Challenges related to ethical and regulatory pathways in emergency situations

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Traditional approach for product approval

Research & development

Clinical trial applications

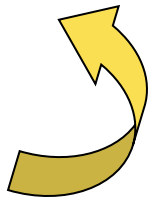
Clinical trials (Phase I, II, III studies)

New Drug Submission

Regulatory evaluation

Market authorization decision

Post market lot release and surveillance



Evolution of product & knowledge

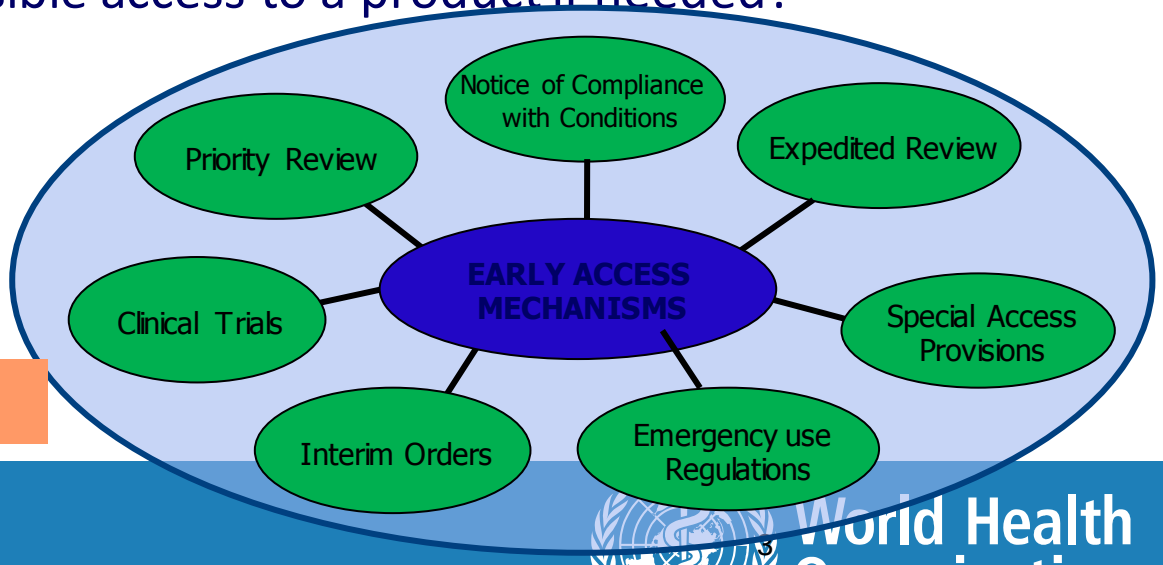
Typical time for completion measured in years

Public health emergencies

Public health emergencies challenge the traditional approach for product approval

- How to authorize use of a promising product in the absence of substantial evidence of safety and effectiveness in humans?
- What if clinical evaluation for safety/efficacy is difficult to obtain in absence/low level of disease?
- How to provide an appropriate degree of regulatory oversight?
- How to permit earliest possible access to a product if needed?

Many NRAs have regulatory options available to provide early access in emergency situations



Typical timeline measured in months

Critical information to trigger outbreak/emergency regulatory options

1. **Current** epidemiologic situation of outbreak in a Member State and/or regionally or worldwide
2. Urgency of the situation
3. Morbidity and mortality of the disease
4. Availability of other possible public health interventions (e.g. quarantine/isolation)

The goal of regulators worldwide concerning candidate Ebola vaccines and therapies

Outcomes of 4/5 September WHO meeting:

- to accelerate development of candidate products towards regulatory approval, including clinical trial approvals
- to facilitate access to investigational therapies and vaccines during the current outbreak
- to ensure rapid regulatory information exchange and collaboration to support accelerated development and access to investigational products

Ethical principles….

The recipients of experimental interventions, locations of studies, and study design should be based on the aim to learn as much as possible, as quickly as possible, without compromising patient care, local community values or health worker safety. Trials should be designed and conducted with the active participation of local scientists and researchers, and with proper consultation with communities and local ethics committees.

Ethical issues related to Ebola vaccine trials

- Priority is to facilitate access to vaccine candidates already showing laboratory safety and efficacy evidence
- There must be adequate infrastructure and equipment to administer the vaccine, monitor efficacy and treat severe adverse effects
- Children and pregnant women are vulnerable and require special protection, but should not be arbitrarily excluded from trials - a risk benefit analysis is necessary
- It is ethically advisable to ensure adequate follow up of participants until the study end point – must consider practicalities in existing complex circumstances

Study design ethics

- All scientifically recognized methodologies and study designs are acceptable e.g., there should be no general ethical taboo on placebo controlled randomized trials - or, conversely, trials that don't involve randomised controls

- While it is ethically acceptable to use a placebo in preventive trials (such as vaccine trials) in the context of the current Ebola epidemic in West Africa, investigators should be mindful that as the disease has a high fatality rate, and there have been tensions between local communities, and their governments and healthcare workers, such trials must be preceded by intense community engagement and buy in.

Accelerating development, regulatory assessment and product licensing

- Guiding principle: the collection of **interpretable data** that informs product development and ultimate approval
- Requires a concerted effort by product developers and regulatory agencies, in cooperation with the WHO
- Interactive, **flexible** and expedited but **rigorous** review processes
- Use product approval mechanisms to enable countries affected by EVD to have products with **appropriate benefit/risk ratio** at their disposal with shortest timelines possible

Facilitating early access to investigational products

- Any regulatory approach for early access should provide **adequate safeguards** for the patients (i.e., best possible assessment of safety profile of products, recommendations for safe use, informed consent, safety monitoring)

- the need for early access to investigational products should not interfere with clinical investigations designed to gather data on the safety and efficacy/expected efficacy of the products

- Practical and feasible clinical trials to evaluate and provide early access are recommended over compassionate use mechanisms, when possible

Regulatory collaboration e.g. through AVAREF

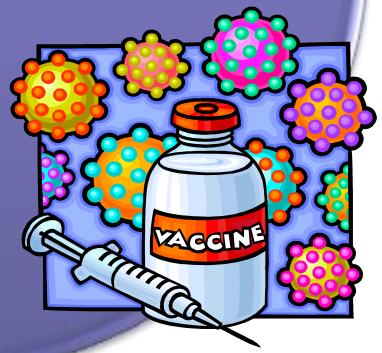
National Regulatory Authorities

Ethics Committee

Scope

Regulation of medicines

Regulation of clinical trials



Support from USFDA, Health Canada, European Medicines Agency

AVAREF members:

Botswana
Niger
Burkina Faso
Nigeria
Cameroon
Rwanda
Central African Rep
Senegal
DRC
Sierra Leone
Eq. Guinea
South Africa
Ghana
Tanzaania
Gabon
Uganda
Kenya
Zambia
Malawi
Zimbabwe
Mali
The Gambia
Mozambique

Joint review of phase II CT applications Background

WHO convened the 9th annual meeting of the African Vaccine Regulatory Forum (AVAREF) on 3–7 November 2014.

The first two days of the meeting were devoted to Ebola, *in light of the global response to the current outbreak in West Africa and the need to accelerate the development and use of products against the disease.*

Joint review of phase II CT applications Background

The ethics committees and regulatory authorities of the 23 African countries present at the meeting agreed to the following:

- That WHO would convene and facilitate a joint review of the GSK ChAd3 Ebola Vaccine Clinical Trials (CT) phase II submission on 15 December 2014.
- That the CT submission to the target countries would follow the **AVAREF common CT application format,** to allow for a joint review.
- That each regulatory agency would designate **reviewers with the mandate to take regulatory/ethics decisions**.
- That NRAs and ECs of the 3 Ebola-affected countries would participate as observers (capacity building)
- That WHO would seek the assistance of the US FDA, EMA, Health Canada, and Swissmedic to provide technical support at the meeting.

Joint review of phase II CT applications

- On 12 Nov 2014 WHO convened a TC with the **heads of the regulatory authorities and ECs** of the target countries (Cameroon, Ghana, Mali, Nigeria and Senegal), as well as Guinea, Liberia, and Sierra Leone, to agree on the joint review process and secure nomination of representatives.
- WHO facilitated the development and submission of CT applications by GSK and its partner, Quintiles, ahead of the joint review meeting.
- GSK completed submission to the ECs and the regulatory authorities by 9 Dec

Joint review of phase II CT applications

At the 15&16 Dec joint review meeting;

- GSK protocol presented, followed by Q&A.
- Queries on SharePoint addressed by GSK, Quintiles, and investigators from the field sites of the clinical trials.
- The characteristics of the field sites, including target populations and clinical and laboratory capacities were presented.
- USFDA, EMA, HC and Swissmedic summarized the outcome of their previous assessments
- Questions were raised by the reviewers and responses provided.
- In the end a closed session of regulators where further issues were raised and posted on the SharePoint site to be addressed by GSK and partners.

The parties signed on to the following from the joint review of phase II CT applications

- GSK – to submit additional data packages by end of January
- All the countries confirmed that they will respond to the sponsor within two weeks (10 working days) from receipt of submission, and approval will be communicated as follows:

1. Ghana (simultaneous review by EC and NRA) – Response in 2 weeks
2. Nigeria (simultaneous review by EC and NRA) – Response in 2 weeks
3. Mali (sequential review by EC followed by NRA) – Response in 2 weeks
4. Cameroon (sequential review by EC followed by NRA) – Response in 2 weeks

Joint review of phase I CT applications

- WHO was approached by J&J to facilitate joint review and approval of their **phase I trials** (Kenya, Tanzania and Uganda, as well as Ghana).
- Joint review - facilitated by WHO - planned for 21 & 22 Jan (Tanzania; EMA, HC, USFDA, MHRA present).
- Rwanda, Burundi and Zanzibar potential observers.
- Planned approval of applications at the meeting.

Joint review of phase III CT applications

- On 17 Dec WHO facilitated meeting in Geneva for sponsors and investigators to brief regulators and ECs of Guinea, Liberia and Sierra Leone on planned **Phase III Clinical Trials** of Vaccines against Ebola.

- Participants: Members of ECs and NRAs of Liberia, Guinea and Sierra Leone, vaccine manufacturers, investigators and sponsors from WHO, CDC, NIH, Merck/Newlink, GSK and J&J.

- Updates by J&J, GSK and Merck/Newlink, on Ebola vaccine characteristics and preliminary safety and immunogenicity data (Phase I trials data and NHP data).

Joint review phase III CT applications

- Three proposals for phase III clinical trials in affected countries were presented.
- Q&A on the ethics and regulatory and safety aspects of the proposed studies.
- Specific issues included the following:
  - *How to set up Pharmacovigilance system to monitor the studies*
  - *Information and knowledge sharing system between the 3 countries*
  - *Joint on site-GCP inspections through the African Medicines Regulatory Harmonization (AMRH) initiative.*

Regulatory challenges: how to move forward?

- WHO is offering (for diagnostics) and developing (for vaccines) a risk-based emergency assessment procedure for procurement
- For the longer term, WHO has initiated guidelines development for regulation of products in a public health emergency
- Managing the transition from the current emergency situation to "business as usual" needs to be carefully considered