

CTR Early phase: Vaccines

FAMHP

BRUSSELS

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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**

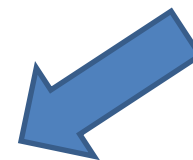
Challenge/passive transfer in controlled laboratory conditions:

- 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

- | | | |
|---|---|--|
| <ul style="list-style-type: none"> • Immunogenicity before FIH, dose response. • Challenge/passive transfer where appropriate. • Safety pharmacology if concern. | / | <ul style="list-style-type: none"> • 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

- | | | |
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| <ul style="list-style-type: none"> • Absence of clin efficacy data expected: challenge studies become! | <ul style="list-style-type: none"> • Distribution: • Live recomb vaccines. • New formulations. | <ul style="list-style-type: none"> • 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

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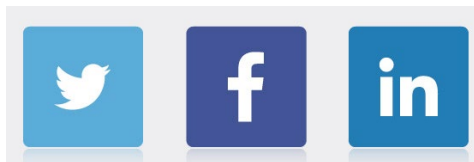
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