

ICH Considerations on Viral/Vector Shedding

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International Conference on Harmonisation (ICH)

- 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
 - <http://www.ich.org/>
 - 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

Viral/Vector Shedding- Non-clinical studies

- Sampling Frequency and Duration
 - Sample more frequently in 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

Considerations Document

- 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>