CTR Early phase: Vaccines

FAMHP

BRUSSELS

15.09.2023

G. DE MEYER

famhp

federal agency for medicines and health products

.be

Content

- Introduction
- Guidelines
- FAQ in assessments/expectations
  - Pharmacology
  - Non clinical safety
  - Other
- Conclusions

Introduction: specificities of vaccines

Potential safety concerns for a vaccine:

- inherent toxicities of the product;
- toxicities of impurities and contaminants;
- toxicities resulting from interactions between the vaccine components;
- toxic side effects due to the immune response induced by the vaccine.

Consideration of population:

- clinical trials: healthy volunteers;
- target population: also healthy population;
- no immediate benefit (more reduction of potential risk)

→ Impact on benefit/risk.

Consistency!

Lots used should be representative of clinical/commercial material!

Main guidelines

- **WHO guideline on nonclinical evaluation of vaccines; Annex 1 WHO Technical Report Series, No. 927, 2005.**
- **Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (WHO 2013).**
- **Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines, EMA/CHMP/VWP/141697/2009.**
- **WHO guideline on the Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations.**

Content of the trial application

	Pharmacodynamics	PK	Toxicology
In general	• Immunogenicity before FIH, dose response. • Challenge/passive transfer where appropriate. • Safety pharmacology if concern.	/	• 1 relevant species, Immune response demonstrated. • General toxicity and local tolerance study. • Dose, route of adm and number cfr clin trial. • Target population includes pregnant women/WOCBP: consider developmental toxicity studies (later stages of dev for WOCBP).
Specific	• Absence of clin efficacy data expected: Challenge studies become!	• **Distribution**: • Live recomb vaccines. • New formulations.	• **Immunotoxicity** (immune complexes, exacerbation of disease, molecular mimicry, hypersensitivity). • Live attenuated vaccine: degree of **attenuation**, stability of attenuation (> passages). • Live recombinant or attenuated (recombinant or not) vaccines with potential neurological tropism (Yellow Fever backbones !) → : **neurovirulence testing.** • **ERA** for GMO; possible shedding, likelihood of exchange of genetic information.

FAQ…

Pharmacology aspects:

- documentation not clearly presented;
- POC (antigen/adjuvant);
- dose justification (in antigen/novel adjuvant);
- schedule of administration;
- full characterisation of immune responses;
- results insufficiently detailed (pathogen loads, histopathology, “data not shown”).

Expectations: pharmacology

General pharmacology studies:

Immunology assessment:

- characterisation of immune responses (innate, cellular, humoral);
- dose response (minimum dose, maximum dose), booster effect (number of doses), compatibility of multivalent vaccines, justification of the addition of an adjuvant, etc.;
- kinetics: onset, magnitude, duration.

→ **Rationale for formulation / dose selection**

Challenge/passive transfer in controlled laboratory conditions:

- proof of concept in a relevant animal model (Influenza, RSV, Covid-19, etc.): the immune response generated by the vaccination confers protection;
- insights on safety: this immune response does not aggravate the disease;
- insight on correlate of protection.

→ **Proof of concept / rationale for dose selection**

Content of the trial application

	Pharmacodynamics	PK	Toxicology
In general	• Immunogenicity before FIH, dose response. • Challenge/passive transfer where appropriate. • Safety pharmacology if concern.	/	• 1 relevant species, immune response demonstrated. • General toxicity and local tolerance study. • Dose, route of adm and number cfr clin trial. • Target population includes pregnant women/WOCBP: consider developmental toxicity studies (later stages of dev for WOCBP).
Specific	• Absence of clin efficacy data expected: challenge studies become!	• **Distribution**: • Live recomb vaccines. • New formulations.	• **Immunotoxicity** (immune complexes, exacerbation of disease, molecular mimicry, hypersensitivity). • Live attenuated vaccine: degree of **attenuation**, stability of attenuation (> passages). • Live recombinant or attenuated (recombinant or not) vaccines with potential neurological tropism (Yellow Fever backbones !) → : **neurovirulence testing.** • **ERA** for GMO; possible shedding, likelihood of exchange of genetic information.

FAQ…

Non-clinical safety aspects:

- GLP status to be confirmed (vaccines with global development);
- absence of disease enhancement;
- adapt monitoring to findings;
- toxicity studies not completed (premature reports);
- contraception/pregnancy.

Expectations: general toxicology

General tox studies:

- **animal species:** should develop an immune response to the vaccine antigen;
- **dose**: no dose response, 1 dose that is equal to maximal human dose planned (full human dose) unless not feasible (→ factor between human and animal dose to be justified);
- **number of administrations**: equal to or more than the number of doses proposed in humans → "N+1" given 2-3 weeks apart;
- **route**: same as clinical;
- **control group:** saline/formulation without antigen;
- **recovery group**;
- **local tolerance:** assessment of administration site at the end of the main study and at the end of the recovery period.

All pivotal non clinical safety studies should be GLP compliant and a certificate should be included in the submission!

Expectations: WOCBP and developmental toxicity

Target population includes WOCBP: consider developmental toxicity studies.

Studies can be deferred during early phases if:

- male/female reproductive organs are examined during the repeated tox studies;
- women NOT of child bearing potential are included;
- when WOCBP are to be included → CTFG guideline!
    - use of highly effective contraceptive means;
    - a negative pregnancy test is obtained just prior to each immunisation.

FAQ…

Other:

- confirm material is representative;
- strain still adequate (e.g. Covid-19 vaccines).

Conclusions: take home messages

- **Vaccines may appear to have a simplified non-clinical development compared to a « small molecule », BUT …**
  - use a stepwise approach, justify the changes, understand your product → science-based approach;
  - premature general toxicity studies: especially if not sure of the clinical dose, or if significant manufacturing changes are anticipated;
  - National/European Scientific Advice.

Thank you for your attention!

Questions?

Contact

Federal Agency for Medicines and Health Products – FAMHP

Avenue Galilée - Galileelaan 5/03
1210 BRUSSELS

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

www.famhp.be

Follow the FAMHP on Facebook, Twitter and LinkedIn

Your medicines and health products, our concern

famhp

.be