ICH Considerations on Viral/Vector Shedding

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ICH was created in 1990
Agreement between the European Union (EU), Japan and the USA to harmonize different regional requirements for registration of pharmaceutical drug products
Unique because a joint effort by regulators and associated pharmaceutical industry trade associations
ICH Gene Therapy Discussion Group (GTDG)

- Monitor emerging scientific issues
- Proactively set out principles that may have a beneficial impact on harmonization
- Ensure that the outcomes of the GTDG are well understood and widely disseminated
  - Public ICH web page
  - Public communications papers
  - Public press statements from the ICH SC
  - Public ICH workshops
ICH Considerations

- Gene therapy is a rapidly evolving field
- It has been difficult to write ICH guidelines on gene therapy topics due to flux of the field
- Consideration papers are a way to proactively set out principles that may have a beneficial impact on harmonization
Published ICH Considerations

- General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (10/2006)
- Oncolytic Viruses (11/2008)
- Viral/Vector Shedding (6/2009)
Viral/Vector Shedding—Introduction

- **Definition**
  - Virus/Vector excretion and/or secretion outside of body
    - Urine, feces, saliva, other
  - Virus/Vector spread within body can be considered biodistribution

- Recommendations on designing non-clinical and clinical shedding studies
  - Analytical assays to be used
Shedding Studies - Introduction

- Why conduct shedding studies?
  - Public health concerns
    - To address the potential risk of transmission to third parties
  - Environmental concerns
    - Excluded from the scope of the document
Viral/Vector Shedding-
Biological Properties of the Virus/Vector

- Properties of the wild-type/parental strain from which the virus/vector was derived
- Replication competence
  - May persist for extended periods
  - May amplify within the patient
- Virus/vector with altered tropism or tissue specific replication
Viral/Vector Shedding - Analytical assays

- **PCR**
  - Should be quantitative
  - Can be sensitive, reproducible, rapid
  - Will not differentiate between intact and non-infectious/degraded virus
  - Useful as first line of analysis

- **Infectivity assays**
  - Can detect intact virus with potential of being transmitted
  - Inherently less sensitive than PCR
  - Not needed if amount of shed material detected by PCR is below LOD
Viral/Vector Shedding - Non-clinical studies

- In conjunction with pre-clinical animal studies, not a stand alone study
- Can help to guide design of clinical shedding studies
- Relevance of animal species
  - Susceptibility & replication
  - Expression and tissue distribution of viral receptors
  - Impact on immunity to the virus/vector
- Disease model
- Dose and Route of administration
Sampling Frequency and Duration
- Sample more frequently in the first day post administration
- Sample until multiple consecutive negatives
- Note that replication competent vectors can have a secondary peak of replication
Viral/Vector Shedding - Non-clinical studies

- Sample Collection
  - Urine, feces are commonly collected
  - When insufficient sample amount, pooling should be done from multiple animals at same time point

- Study Interpretation
  - Use to guide design of clinical study
  - Not a substitute for clinical studies
  - If shedding observed indicates the possibility of transmission, cage mate transmission studies might be useful
Viral Shedding - *Clinical Studies*

- Data from pre-clinical studies
- Virus/Vector properties
- Sampling frequency and duration
  - More frequent in first days
    - Sample until multiple consecutive negatives
  - Dependent on replication capacity
  - Consider patient immune status
Viral/Vector Shedding - Clinical Studies

- Sample Collection
  - Characteristics of virus/ vector, ROA
- Interpretation
  - Characterize what is shed and how much
  - How is it shed and how is this related to normal mode of transmission
  - What are the potential pathogenic properties of the virus/ vector and what are the transgene properties
- Third party transmission
  - Consider evaluating close contacts
The GTDG is proposing to further develop this Considerations to a formal ICH guideline.

The ICH GTDG is requesting comment on this Considerations:

- Can send through ICH web site on the gene therapy page
- Comment on the document and what additional information should be in a guideline
Additional Information

- Comments and Questions
  - daniel.takefman@fda.hhs.gov

- ICH & GTDG web site
  - http://www.ich.org