# CURRENT REGULATORY THINKING FOR VIRAL SHEDDING STUDIES IN THE EUROPEAN UNION

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# EU LEGISLATION – Clinical Trials

**Definition of a clinical trial (Directive 2001/20/EC):**

**"…..to study adsorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy"**

# Guidance currently available in the EU

- All available quality, pre-clinical and clinical experience with the vector should be included in the IMP dossier:

- Pre-Clinical Studies (general requirements)
  - Pharmacokinetic
    - Exposure data in animals should be evaluated prior to human clinical trials
    - Distribution, metabolism and excretion in animals should be made available to compare human and animal pathways. This information should be available by the time phase I studies are completed

(CPMP/ICH/286/95)

# Guidance currently available in the EU

- Pre-Clinical Studies (specific to GTMP's)
  - Biodistribution
    - Investigation of GTMP persistence, mobilisation and shedding are recommended

    (CHMP\GTWP\125459\2006)

- Clinical Trial Investigations
  - Viral shedding should be monitored in an adequate number of patients and this should form the basis upon which the continuation of such monitoring is decided

  (CPMP\BWP\3088\99)

# Considerations for pre-clinical shedding investigations

- Biology of the vector
  - Replication deficient or competent
  - Transient or integrating
  - Altered tropism of the vector from wild-type
  - Impact of transgene on shedding
  - Risk of mobilisation
  - Risk of recombination with another transmissible agent

- Route of administration
  - Intra-cerebral injection reduced shedding compared to oral?

# Considerations for pre-clinical shedding investigations

- Suitability of the animal model
  - Is this model susceptible to infection by the wild-type virus from which the vector is derived?
  - Is it preferable to use vectors homologous to the human vector, but able to replicate/mobilise/recombine in the animal chosen for non-clinical shedding studies?
  - Ease of collection of samples and volume. Will there be sufficient to test?

# Considerations for pre-clinical shedding investigations

- Dose range
  - Bracketed approach – fewer animals (more ethical).
  - Evaluation of all clinical doses – more animals (less ethical), but might indicate a cut-off point for dose where shedding does not occur.
  - Equivalence of dose to be given in clinical study – vp/kg may not be appropriate if the route of administration is intra-tumoural for example

# Considerations for pre-clinical shedding investigations

- Analytical Methodology
  - Volume of sample may dictate the assay of choice
  - Is it possible to relate a positive PCR signal to infectious virus?
  - Endpoint: if a positive PCR signal is observed pre-clinically, clinical investigation is mandatory – determination of infectivity/transmissibility of shed virus being the aim?
  - Any consequences of vector transmission should be investigated

# Considerations for viral shedding monitoring during clinical trials

- Clinical trials are approved by national competent authorities
- Clinical trial definition includes the ‘study of excretion’ – viral shedding studies are therefore implied
- No defined EU protocol guidance on how these studies should be approached

# Considerations for viral shedding monitoring during clinical trials

- Patients treated as in- or out-patients?
  - If monitoring shedding frequent samples are needed – argument for in-patient
  - If infectious virus shed there are environmental considerations – argument for in-patient
- Number of patients monitored
  - Every patient in the trial or enough to determine if infectious virus is actually shed?
- Frequency of samples taken
  - depends on supportive pre-clinical data
  - initially daily until no signal observed?

# Considerations for viral shedding monitoring during clinical trials

Samples to be taken

- May depend of route of administration and/or pre-clinical data
  - Blood (whole blood and plasma)
  - urine & stool
  - buccal / nasal swabs / saliva
  - semen

# Analytical Methodology

## PCR/qPCR

- Advantages
  - Can be quantitative or qualitative
  - Biochemical endpoint – less subjective that bioassay
  - Heterogeneous samples may be easier to analyze
  - Can be used to detect ‘unexpected’ recombinants

- Disadvantages
  - Measures DNA and not infectious virus
  - Inhibitors in samples
  - Potential for false positives

# Analytical Methodology

## Infectious Virus Titration

- Advantages
  - Measures infectivity rather than just DNA
  - Can be quantitative, semi-quantitative or qualitative
- Disadvantages
  - Read-out is more subjective than PCR analysis
  - Samples may need treatment prior to assay to minimise cell toxicity
  - Sample components may impact on results i.e. EDTA used in blood collection; neutralising Ab's
  - Sensitivity often lower than that of PCR assays

# Analytical Methodology

## Immuno-Assays

Quantification of:

- viral proteins
- transgene expression
- neutralising antibodies to the vector

## Assay validation

- Validation of specificity / LOD as a minimum for phase I trials.
- Full assay validation at time of phase III / MAA (if monitoring plan is necessary).

# EU LEGISLATION
# Market Authorisation

Requirements for a MAA:

- A copy of any environmental CA's written consent to deliberate release for research and development purposes
- Technical and scientific information on the GMO specified in annexes III and IV of directive 2001/18/EC
- An Environmental Risk Assessment (ERA) following the requirements of annex II of directive 2001/18/EC
- The results of any investigations performed for the purposes of research and/or development.

# Relevance of this viral shedding?

- Calculation of environmental risk is based on the probability of transmission of the viral vector from the patient to a third party, animals, plants or the environment at large.
- Experimental or clinical observations may contribute to ERA:
  - recommend incorporation of shedding studies in animal models in to the pre-clinical development program
  - Recommend incorporation of shedding studies in one or more clinical trials during clinical development
  - Shed GMO's may require further characterisation

(EMEA\CHMP\GTWP\125491\2006 – draft)

# SUMMARY

- Clinical trial and marketing authorisation directives do not dictate the need for viral shedding studies – though their requirement is implied.
- Marketing authorisation of a medicinal product containing a GMO is considered deliberate release and thus requires an ERA.
- Assessment of environmental impact can not be fully achieved without viral shedding studies to assess the risk of dissemination from the patient
- Strongly recommended that pre-clinical and clinical development programs incorporate such studies.