# Federal agency for medicines and health products

Regulatory and ethical considerations of human challenge trials

Nele Berthels

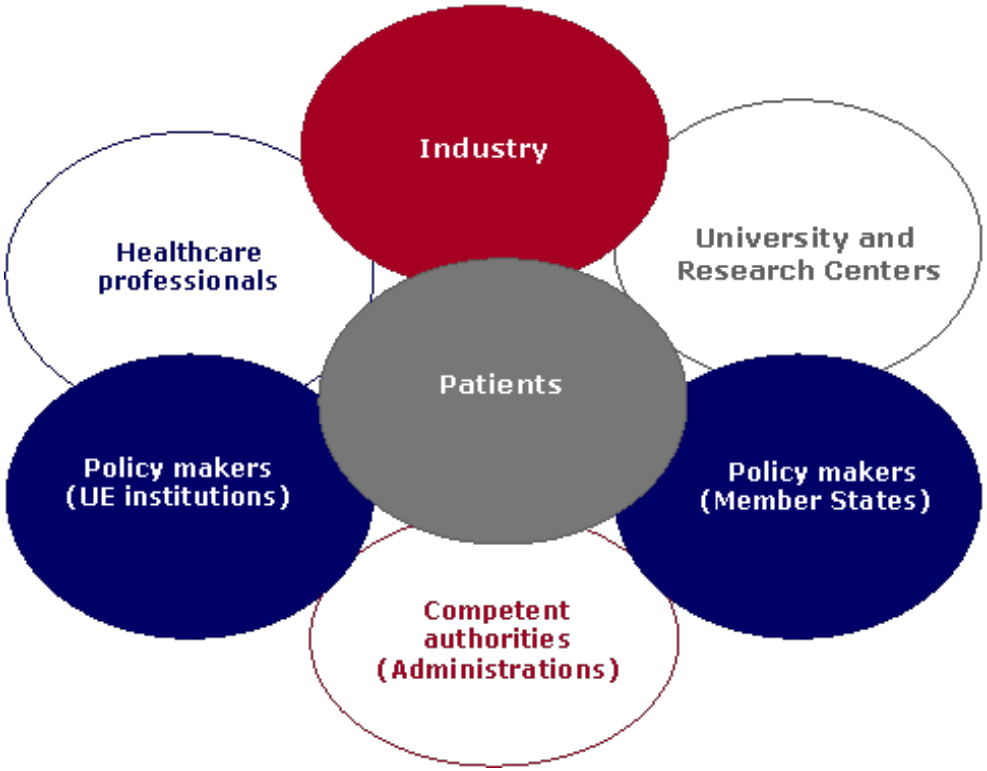
FAMHP Vaccine Symposium, BRUSSELS, 9 September 2017

# Disclaimer

**This presentation reflects my personal point of view, and not necessarily the official opinion of regulatory authorities such as EMA or the FAMHP.**

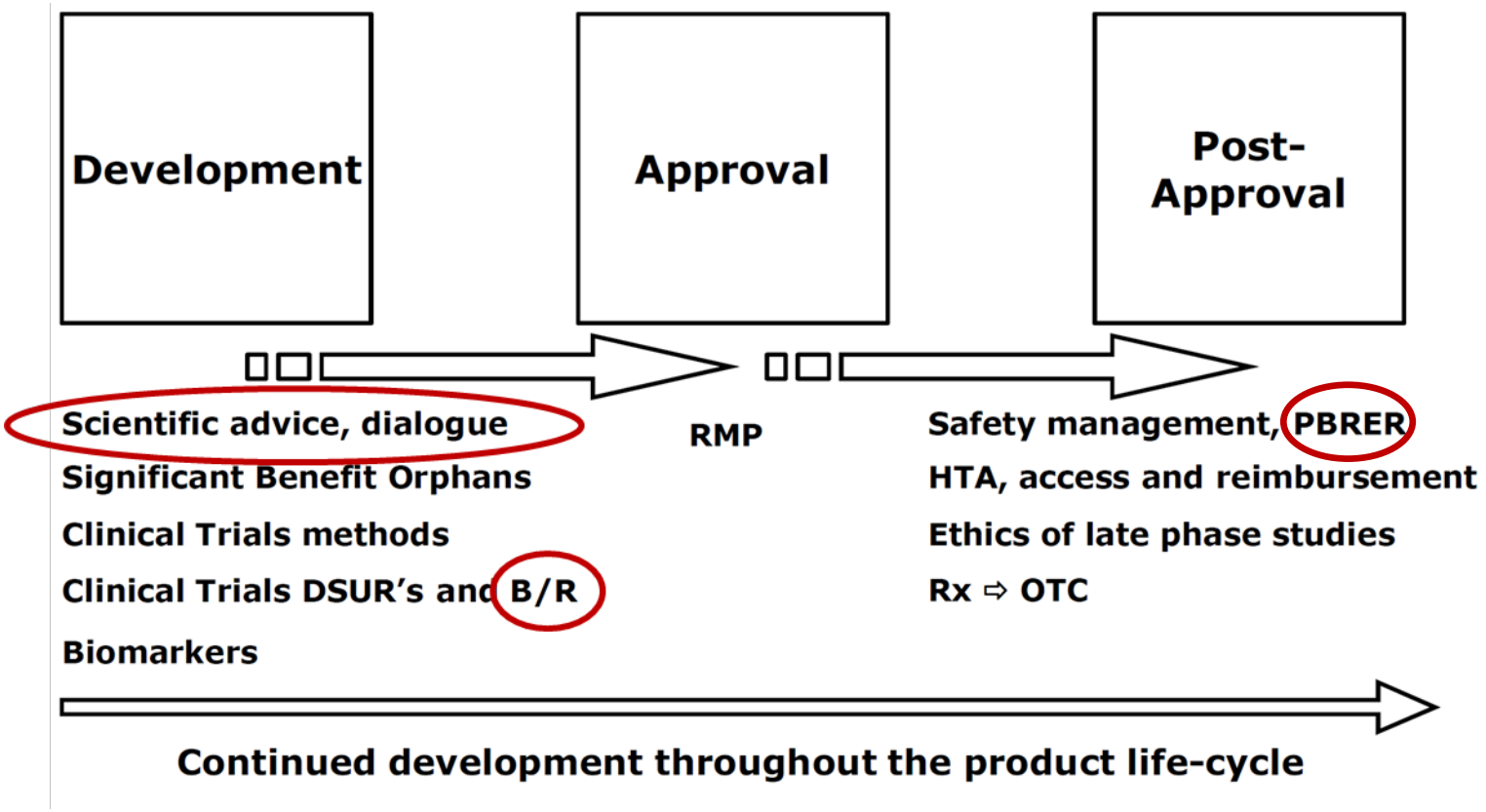
# Role of the Belgian regulator FAMHP

**In the interest of public health**, the FAMHP ensures the **quality, safety and efficacy** of medicines and health products
**in clinical development** and on the market.



# Role of the Belgian regulator FAMHP

**In the interest of public health**, the FAMHP ensures the **quality, safety and efficacy** of medicines and health products
**in clinical development** and on the market.



# Regulatory considerations

**Challenge trials: what is common with other clinical trials?**

- Clinical trials often involve the exposure of healthy volunteers who have been informed appropriately about the uncertainties and the potential risks of their participation (informed consent).

- Clinical trials are often performed in well-controlled, selected populations. Although RCT are the gold standard for demonstration of clinical endpoints, they have limitations with regard to external validity.

# Regulatory considerations

**Challenge trials: what is common with other clinical trials?**

- The concept of a challenge agent exists in several types of clinical trials
  - Skin prick test: exposure to allergens such as pollens, house dust, animal dander and foods. This test may be used as part of the inclusion criteria for a clinical trial of a new medicine to control or prevent symptoms from allergic reactions.
  - Blood pressure: exposure to oral tyramine following treatment with anti-hypertensive product to test blood pressure response in healthy volunteers.

# Regulatory considerations

**Challenge trials: what is common with other clinical trials?**

- All regular legislation regarding clinical trials apply (CT Directive -> Regulation)
  - GMP-grade medicinal products
  - Approval required from Regulatory Agency + Ethics Committee
  - Informed consent
  - Safety reporting – GCP compliance
  - Environmental risk assessment: approval from Biosafety Commission

# Regulatory considerations

**What if the challenge agent is a live infectious organism or pathogen?**

- **Characterisation of the infectious organism**
- **Quality aspects**
  - Origin - Virus isolation
  - Manufacturing – able to be cultivated in a lab with consistent purity and identity that can be prepared repeatedly under GMP requirements
  - Adventitious contamination
  - Wild-type? Have mutations been introduced? GMO?
  - Genetically stable
  - DNA sequence of the virus – absence of known virulent polymorphisms, screening for point mutations that are known to be associated with a higher pathogenicity (e.g. myocarditis in influenza virus)

# Regulatory considerations

**What if the challenge agent is a live infectious organism or pathogen?**

- **Non-clinical / Clinical aspects**
  - Pathogenicity
  - Clinical endpoints

- **Environmental aspects**
  - EU + BE legislation
  - Deliberate release of GMO
  - Contained use of GMO and pathogens
  - Quarantineable facility: Class II biosafety specifications?
  - Storage, access and potential spread

# Regulatory considerations

**Using an infectious organism within a clinical trial setting**

- **Trial design**
  - Possibility of pre-infection – Running the trial outside the peak season with regard to epidemiology of the disease may reduce pre-infection.
  - Timing of trial irrespective of disease epidemiology is more practical but requires a quarantine period before inclusion and cross-contamination measures.
  - Possibility of secondary infection - Volunteers may infect each other if they are allowed to stay in the same room. Staff members may be infected and re-infect the trial participants.
- **Volunteer selection**
  - Willing and able to comply with restrictions needed to prevent transmission.

# Regulatory considerations

**Validity of the challenge model: what is the trial going to tell us?**

- **Mimicking a natural infection in a controlled environment**
  - Precise dose *vs*. the naturally infectious dose
  - Specific method of exposure *vs*. the natural way of infection
  - Altered infectivity or pathogenicity *vs*. wild-type pathogen
  - Healthy volunteers *vs*. at risk population (children, immunodepressed, older age …)
  - Underlying disease in an otherwise healthy volunteer?
  - The challenge trial provides **a model**: how credible are the data?
  - Do we accept the strenghts and weaknesses of this model?

# Regulatory considerations

**Validity of the challenge model: what is the trial going to tell us?**

- **Relevance of the clinical endpoints**
  - Reproducible viremia indicating infection
  - Mild to moderate symptoms (headache, rash, neutropenia, fatigue …)
  - None of the symptoms associated with the real disease (vascular leak, myocarditis …)

# Regulatory considerations

**Human challenge trials: what purpose do they serve?**

- **Early phase / Phase I / Phase II**
  - Characterisation of the challenge organism – pathogenesis, dose titration, disease kinetics, shedding, transmissibility
  - Screening of antigens or vaccine constructs, selection of best candidate
  - Insight for vaccine design
  - Proof of concept
  - Identification of potential immune correlates of protection
  - Go/No Go for further efficacy studies
  - Generation of appropriate hypotheses to be tested in traditional efficacy or effectiveness trial

- **Emergency use**
  - Support for emergency use of a vaccine e.g. in an influenza pandemic

# Regulatory considerations

**When is a (human) challenge trial justified or considered?**

- **Demonstrating protection in a vaccine trial can be challenging**
  - when the infectious disease rarely occurs
  - e.g. polio, pertussis, Haemophilus meningitis …
  - or occurs during unpredictable epidemics e.g. Ebola, Zika
  - efficacy studies not feasible (sample size too big, disease not circulating)

- **Absence of a relevant animal model**
  - dengue, influenza …

# Regulatory considerations

**When is a (human) challenge trial justified or considered?**

- **Absence of clear correlates of protection**
  - influenza
- **Complementary to other approaches**
  - data gained through animal models
  - data from robust serological assays (in vivo or in vitro response)

# Ethical considerations

**Are human challenge trials ethically acceptable?**

- **Basic ethical concept in clinical trials**
  - Minimizing the risks to subjects and maximizing benefits
- **Challenge trials not ethical in children …**
  - Voluntary, informed consent?
- **Ethical considerations**
  - Risks may be greater than minimal
  - Accept acute, but manageable, disease
  - No or little potential individual benefit
  - Potential benefit if the participant becomes immune
  - Knowledge gained to the benefit of larger society

# Conclusion

## TAKE HOME MESSAGES

- **Human challenge trials are full clinical trials that are regulated by the CT Directive / Regulation within Europe.**
- **In a human challenge trial, healthy volunteers are deliberately exposed to an infectious agent or pathogen. This provides interesting options to study disease pathogenesis and the immune response to both the pathogen and new vaccine candidates.**
- **As regulators operating in the interest of public health, we continuously search to strike a balance between understanding the risks involved in a clinical trial and advancing clinical research with the ultimate goal of delivering new vaccine candidates quickly, yet responsibly, to the market.**

# Contact us

## Thank you for your attention.

## Questions?

**Federal Agency for Medicines and Health Products - FAMHP**

Place Victor Horta 40/40
1060 BRUXELLES

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.afmps.be

# Your medicines and health products, our concern

10 jaar

famhp

.be