Complexities around the Clinical Development of Novel Vaccines – an Industry perspective

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Vaccine Development Complexities

- Development of a vaccine includes the need for various clinical trials to establish its safety, immunogenicity and efficacy.
- Infectious diseases know no borders, and the clinical testing of vaccines is a vital process to ensure safety, efficacy, and quality for all populations across the world. The globalization of clinical development requires therefore the conduct of multi-country clinical trials.
- Before clinical studies can be initiated, approvals have to be obtained from various Ethical and Regulatory bodies through different (often interdependent) processes.
- This presentation focuses on regulatory complexities around Clinical Trial Applications (CTA) showing the need for facilitation, harmonization, reliance and work-sharing.
Current Challenges with Clinical Trial Applications

- **Sequential process** of (multiple) Ethic Committees (ECs) and National Regulatory Authorities (NRAs)
- CTAs can take a **long (and unpredictable) time** significantly affecting trial conduct and delaying access to innovative (vaccine) products
- **Lack of transparency** with regards to status of the CTA
- Lengthy Genetically Modified Organisms (GMO) applications reviewed by separate bodies with variable requirements
- Significant **differences in application** format and content
- Differences in labelling requirements, stability requirements and Lot release testing lead to a complex supply chain
- Often **no possibility to pre-discuss CTA** with involved authorities, a challenge given the often highly complex products and trial designs.
Challenge 1: Sequential vs. Parallel Review

- (Bio-) Ethics Committee (EC) Approval(s)
- National Regulatory Authority (NRA) Approval(s)
- Local Regulatory Authority Approval(s)
- Ministries of Health
- Genetically Modified Organisms (GMO) Approval(s)
- Import License(s)

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Challenge 2: Multiple Review Bodies

GLOBAL DISEASE

1 Clinical Trial

5 Countries

27 Clinical Sites

>66 Review Bodies

whereas

CTA APPROVALS ARE mostly NATIONALIZED

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Challenge 3: Global differences in CTA Approval Timelines

Benchmark:

Country 1
Country 2
Country 3
Country 4
Country 5
Country 6
Country 7
Country 8
Country 9
Country 10
Country 11
Country 12
Country 13
Country 14
Country 15
Country 16
Country 17
Country 18
Country 19
Country 20
Country 21
Country 22
Country 23

Regions:
- Asia-Pacific
- Africa
- Latin America
- Europe/Middle-East

Time from First Submission to Final Approval [Days]

Depicted Countries: N=329 Clinical Trial Applications

*Benchmark: ICH founding members, N=931 Clinical Trial Applications
Challenge 4: Differences in CTA Dossier Requirements & Format

• No Global Standard
• Country specific (unique) requirements
• Electronic vs. Paper submissions
• (e)CTD vs. country specific formats
• Reality often differs from available guidance
• Adding complexity to run global, multi regional trials
Challenge 5: Complex Supply Chain

- Initially, only limited stability data available
- Extrapolation of stability data (based on representative lead batches) is essential
- Some countries only accept shelf life stability extrapolation based on actual batch used in the Clinical Study
- Lengthy importation processes and challenging cold chain
- Differing Clinical Labelling Requirements
- Some countries do Lot Release testing for Clinical Trial Materials

Complexity to bring clinical materials with sufficient shelf-life to the clinical sites
What is the impact?

• Impact on study organization and logistics
• Often non-transparent processes, difficult to plan activities
• Healthy populations and Patients are waiting:
  • During a normal product development, almost 3 years are lost waiting for CTA Approvals
  • Shortening of timelines could potentially save millions of lives e.g. in the case of highly prevalent diseases (HIV, TB vaccines etc.)
Where to start - Possible solutions?
Need for dialogue

- Complex vaccines (e.g. heterologous prime-boost regimens)
- Complex manufacturing processes
- Complex study design and statistics
- It is more than ever important to have a platform for open communication between NRAs, ECs, and Study Sponsors
- In reality, only a minority of NRAs allow for formal Scientific Advice Meetings
Convergence and Harmonization of CTA requirements

- The current complexity of global regulatory processes for CTAs is a threat to innovation, slowing down access to innovative products.
- There is an urgent need to establish a common, **global set of requirements** for CTAs per Phase of Development:
  - Could be a guidance document issued by WHO, ICH or other unifying bodies
  - One dossier fits all
- **Parallel EC/NRA review** rather than sequential reviews
- Clear and transparent assessment **timelines**
- **Transparency**, consistency and predictability in regulatory outcomes and decision making
Mutual Recognition and Joint Reviews

- Closer harmonization and specialization of NRAs, where possible, leading to **reliance and potential mutual recognition** similar to the processes established for initial registration and Post-Approval changes
- **Joint Reviews** of CTA
- **Expedited approval** of certain CTAs that are of significant benefit to the healthy population and patients
- Focus on **reduced regulatory burden** overall both for NRAs, ECs and Study Sponsors
- **Legal Framework** to support these processes
- An **Open dialog** is needed involving all relevant stakeholders

AVAREF reviews as a potential process to accelerate?
Conclusion on AVAREF process (Ebola Vaccines)

- **Opportunity to engage** with key stakeholders at WHO, NRAs and ECs
- Important process for the future of regulatory and Ethics CTA reviews in AFRICA:
  - builds expertise and experience;
  - utilises larger agency (US FDA, MHRA, Health Canada, EMA) knowledge and experience
- If commitments can be met then likely faster route than local sequential process
- Further develop process as an optional pathway for CTA review outside of an emergency
- Possibility to extend to other regions or even to global clinical trial applications for diseases with global impact?
Call to Action

- Establish a common, **global set of requirements** for CTAs per Phase of Development, e.g. as part of a WHO guidance document

- **Streamlined and transparent assessment** processes including a possibility to have **Scientific Advice** with the reviewing bodies

- **Faster CTA Approvals** can save precious development time, potentially saving millions of lives

- **It is time to act...** Healthy Populations and Patients are waiting for new innovative (vaccine) products
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