as well as for clinical trials.

Table 3. Challenges identified or perceived by developers for clinical pathways for vaccines for emergency situations

Pre-clinical	Phase I	Phase II	Phase III/ Effectiveness study in outbreak
Limited standardization for use with: • animal models • viral stocks • assays Variation of toxicological requirements across: • countries, • platform experiences, • acceptance of non-Good Manufacturing Practice material (GMP) material	Limited opportunities for parallel review of ethical and regulatory issues and procedures. Lack of technical capacity within some NRAs. Lack of capacity and resources within USFDA/EMA to support less resourced NRAs to intensify, and accelerate partnership Lack of clarity on specific issues, such as: - timing of special populations entry into phase I (elderly, children); - post dose 1 safety assessments in adults, or "post-immuno". - use of contraceptives as in exclusion criterion (female/male) - breast feeding during study.	Lack of consensus on which level of qualification/validation is needed for immune read outs at the initiation of phase III. Lack of clarity over the data requirements needed for "emergency use" and "stockpiling". Different classifications for safety (regulators) i.e. use in adults, and in special populations: elderly, pediatric, pregnant and lactating women, immunocompromised persons, HIV. Lack of consensus on CMC/manufacturing (bioprocess/formulation/analytical) development. Lack of clarity on the use of modelling for immunobridging (regulators).	No pre-approved protocol, ready to go in an outbreak or emergency situation. No consensus on design for efficacy/effectiveness. Randomized Controlled Trials (RCT) are the gold standard, but may be difficult in emergency context, eg. Ring vaccination may be studied as an approach to slow spread/contain the disease in some circumstances, but may conflicts with design and regulatory requirements for efficacy under non-emergency situations. Inflexibility of Phase III requirements in an emergency situation. Challenges in infrastructure and capacity to conduct clinical trials. Challenges with infrastructure to collect long-term data on efficacy in case of an emergency. Liability under these circumstances

5. Current regulatory harmonization/alignment efforts: scientific advice procedures, regulatory pathways and harmonization/alignment initiatives for vaccines falling within the scope of CEPI

The authors of the paper have mapped existing harmonization, alignment, and other collaborative efforts among NRAs, and some important network and harmonisations efforts of importance for CEPI are:

- African Vaccine Regulatory Forum (AVAREF),
- African Medicines Regulatory Harmonization initiative (AMRH)
- Pan-American Network for Drug Regulatory Harmonisation (PANDRH)
- African Network for Drugs Diagnostics and Innovation (ANDi)
- International Coalition of Medicines Regulatory Authorities (ICMRA),
- Actions out of WHO R&D Blueprint,
- ASEAN-Network for Drugs, Diagnostics, Vaccines, and Traditional Medicines Innovation (ASEAN-NDI),
- The Pacific Alliance between Chile, Mexico, Peru and Colombia.
- The Caribbean Regulatory System initiative (PAHO and CARICOM/CARPHA)
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- The WHO PQ collaborative and joint review processes
- The EMA Article 58 procedure
- The Swissmedic scientific advice and marketing authorization procedures for global health products (SAGHP and MAGHP)

In addition to the above organisations, other informal bilateral initiatives exist and are being fostered, for example, work is being undertaken between India and Bangladesh and between WHO and Bangladesh as Bangladesh works to improve its capacity to meet standards applied by WHO.

From our consultations, it is clear that there are varying levels of harmonization/alignment. The ability for NRAs to harmonize/align can be related to the level of technical capacity within NRAs; for example, one partner discussed the difference between harmonization in middle-income countries compared with low-income countries. Harmonization can be a difficult thing to work for in middle-income countries as they have some capacities, but not necessarily, the same regulatory procedures as partner countries, and in the case of low-income countries, it can be easier as there are frequently fewer established procedures that have to be accommodated.

An overview of existing networks and collaborative efforts between national regulatory agencies and between NRAs and WHO is presented in the appendix 1 (table 4), examples of active global harmonisation efforts are listed below:

AVAREF is a regional regulatory network that brings together NRAs and ethics committees of many countries in the WHO Africa Region. AVAREF aims to support NRAs and national ethics committees in

regulatory decision-making with respect to CTA assessment and authorization. It provides information to countries on vaccine candidates and timelines for clinical trials, and promotes communication and collaboration between African NRAs and ethics committees, often by organising convenings where CTAs can be reviewed in a collaborative manner. It also provides opportunities to bring in the expertise and advice of regulators from well-resourced NRAs – including Health Canada, the EMA, Swissmedic, and USFDA's Center for Biologics Evaluation and Research (CBER) – to collaborate with their African regulatory colleagues on these evaluations. AVAREF has established innovative regulatory pathways for clinical trials, developed use of common guidelines for submission of clinical trial applications, and organized joint reviews of multi-country clinical trial applications and joint good clinical practice (GCP) inspections. These strategic forms of collaboration can significantly improve timelines for product development for CEPI. AVAREF has just undergone a major refocus of its TORs and its working model, all of which are designed to build upon the lessons learned during the use of the AVAREF platform during west African Ebola crisis and to make help optimize the process further.[11]

PAHO and Pan American Network on Drug Regulatory Harmonisation (PANDRH) is an initiative of the NRAs within the WHO's Americas Region and PAHO that supports the processes of pharmaceutical regulatory harmonization in the Americas, within the framework of national and sub-regional health policies and recognizing pre-existing asymmetries. Under this scheme, several NRAs have been assessed by PAHO as "regional reference agencies" with the goal of other less resourced agencies relying on them for work products they can use to help inform their own regulatory decision-making. In addition, a new regional economic community effort to form a regional regulatory authorization process has started in the CARICOM region (Caribbean).[12]

ICMRA is a voluntary, senior executive (CEO) level, strategic coordinating, advocacy, and leadership entity of the chief executives of national and regional medicines regulatory authorities (NRAs) that work together to provide direction for a range of areas and activities common to many regulatory authorities' missions and goals. They identify areas for potential synergies to be made and, wherever possible, leverage existing efforts to maximize the global regulatory impact.[13]

ICDRA: The International Conference of Drug Regulatory Authorities (ICDRAs) provide drug regulatory authorities of WHO Member States with a forum to meet every two years and discuss issues of common interest, share best practices, and explore ways to strengthen collaboration. The ICDRA meetings have been instrumental in guiding less well-resourced regulatory authorities, WHO and interested stakeholders and in determining priorities for action in national and international regulation of medicines, vaccines, biomedicines and herbals, primarily in the LMIC space. ICDRA is a strategic opportunity for drug regulatory authorities to become more collaborative, discuss trends and challenges, but also to share solutions found at different parts of the globe.

ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) is now over twenty years old and continues to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug development and registration (safety, efficacy, quality, and multidisciplinary activities). Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development with a new legal charter, new governance model, and an openness for membership in various capacities outside the original three geographic regions. ICH's mission is to achieve greater harmonisation on the technical requirements for pharmaceuticals for human use worldwide to

ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.[14]

WHO R&D Blueprint is a global strategy and preparedness plan to faciliate targeted research and development that can strengthen the global response to public health emergencies by bringing medical technologies such as vaccines to patients during epidemics. The blueprint has prioritized accelerating research and development processes, and includes all actions needed to implement critical research in an ethical, safe, effective and timely way. WHO's facilitating role is to ensure that priority actions are designed and implemented in a consensual and coordinated fashion.[15]

Regulatory pathways for product development and evaluation in public health emergencies have been outlined. Joint clinical trial reviews of candidate products have been conducted in past emergencies. In addition, in these situations, production of international reference preparations to support product evaluation was coordinated, and collaborations between expert regulatory laboratories were established. Guidelines on the quality, safety, and efficacy of specific candidate products were developed. Guidelines on regulatory work sharing in public health emergencies were drafted.[16] Multi-country study designs to support safety and efficacy evaluations were outlined. Initial steps were undertaken to explore insurance options to address issues of liability in case of use of an experimental vaccine or product, which has not yet received full authorization for use.

Future plans will include further efforts to strengthen national regulatory and ethics bodies to respond to public health emergencies. A cadre of regulators working together on products being developed for priority pathogens will be established. Collaborations between expert regulatory laboratories will be continuously fostered. Discussions will be completed on insurance options to cover liability.

6. Case study describing a scenario where regulatory pathways have been accelerated

The outbreak of Ebola during 2014 and 2015 represented a PHEIC and underscored the need for a vaccine against Ebola. This was the start of an unprecedented and collaborative effort to accelerate the timelines for vaccine development built on the availability of a number of candidate vaccines that could enter into clinical phase evaluations.

Based on different literature resources, consultations and work carried out by the CEPI Task Team 1, a case study highlighting the actions taken, gaps and lessons learned with respect to the regulatory pathways for the Ebola candidate vaccines are presented below:[1,17]

The example of development of an Ebola vaccine – how did the regulatory pathways work, actions implemented, challenges and gaps

Actions implemented during the Ebola crisis:

- WHO convened international meetings with all relevant stakeholders, reviewed all available Ebola vaccine options, discussed and agreed on how to fast track the testing and deployment of promising vaccines.
- A series of consultations on regulatory approaches for expediting development and availability of Ebola vaccine.
    - Debate around the critical clinical trial designs and subsequent regulatory pathway for the lead candidate, the main regulatory challenges
    - Agreements on anticipated timelines for availability of these vaccines for both clinical trials and potential future large scale deployment
    - Mapped out possible avenues to address regulatory challenges, while keeping safety as a main concern
- Open discussion with regulators, all agencies were included in data sharing and decision making (e.g., EMA, WHO, USFDA, Health Canada, Swissmedic, NRAs in the affected countries)
- Regulatory support provided through AVAREF platform. AVAREF (under direction of both AFRO and WHO-Geneva) enabled authorities with experience of pre-licensure vaccine trials (EMA, USFDA, Swissmedic, Health Canada) to support those in the most affected countries with less experience with clinical trials. Joint review of clinical trial application for the Phase II trial of the GSK vaccine, including regulators and ethic committee chairs from the affected countries.
- WHO developed a process/mechanism for the EUAL of vaccines and diagnostics intended to assist interested UN procurement agencies and Member states on the applicability for use of a specific vaccine during public health emergency.

Challenges and gaps identified:

- Lack of clarity and understanding surrounding the coordinating role of WHO - need to clarify the role of WHO in facilitating the clinical trial development and regulatory and ethics review processes at the national, regional and global level.
- Need to resolve, as early and as quickly as possible, questions on design of trials to evaluate the safety and efficacy of products to support appropriate use in emergencies and to support regulatory assessment and approval (full or emergency) for the Ebola vaccines
- Need for standardization of preclinical models, and full transparency on data to allow evaluation/comparison of pre-clinical vaccine candidates.
- Need to identify the potential basis for regulatory approval (full or emergency) of Ebola vaccines without clinical efficacy data (emergency)
- Future collaborative data-sharing should be enhanced among vaccine developers, WHO, and NRAs
- Future emergency research efforts should be better coordinated
- Development of a plan to launch phase III efficacy studies and/or phase 4/post-marketing studies of licensed or emergency-authorized Ebola vaccines at the outset of the next outbreak
- A global mechanism should be developed to enable regulators (in collaboration with appropriate experts and product developers) to support discussions on:
    - Target Product Profiles/ Preferred Product characteristics
      and make recommendations as to:
        - Disease models/ correlates of protection
    - Pathways for emergency authorization scenarios including data requirements and criteria

7. Actions to facilitate regulatory pathways for CTA and MAA assessment and authorisation for vaccines for use in emergency situations

CEPI should focus on developing the platforms for the rapid conduct of clinical trials during emergencies to determine efficacy and safety of the products and to expand access to the products, including developing consensus on the appropriate clinical trial designs for these situations before the outbreak so that precious time is not lost designing and starting up clinical trials once an outbreak occurs.

An important action for CEPI will be to work and share knowledge on efforts to foster collaboration and communication between and among regulators and product developers to help accelerate product development and assessment and reduce regulatory challenges and clarify regulatory pathways by:

- Assisting private sector partners in the development of regulatory strategies and design and execution of clinical studies for needed medical countermeasures

- Involving regulatory experts in providing technical assistance on projects supported by CEPI

- In collaboration with WHO and major NRA's promote early and continuing engagement and discussion of vaccine development and evaluation plans, including for pre-clinical, clinical studies and manufacturing and quality issues.

- For CEPI candidate vaccines, develop early consensus on the data priorities and likely requirements on safety, efficacy and immunogenicity and manufacturing quality data requirements for CTA and MAA regulatory and EUAL approval or access for vaccines for use in emergency situations developed by WHO and regulatory authorities or other competent national bodies to optimize the vaccine development process

- Implementing guidance and standardized templates for issues such as data and sample sharing and liability, developed by WHO and regulatory authorities or other competent national bodies to optimize the vaccine development process.

- Utilising expertise from national and regional regulatory authorities to inform CEPI's priorities, policies, investment decisions, and portfolio management

- Contributing to the development and implementation of the WHO R&D Blueprint regulatory science agenda such as:
    - Being supportive of global coordination mechanisms established by WHO, and thereby provide a mechanism to coordinate and communicate across global vaccine development stakeholders.

    - Facilitating communications of the regulatory guidance and globally aligned scientific advice provided through WHO so that it can be utilized by CEPI's implementing partners.
- CEPI should continuing cooperation with WHO and convene representatives from national and regional regulatory authorities to facilitate discussions and enable recommendations to be made on critical issues of concern to foster regulatory alignment and optimization, and to aim for globally aligned scientific advice on vaccine development for emerging infections. Especially, this applies to areas specific to CEPI concerns, such as "development through proof of concept", potential use of EUAL or other mechanisms to authorise products based on animal or other models prior to an outbreak, with agreed protocols for use of the product during the outbreak, both to try to stem the outbreak and to develop more robust data as to the clinical benefit of the product; stockpiling product until such time as it is needed.

- Progressing efforts to foster international regulatory collaboration to optimize and align regulatory processes between national and regional regulatory authorities and ethics committees, in order to accelerate regulatory input into and review of clinical trial applications and ethics committee review of protocols with respect to vaccine development during public health emergencies.

Efforts to improve regulatory harmonization/alignment through appropriate mechanisms should be continued. Regulatory alignment and optimization and a mechanism for a global discussion on scientific advice on vaccine development for emergency situations will improve and ensure a faster and more efficient development, both in relation to requirements for "proof of principle" in the absence of an ongoing outbreak as well as requirements for effectiveness studies during an outbreak

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