Regulatory collaboration

The African Vaccine Regulatory Forum (AVAREF): A platform for collaboration in a public health emergency

The Ebola virus disease outbreak in West Africa has been followed by a global multi-stakeholder response, led by WHO, to make medical products available to treat and prevent the disease. The swift pace of product development has challenged regulatory systems globally, and especially those of resource-constrained sub-Saharan African countries.

To address the challenge of authorizing clinical trials of Ebola candidate vaccines with limited available data, the WHO African Vaccine Regulatory Forum (AVAREF) was used as a collaboration platform enabling regulators, ethics committees and sponsors to reach consensus on key ethical and regulatory questions. Given AVAREF’s crucial role in speeding up product development through coordinated regulatory efforts to combat Ebola it is essential that necessary resources are allocated to further strengthen its capacity.

Challenges of product development during public health emergencies

Medical products are complex, and high levels of scientific expertise are needed to ascertain their quality, safety and efficacy. Traditionally, product development and approvals take years, with carefully planned, robust and systematically executed, large clinical trials serving as basis for safety and efficacy data to inform regulatory decision-making.

While developed countries have adequate regulatory systems and capacity in place to assess and authorize clinical trials in order to ensure their scientific integrity, most African regulatory authorities have severe resource constraints and therefore lack the capacity to adequately review and authorize clinical trials and to ensure the safety of trial subjects during the clinical development of products (1).

Public health emergencies impose on African regulators the additional pressure of having to accelerate access to needed products for the public good by approving clinical trial applications and products within much shorter timelines than usual. The fundamental question regulators have to grapple with is: How to authorize a promising product with very limited evidence of safety and efficacy in instances where large clinical trials are not possible?

This is the scenario created by the largest-ever outbreak of Ebola Virus disease, which started in Guinea, Liberia and Sierra Leone with a few cases in other
West African countries, Europe and North America (2).

As part of the global response to this public health emergency, WHO convened several consultations on different aspects of product development with a view to accelerate development and access to promising products including vaccines. One of the outcomes of these consultations was the decision to use existing regulatory networks as platforms to support accelerated product development and approvals.

The African Vaccine Regulatory Forum (AVAREF)

AVAREF is a regional regulatory network founded by WHO in 2006, at a time when the focus on clinical trials of vaccines began to shift from developed countries to developing countries, including those in sub-Saharan Africa. The network brings together national regulatory authorities (NRAs) and ethics committees of the countries in the WHO African Region. It currently has 23 members1.

AVAREF aims to support NRAs in regulatory decision-making. It provides information to countries on vaccine candidates and timelines for clinical trials, and promotes communication and collaboration between African NRAs and ethics committees. It also provides opportunities to bring in the expertise and advice of regulators from Europe and North America – including Health Canada, the European Medicines Agency (EMA) and the United States’ Food and Drug Administration (FDA)’s Center for Biologics Evaluation and Research (CBER) – for the benefit of their African counterparts. At the same time AVAREF promotes convergence towards harmonization of regulatory practices and processes to ensure timely regulatory evaluations and approvals of clinical trial applications and products.

Key among AVAREF’s achievements has been firstly the establishment of innovative regulatory pathways for clinical trials, secondly the development and use of common guidelines for submission of clinical trial applications, and thirdly the use of joint reviews of multicountry clinical trial applications and joint good clinical practice (GCP) inspections. These strategic forms of collaboration can significantly improve timelines for product development (3, 4).

Joint reviews and GCP inspections have played a key role in ensuring timely regulatory authorization and approvals of MenAfriVac®, the meningococcal A conjugate vaccine whose rollout in the meningitis belt of Africa has eliminated epidemic meningitis due to Group A Neisseria meningitidis as a public health problem (5). A joint review approach was also used to coordinate and expedite the review of the multicountry Phase III clinical trial for the lead malaria candidate vaccine, RTS,S/AS01, which is about to conclude in seven African countries.

WHO’s use of the AVAREF platform in responding to the Ebola emergency

The Ebola outbreak created a global urgency and a need for accelerated development of vaccines and treatments. In the wake of the outbreak, prompt authorization of clinical trial applications and overall regulatory oversight of
products that could help to prevent or treat Ebola are particularly challenging: The design of clinical trials is becoming more difficult due to very specific features of the disease, and the capacity constraints are greater than ever in affected countries.

In response to this situation, the annual meeting of AVAREF, held in Pretoria, South Africa on 3–7 November 2014, devoted two days to discussions addressing the key regulatory questions around the Ebola outbreak. Participants discussed ways to put into place mechanisms for the review and authorization of clinical trials while planning for the approval of products for emergency use.

The meeting enabled regulators and manufacturers to achieve progress in three principal areas: firstly, pre-submission discussions with sponsors and manufacturers, secondly the general principles and mechanisms for the authorization of clinical trials and products, and thirdly the organization of joint reviews to facilitate timely approvals of clinical trials.

**Pre-submission discussions**

Pre-submission meetings with regulators in Africa can be very challenging for manufacturers, especially when they are dealing with several countries with different requirements. The AVAREF meeting provided a unique opportunity for sponsors and manufacturers to present and discuss the characteristics of their products, preclinical data available from non-human primate studies and from first in-human studies where available. All known and potential target countries for clinical trials were represented in one place for discussions on the products and the designs and timelines of clinical trials. In addition, the African regulators as well as ethics committee members and regulators from Europe, the U.S. and Canada – where some first trials for some of the products in humans have been approved – were able to make suggestions to sponsors about clinical trial designs and data to submit for approval of trial applications.

**Clinical trial and product approvals**

The AVAREF meeting opened discussions on how regulatory authorizations of clinical trials and approvals of products for emergency use can be addressed in the current Ebola outbreak without compromising the safety of populations. These discussions were based on available regulatory experience and expertise of the U.S. FDA, Health Canada and EMA. Most African countries lack specific regulatory pathways and mechanisms and could therefore adopt or adapt some of the mechanisms used in other countries. The session also highlighted the need for a global regulatory mechanism to be put into place for product development in emergencies such as the Ebola outbreak and the earlier pandemic influenza.

The meeting participants reached consensus around the use of AVAREF as a collaborative platform, and the value of joint reviews as a useful means of ensuring that clinical trial applications for products against Ebola are reviewed adequately and that shorter timelines consistent with accelerated product development and manufacturer timelines are met.

**Joint reviews**

WHO convened three joint reviews of clinical trial applications utilizing the
AVAREF platform. To date, ethical and regulatory approval has been secured within 90 days from the completion of the joint review. WHO played a convening and supportive role in the joint review sessions by:

- facilitating agreement on the format for the clinical trial applications;
- ensuring the participation of supporting agencies (the regulatory authorities of Ghana, the United States, Europe, the United Kingdom, Canada and Switzerland);
- liaising with sponsors regarding information-sharing among supporting agencies about products under review;
- setting up an electronic platform to manage the review process and to make necessary documents available to regulators and ethics committee members; and
- facilitating the finalization of a summary report stating agreed-upon actions and timelines following the review.

**Recommendations**

The meeting recommendations were circulated among all stakeholders, NRAs, ethics committees, manufacturers, sponsors and partners. The agreed recommendations are presented in Annex 1.

**Support and funding**

The ninth annual plenary meeting of AVAREF was organized with support from the Bill & Melinda Gates Foundation and the Programme for Appropriate Technologies in Health/Malaria Vaccines Initiative (PATH/MVI). In addition, the Center for Biologics Evaluation and Research of the U.S. FDA (CBER FDA), the Health Products and Food Branch of Health Canada and the EMA contributed through the participation of their experts. The joint reviews were supported by WHO.

**Conclusion**

To ensure that health products are safe, effective and of good quality, regulatory oversight of product development in countries should be consistent with ICH and other relevant international guidelines. Regulatory agencies of developing countries which lack the full capacity to meet these requirements should be supported to build or strengthen their capacities in line with international regulatory standards. WHO fully recognizes this and is actively supporting Member States to strengthen their regulatory systems through regular assessments, capacity-building in a variety of ways and by promoting regional harmonization efforts.

AVAREF is a WHO-supported platform that has proven to be instrumental in providing regulatory support to accelerate product development during public health emergencies, as exemplified with products in development against Ebola. Going forward, these achievements will also support the work of African regulators on vaccines for diseases such as HIV, tuberculosis and malaria, which are affecting many millions of people in the African region. Lastly, AVAREF may serve as an important regional platform linked with international networks such as the Developing Countries Vaccine Regulatory Network (DCVRN) to promote the increasing number of multi-regional or global trials.
References


### Annex 1: 9th AVAREF meeting recommendations

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<th>Sponsors/manufacturers:</th>
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<td><strong>Ebola</strong></td>
<td><strong>National RAs and ethics committees (ECs) / institutional review boards (IRBs):</strong>&lt;br&gt;1. To prioritize assessment of clinical trial applications in parallel (regulatory/ethics) to minimize delays and to apply fast-track procedures&lt;br&gt;2. To immediately release all national/regional provisions governing the area of clinical trials and highlight aspects favourable to fast track procedures&lt;br&gt;3. To accept to review all clinical trials submitted by manufacturers/sponsors&lt;br&gt;<strong>Supporting RAs (EMA, USFDA, Health Canada):</strong>&lt;br&gt;1. In collaboration with WHO, do everything in their power to share data relevant to clinical trials with the NRAs of participating countries&lt;br&gt;2. To provide expertise to support NRAs in the joint reviews when requested</td>
<td>1. To request Heads of RAs to:&lt;br&gt;a. Identify and named senior regulators staff as the agency entry focal points for Ebola&lt;br&gt;b. Designate named reviewer(s) to participate in a joint review process with the mandate to take regulatory/ethics decisions (reviewers are empowered to take decisions during the joint review meeting).&lt;br&gt;2. To facilitate a joint review session of the clinical trial applications with a target date of 15 December 2014&lt;br&gt;3. To involve the NRAs of the Ebola-affected countries in the joint review process&lt;br&gt;4. To provide expertise and develop briefing materials for ethics committees&lt;br&gt;5. To develop additional briefing materials on the vaccines, and novel clinical trial designs, to assist the national/regional reviews&lt;br&gt;6. To proactively play the needed broker role in facilitating the interaction between manufacturers and countries&lt;br&gt;7. To engage with heads of Institutions and research institutions and provide necessary support to countries to develop procedures for accelerated review of Ebola related research.&lt;br&gt;8. To ensure that ethics committees have the necessary support to follow up approved trials and research studies through site monitoring and having mechanisms to rapidly review amendments etc.</td>
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<td><strong>Tuberculosis, HIV/AIDS and malaria vaccines</strong></td>
<td>1. To gradually strengthen regional harmonization of technical processes and procedures&lt;br&gt;2. To emphasize utilization of joint process implementation&lt;br&gt;3. To establish mechanisms for strengthening Transparency on processes/procedures and on country/regional performance (including adapting indicators for research ethics systems)&lt;br&gt;4. To interact actively with the African Medicines Registration Harmonization Initiative (AMRH)</td>
<td>1. To support and strengthen collaborative mechanisms among NRAs and ethics committees including capacity building through regular trainings&lt;br&gt;2. To encourage multiplication of joint implementation of regulatory activities including joint reviews and joint inspections&lt;br&gt;3. To host and manage the AVAREF virtual community platform developed by Health Canada, the secretariat to implement the transition by end January 2015&lt;br&gt;4. WHO to provide specific guidelines for evaluation of clinical trial applications for vaccines against TB and HIV, build capacity to efficiently address other anticipated products in the pipeline</td>
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