EUROPEAN MEDICINES AGENCY
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# Regulatory perspective on human challenge studies

Accelerating vaccine development in the UK safely: enhancing Human Challenge Studies to combat infectious diseases
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# Disclaimer

- EMA does not approve clinical trials in the EU – competence of National Regulatory Agencies
- EMA does not approve the Human Challenge Studies protocols
- **However:** human challenge studies are discussed by developers with EMA in the context of Scientific Advice procedures or other frameworks for interaction with sponsors of investigational vaccines
- Main discussion is on the role of human challenge studies in the clinical development of vaccines and their support towards licensure
- Comments on measures in place to guarantee safety of participants could be included

# Regulatory value of human challenge studies in the development of vaccines

- **Role in early clinical development:**
- Proof-of-Concept studies
- Definition of immune markers of relevance
- Investigation of correlates of protection
- Support to dose selection

# Regulatory value of human challenge studies in the development of vaccines

- **Role in late clinical development and for licensure:**
- Supportive data for the establishment of correlates of protection
- Supportive data for licensure
- Pivotal data for licensure
- Role in defined sub-populations

# Factors to be considered (I)

- Strain attenuation:
  - Major point of concern if the challenge organism has to be attenuated to the extent that is no or mildly pathogenic
  - How does this reflect natural infection?
  - Possible to balance safety of participants against an adequate level of virulence?
  - Impact on studies aimed at defining immune correlates of protection for disease
  - In vulnerable group, the option of challenging with an approved vaccine containing a live organism has been considered, e.g. rotavirus vaccine

# Factors to be considered (II)

- Route and dose of challenge:
  - Is the route of challenge well mimicking route of natural exposure?
  - Is the (fixed) dose of challenge well reflecting the pathogen load associated with natural exposure?
- Generalisation from single strain:
  - The extrapolation of efficacy from human challenge studies with a single pathogen strain (maybe homologous to the vaccine) might be misleading whenever different genetic variants of the pathogen circulate and are associated with a significant burden of disease, e.g. malaria

# Factors to be considered (III)

- Timing from immunisation:
  - In consideration of operational constraints, human challenge is often conducted soon after vaccination and close to the peak of the humoral response
  - Is this early protection indicative of longer term protection?
  - Fro some pathogens, information on longer term protection would be needed to understand the ability of the vaccine to have substantial efficacy, e.g. dengue vaccines related risk of short-lived cross-protection for the different serotypes
- Impact of pre-existing immunity:
  - Extrapolation to other settings or populations, e.g. from naïve population to population in endemic areas or from adults to young children
  - Clear-cut definition of pre-existing immunity still problematic with some pathogens, e.g. influenza

# Pivotal data for licensure – possible but not the norm

**FDA News Release**

## FDA approves vaccine to prevent cholera for travelers



**For Immediate Release** June 10, 2016

**Release**

The U.S. Food and Drug Administration today approved Vaxchora, a vaccine for the prevention of cholera caused by serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas. Vaxchora is the only FDA-approved vaccine for the prevention of cholera.

Vaxchora's efficacy was demonstrated in a randomized, placebo-controlled human challenge study of 197 U.S. volunteers from 18 through 45 years of age. Of the 197 volunteers, 68 Vaxchora recipients and 66

# Human challenge studies for estimating vaccine efficacy

**Prerequisites**:

- Field efficacy trials not feasible
- No immune correlates of protection to gauge efficacy
- Not possible to compare immunogenicity with a licensed vaccine that showed clinical efficacy
- The human challenge studies address the potential issues described above

# ETHICAL CONSIDERATIONS FOR ZIKA VIRUS HUMAN CHALLENGE TRIALS

## REPORT & RECOMMENDATIONS

**February 2017**

**2:** Whether a Zika virus human challenge trial has sufficient social value to proceed depends on the reasons for doing it and whether there are alternative ways to obtain the information. The most compelling rationale for conducting a Zika virus human challenge trial, given the risks and uncertainty, would be if field trials were prohibitively difficult to conduct in light of a waning epidemic. This rationale is not currently met, but it could come to pass in the future. Another valuable reason to conduct a challenge trial would be to accelerate the development of a vaccine that could prevent congenital Zika infection. This rationale must be accompanied with strong evidence that results from a Zika virus human challenge trial would be used by stakeholders (e.g., indication from regulatory agencies that finding a correlate would speed up the licensing of a vaccine). The committee did not hear sufficient evidence that this rationale is currently met. Finally, using a challenge trial solely to learn about the pathogenesis and natural history of Zika infection is unlikely to justify the risk involved given the alternative ways to obtain similar information.

# Final remarks

- EMA eager to discuss proposal from sponsors and determine the impact that these studies can have on regulatory decisions
- Safety of participants needs to be duly factored in the discussion on the studies
- HCTs for establishing immune correlates of protection and as pivotal data for licensure not the standard but possible in certain circumstances
- EMA Paediatric Committee (PDCO) currently not convinced about the conduction of HCTs in paediatric populations, but open for discussion
- Any level of confirmation of predictive value from field clinical trials would help in strengthening the role of HCTs towards rapid access of new vaccines

# Thank you for your attention

## Further information

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