FDA Perspectives On Viral & Vector Shedding Studies

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ICH Workshop: October 31, 2007

Overview

- Define shedding studies
- Outline basis for need of shedding studies
- Provide general considerations for design of shedding studies
- Outline differences in shedding studies performed for public health concerns and for environmental concerns

Viral/Vector Shedding-Definition

- Virus/Vector excretion outside of body
  - Urine, feces, saliva, other
- Virus/Vector spread within body can be considered biodistribution

Shedding Studies-Why and When

- Public health concerns- human to human spread
  - Addressed during initial clinical studies
- Environmental concerns
  - Used to provide information for environmental assessment (EA)
  - Part of license application

Viral/Vector Shedding- *Considerations for INDs*

- Public Health Concerns
- Regulations/guidance- no specific guidance
  - Public Health Service (PHS) Act
    - Prevention of spread of communicable diseases
- FDA approach for shedding studies
  - Science and risk based
  - Not prescriptive and considered in the context of the proposed clinical study

Viral/Vector Shedding- General *Considerations for INDs*

- Factors used to assess need for and design of shedding studies for initial clinical trials
  - Virus/Vector properties
  - Route of administration (ROA)
  - Dose
  - Indication
  - Pre-clinical animal studies
  - Prior experience
  - Ex vivo transduced cells not typically considered

Viral/Vector Shedding- *Considerations for pre-clinical studies*

- In conjunction with pre-clinical animal studies, not a stand alone study
- Relevance of animal species and disease model
  - Tropism
  - Biodistribution / Pharmacokinetics
  - Viral Replication
  - Clearance
    - Immune response
  - Disease model characteristics
    - e.g. tumor model for oncolytic vectors

Viral Shedding-
Considerations for pre-clinical studies

- Detection Assays
  - PCR
    - FDA guidance for LTFU
  - Infectivity
- Samples for analysis
- Sample time points
- Horizontal transmission studies

Viral Shedding-
Considerations for Clinical Studies

- Clinical shedding studies
  - Data from pre-clinical studies
  - Virus/Vector considerations
    - Replication competent vs. incompetent
    - Biology (mode of transmission, ability to recombine, etc.)

Viral/Vector Shedding- *Considerations for Clinical Studies*

- Samples for analysis
  - Based on route of administration
    - Analysis of urine if injection into bladder
    - Analysis of saliva and/or nasopharyngeal swabs for head & neck cancer
  - Detection assays
    - PCR vs. Infectivity, step wise approach
- Time points

Viral Shedding-
Considerations for Clinical Studies

- Horizontal transmission studies
  - Virus/Vector found to shed
  - ROA that has high risk for transmission
- Complexity/ Logistics
  - Sample collection procedure to avoid mix-ups
  - Adequacy of sample collection

Environmental assessment

- The National Environmental Assessment Policy Act of 1969 (NEPA)
  - Requires all Federal agencies to assess the environmental impacts of their actions
  - Inform the public
- FDA regulations 21 CFR part 25
  - Environmental assessments (EAs) must be submitted as part of IND, NDA, BLA, and supplements

Environmental assessment- *exclusions*

- Investigational New Drug (IND) Application
  - Can request categorical exclusion [21CFR25.31(e)]
    - Small scale production, low number of clinical trial participants
  - Required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21CFR 25.21)

Environmental assessment- *exclusions*

- Biologics license application (BLA)
  - Categorical exclusion if
    - ***Substance is naturally occurring in the environment [21CFR25.31(c)]***
    - Approval will not increase the use of an active moiety [21CFR 25.31 (a)]
    - Applications for marketing approval of a biologic product for transfusable human blood or blood components or plasma [21 CFR 21.31 (j)]

Shedding Studies-
Considerations Relating to Environmental Assessment

- Shedding studies can inform EAs
  - No substance is shed
  - Substance is shed, but in a degraded form
    - Role of infectivity assays
  - Point of entry into the environment

Shedding Studies vs. Environmental Assessment

- Some products may warrant shedding studies for public health concerns, but may be categorically excluded from EA requirements if “naturally occurring”
  - Oncolytic viruses containing no transgene
- Some products that are not assessed in shedding studies for public health concerns may need EA (e.g. plasmids)
  - Currently no experience with EAs for gene therapy products as no products have been licensed

Summary

- Shedding studies performed at initiation of IND for public health concerns
  - Science and risk based approach
  - Need and design based on numerous factors specific to the product and clinical study
- Shedding studies can be performed to inform EAs
  - EAs part of license application