# Reliance and Work-sharing during the Development of New Vaccines – an Industry perspective

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# Introduction

- Development of a vaccine includes the need for various clinical trials to establish its safety, immunogenicity and efficacy

- 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

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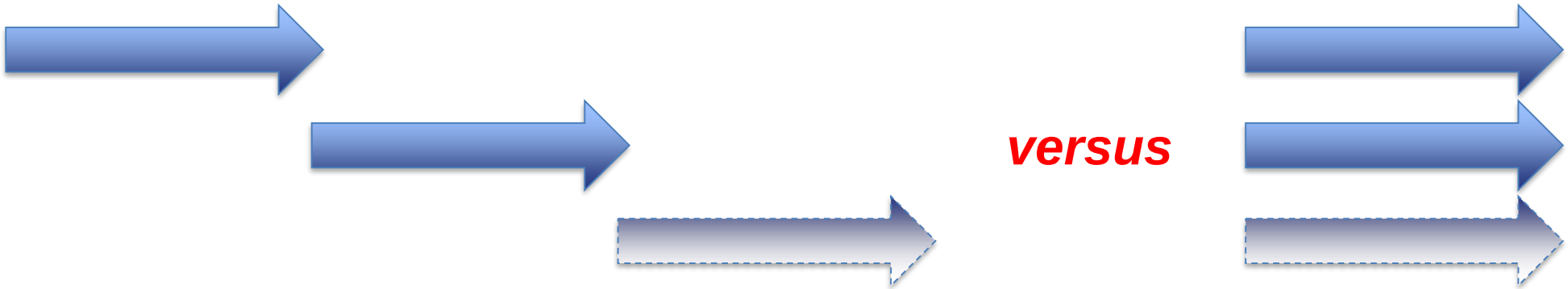
# Sequential vs. Parallel Review

- (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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# Multiple Review Bodies

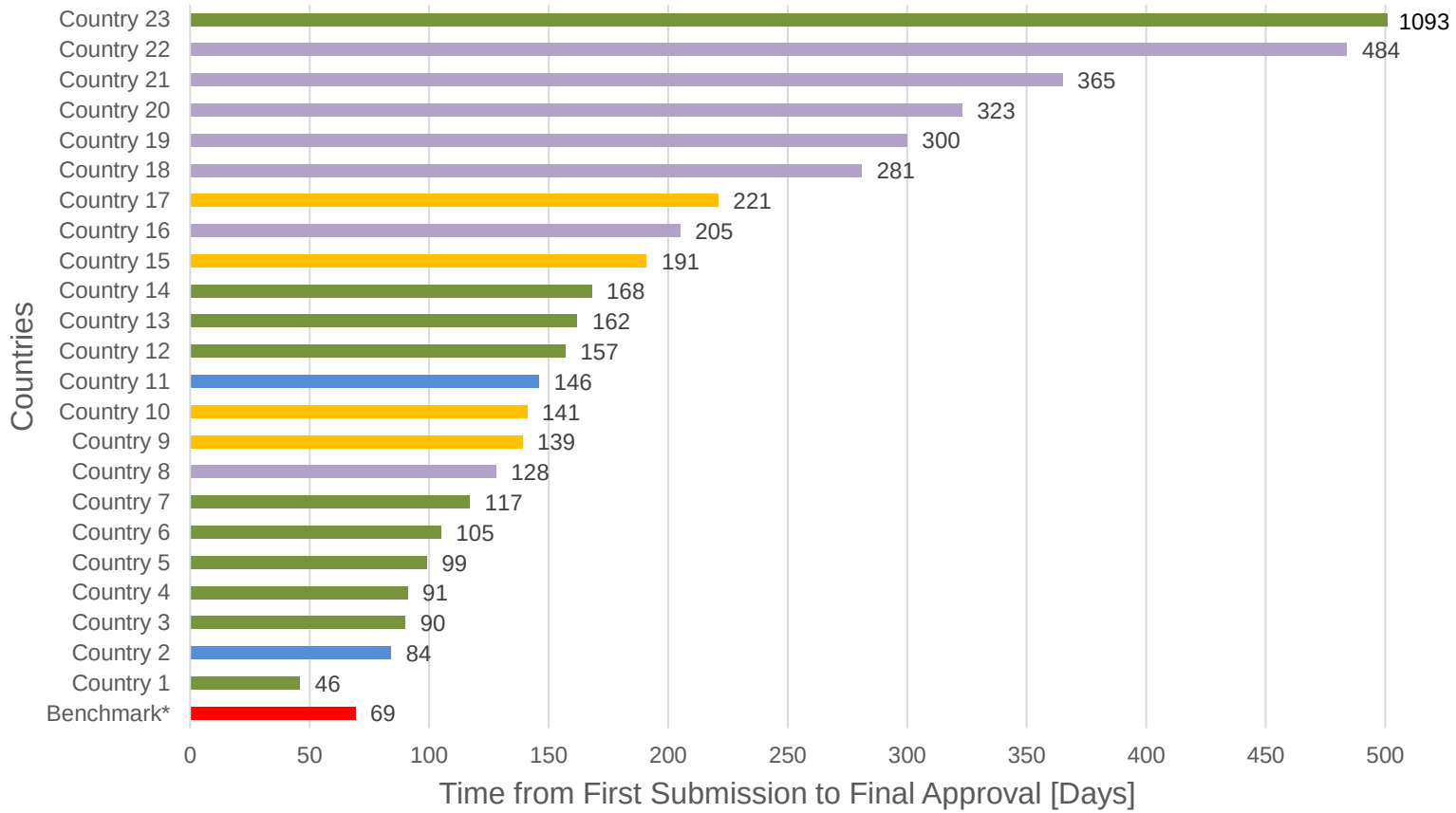
**GLOBAL DISEASE**

***whereas***

**CTA APPROVALS ARE mostly NATIONALIZED**

| 1 | 5 | 27 | >66 |
|---|---|---|---|
| Clinical Trial | Countries | Clinical Sites | Review Bodies |

# Global differences in CTA Approval Timelines




**Regions:**

Asia-Pacific

Africa

Latin America

Europe/Middle-East

Depicted Countries: N=329 Clinical Trial Applications

*Benchmark: ICH founding members, N=931 Clinical Trial Applications

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# Why is this important?

- 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.)


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# 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

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# Complex Supply Chain

- Initially, only limited stability data available
- Extrapolation of stability data (based on representative lead batches) is essential
- Some countries only accept 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

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# Need for dialogue with NRAs

- 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, Ethics Committees and Study Sponsors
- In reality, only a minority of NRAs allow for formal Scientific Advice Meetings

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# Current Challenges with CTAs

- 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
- Sequential process of (multiple) ECs and NRAs
- Lengthy 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 applications with involved authorities, a challenge given the often highly complex products and trial designs.

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# Where to start - Possible solutions?

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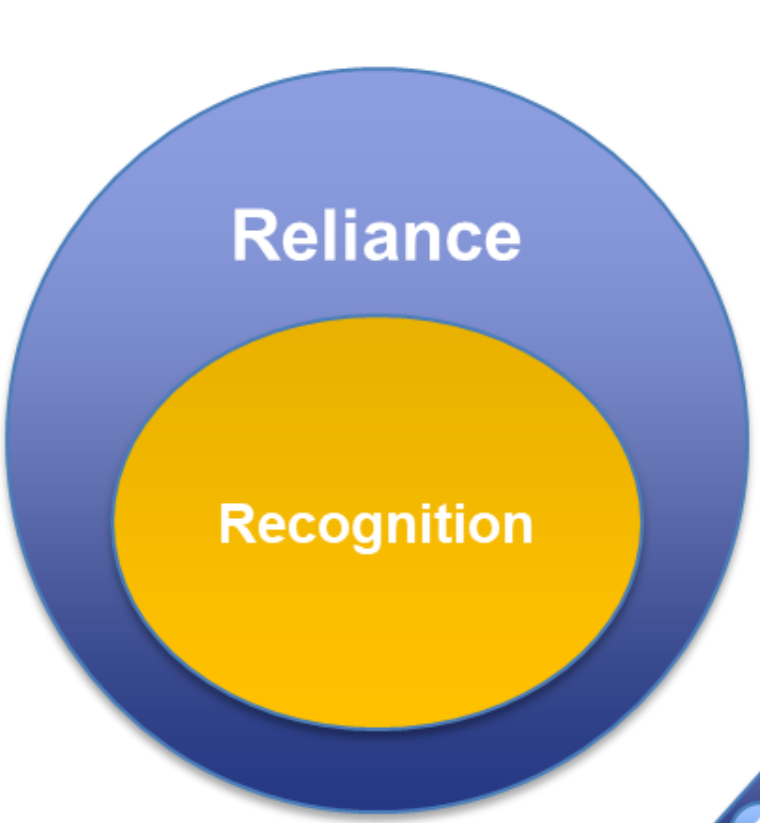
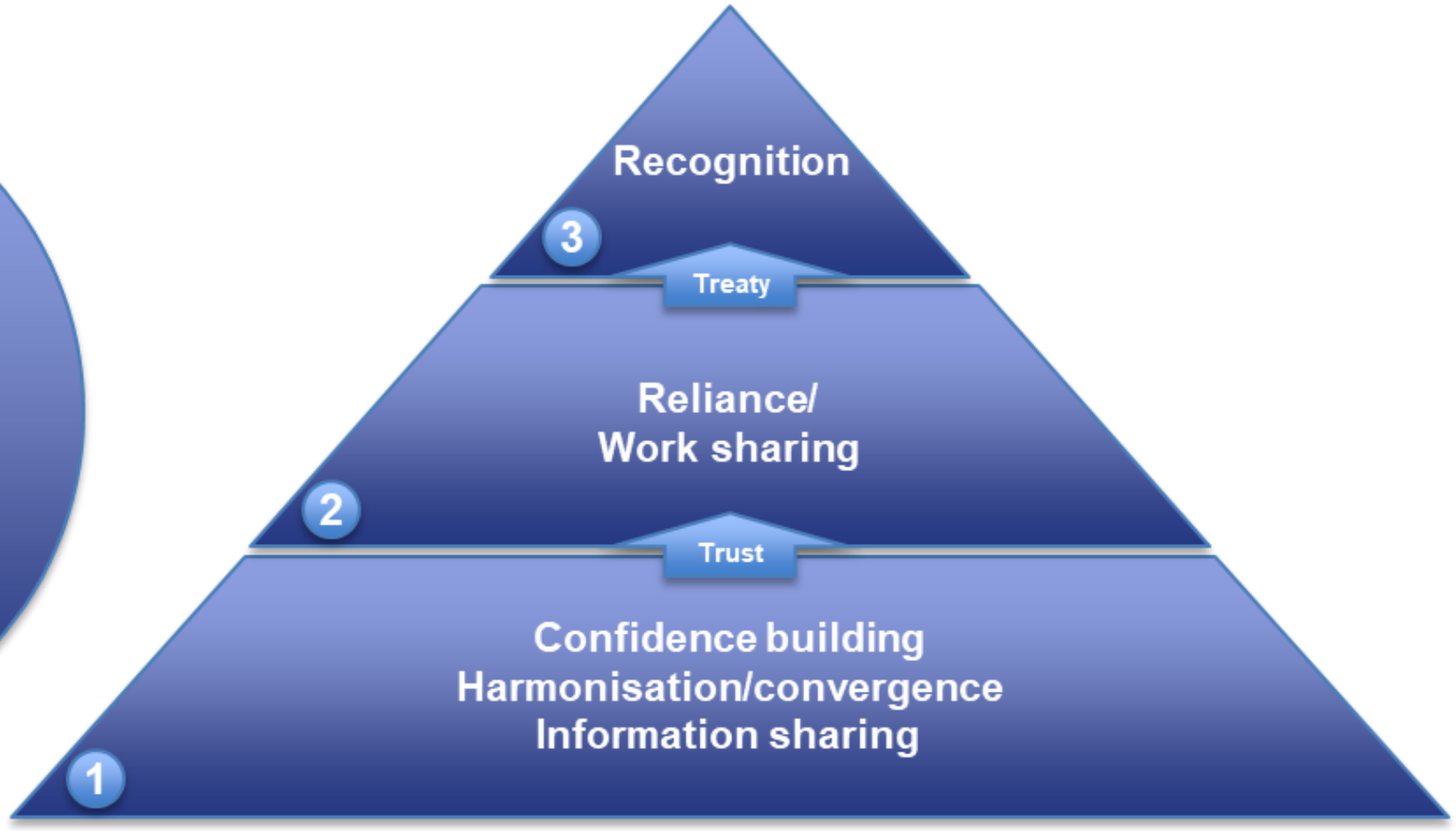
# Reliance and Recognition




Adapted from: Why is Reliance Important? Mike Ward, WHO, Euro-DIA 2019

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# Convergence and Harmonization of CTA requirements

- The current complexity of global regulatory processes for Clinical Trial Applications 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

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# Mutual Recognition and Joint Reviews

- Closer harmonisation and specialization of NRAs, where possible, leading to **reliance and potential mutual recognition**
- **Joint Reviews** of CTA applications
- **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

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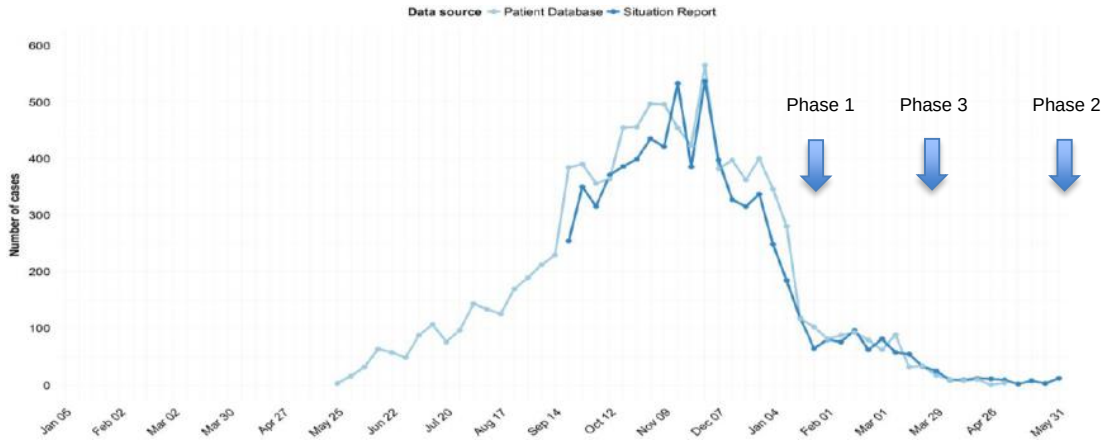
# Joint Reviews of Clinical Trial Applications – AVAREF Experience for the Ebola vaccine (1)

- 9th AVAREF meeting in Nov 2014 - NRAs and ECs of 20 AVAREF countries agreed to a WHO facilitated, expedited CTA review process supported by larger, mature NRAs (FDA, MHRA, Health Canada, EMA)
- Through discussions with WHO, Janssen proposed to utilise this review process for the Ebola CTAs
  - Phase 1 (3-4 Feb in Arusha, Tanzania), CTAs in Tanzania, Ghana, Uganda, Kenya
  - Phase 3 (8-10 April in Accra, Ghana), CTA in Sierra Leone
  - Phase 2 (9-11 June in Accra, Ghana), CTAs in Uganda, Kenya, Ivory Coast, Burkina Faso



# Joint Reviews of Clinical Trial Applications – AVAREF Experience for the Ebola vaccine (2)

- Cross-functional Janssen team interfaced with WHO and NRAs
- Intense Process primarily over the few days of the review; virtually all questions were answered satisfactorily during the face to face meetings and agreed protocol amendments submitted for review shortly after the meeting
  - Phase 1: >400 questions; intense process but led to very rapid approval (1.5 to 4 months) in all countries
  - Phase 3: 160 questions, complex protocol in the context of the waning epidemic. Approval went to schedule and was dependent on local site start-up times (staff recruitment, facility build etc.)
  - Phase 2: 169 questions. Epidemic waning; NRAs and ECs were less empowered; faster approval in some countries but timelines drawn out and reverting to normal sequential process for others. Key advantage – agreed study design (including high risk groups) and development of acceptable protocol amendment covering all countries.

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# Overall Conclusion of AVAREF process

- 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 to be faster route to approval than local sequential processes
- Discussions continue on African NRA and EC capacity building.
  - Further develop process as an optional pathway for CTA review outside of an emergency setting
- Possibility to extend to other regions or even to global clinical trial applications for diseases with global impact?

**GLOBAL DISEASE**

***AND***

**CTA APPROVALS ARE reviewed GLOBALLY**

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# Call to Action

- Healthy Populations and Patients are waiting for new innovative (vaccine) products
- Convergence and Harmonization of CTA Requirements, Reliance and Mutual Recognition of CTA Approvals can save precious development time, potentially saving millions of lives
- It is time to act…


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# Thank you!

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