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EDITORIAL

Regulatory policy for research and development of vaccines for public health emergencies

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The recent outbreak of the Ebola virus disease (EVD) with an average case fatality rate of around 50% – and case fatality rates from 25% to 90% in past outbreaks [1] – highlighted the need to strengthen national and international systems to detect, respond to, and prevent the spread of future health threats [2].

The Ebola public health emergency challenged research and development frameworks, including regulatory systems, both globally and in affected countries. Given the urgent need to provide access to treatments and identify effective interventions, an international Ethics Panel, convened by WHO, confirmed in August 2014 the ethical imperative to use and evaluate unregistered medical interventions under the specific circumstances of the Ebola outbreak, and defined the conditions that needed to be met in terms of safety, clinical care, ethical standards, data collection, transparency, and information-sharing [3]. In September 2014, WHO convened experts in the areas of public health, ethics, policy, research and development, manufacturing, and regulation to articulate interim WHO guidance on the development and potential use of Ebola vaccines and therapies [4]. Between February and April 2015, vaccine Phase 3 clinical trials were initiated in the three most affected countries with two candidate vaccines which had never been tested in man before September 2014, demonstrating that compressing steps which usually take several years into just five months was possible in case of emergency. Based on this experience and at the request of its 194 Member States in May 2015, WHO convened a broad coalition of experts to develop an R&D Blueprint for Action to Prevent Epidemics [5]. The R&D Blueprint will develop options to reduce the time lag between the identification of a nascent outbreak and approval of the most advanced products that can be used to save lives and stop larger crises. In November 2015, the report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola recognized positively WHO’s efforts related to Ebola R&D [6].

1. Lessons learned

Based on the lessons learned during the Ebola outbreak, we point out a number of approaches that are helpful to accelerate regulatory review and access to products needed in emergencies, including vaccines for emerging infectious threats.

1.1. Concerted effort in development and regulatory review and approval

Rapid development and approval of required products needs a concerted effort. Decisions on which products to consider should be transparent and should involve all stakeholders, including in the countries affected. Interactive, flexible, and fast but rigorous review processes, with the collection of interpretable data for further assessment, are essential. While a product may be used on a compassionate basis in an ongoing emergency, the ultimate goal should be to have product approval prepared for future outbreaks.

To create efficient regulatory pathways for emergencies, regulatory authorities from affected countries and from countries where products are being developed should share information and, to the best possible extent, develop harmonized data requirements.

The risk–benefit assessment will depend on the category of product: therapeutic products for sick patients will have a different threshold of acceptance than prophylactic products which will be given to healthy people. Quality requirements – such as Good Manufacturing Practice compliance – may be less demanding for clinical trials than for product approval. However, the quality and consistency of batches must be assured, and changes during product development must be properly controlled, evaluated, justified, and documented.

1.2. Coordinated ethics committee reviews

The development of candidate products is typically an effort of multiple institutions based in different countries. National ethics committees are required by regulation to approve research protocols. The committees concerned should harmonize their review principles, synchronize their review processes, and share and discuss the review outcomes with each other. Early discussions with drug regulatory authorities should be encouraged.
The ethics committees should further ensure that communities are appropriately engaged in pre-trial discussions and are clearly informed about the outcome of the risk–benefit assessment.

The Ebola-affected countries had very little or no experience of running clinical trials or for the review of complex clinical trial protocols. To bridge the capacity gaps, WHO facilitated a regulatory and ethical examination of an Ebola efficacy vaccine trial in Guinea by twinning the country’s national authorities with regulatory and ethics experts from a well-resourced setting.

1.3. Clinical trials

It is critical to balance the need for rapid access to investigational products with the need to gather data on their safety and efficacy. Any regulatory approach for early access should provide adequate safeguards for the patients (e.g. informed consent and safety monitoring), However, executing certain pragmatic flexibility rather than the ‘normal’ phased approach seemed effective, e.g. several independent Phase 1 vaccine trials were run in parallel to reduce the risk that a delay in one of the sites would delay the whole process, and to accumulate enough subjects to remove the need for Phase 2 evaluation before starting Phase 3.

The highest strength of data will be generated by a randomized, double-blind, placebo-controlled trial, but such design may not always be possible or ethically acceptable in circumstances of a public health emergency. In such situations, other randomized controlled designs can prospectively collect standardized clinical data to provide evidence for analysis.

Regulators should work together in advance to identify acceptable clinical trial design options for use in emergencies. The aim is to identify pragmatic, simple designs that accommodate the issues inherent in the specific epidemic – such as safety, personnel, and other resource limitations of participating facilities – while minimizing bias in evaluating the causal effect of the intervention.

All contributors should collect a unified core data set. Data from both randomized control trials and observational studies would provide information about prognosis and prognostic factors that will help to determine sample requirements for future trials. Data sharing and analysis should occur in real time to inform rapid adjustments of actions.

The discussions on clinical trial designs for emerging infectious diseases were been taken up by major regulatory agencies. In November 2015, the US FDA, together with other concerned organizations, hosted a workshop that explored clinical trial designs; it has also opened a public docket on these issues and invited public comments [7].

1.4. Emergency use assessment and listing procedure

The WHO emergency use assessment and listing procedures (EUAL) propose principles for assessing and listing vaccines [8], medicines, and diagnostics for use in a public health emergency. In the context of the Ebola outbreak, WHO made use of these procedures and listed after quick rigorous assessment several diagnostics as acceptable for use. It must be noted that the EUAL procedure is not the same as WHO prequalification. Its requirements are specifically tailored to emergency situations, when communities may be willing to tolerate less certainty about the efficacy and safety of products given the consequences of the disease and the shortfall of treatment or prevention options.

The EUAL procedures are also applicable in emergencies other than the Ebola outbreak. In each situation, it is paramount to determine the minimal level of information needed to make a product available for a limited period while further data are being gathered and evaluated.

1.5. Leveraging regional and global networks

Various existing regulatory networks can play an important role in facilitating rapid concerted decisions, action, and information exchange to make urgently needed products available. Two examples follow:

- To address the challenge of authorizing clinical trials of Ebola candidate vaccines for which limited data were available, the WHO African Vaccine Regulatory Forum (AVAREF) was used as a collaboration platform for regulators, ethics committees, and sponsors to reach consensus on key ethical and regulatory questions. WHO convened three joint reviews of clinical trial applications with AVAREF playing a convening and supportive role. Regulators from Europe and North America provided their expertise and advice on key ethical and regulatory questions. The AVAREF platform accelerated regulatory approval and the experience can serve as model for further collaborative efforts [9].
- The International Coalition of Medicines Regulatory Authorities is a new executive level voluntary global collaboration bringing together senior regulatory leaders to provide coordinated and strategic leadership in an increasingly complex globalized regulatory environment. Its current membership includes the heads of 20 regulatory authorities with WHO as an observer [10]. This powerful consortium of regulators is well placed to take a leadership role in designing a regulatory policy framework for products needed in emergencies.

2. Conclusion

The development of vaccines for public health emergencies has yet to fully benefit from the latest scientific innovations, and an effective global regulatory policy framework for products required in emergencies remains to be defined and implemented. The WHO R&D Blueprint is defining essential elements for such a framework. The current ongoing Lassa Fever outbreak in Guinea is a good opportunity to test new regulatory approaches. As was the case of the West-African EVD outbreak, at least two vaccine candidates are available to control Lassa fever. A key issue remains who will pay for clinical trials, and therefore innovative and effective funding mechanisms should be brought to play to stimulate commercial interest in accelerated product development.
Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


* Describes important initiative to follow.


** Comprehensive analysis of pandemic response to Ebola with clear recommendations for the future.


* Unique set of minimum regulatory requirements for vaccines, medicines and diagnostics in case of emergency.


* Good overview of a promising regulatory network in Africa with accent on its role during Ebola crisis.


* Unique article about the new Global coalition of important regulatory authorities.