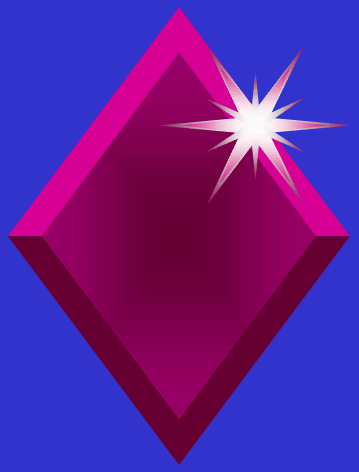
FDA Perspective on the Development of an Adenoviral Standard



Stephanie L. Simek, Ph.D.

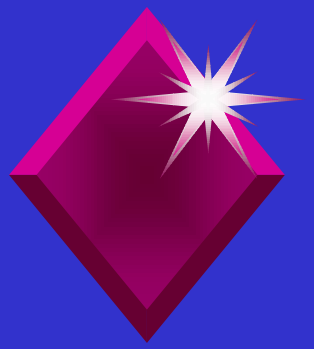
CBER/OTRR

Background/History

- 1993 Adenoviral vectors used in CF Protocols
- CF Foundation calls for vector standard
- 1999 Development of RAC AdSAT working group
- 1999 RAC Safety Symposium
- Oct. 5th Williamsburg BioProcessing Foundation meeting

Recommendations of RAC AdSAT Working Group

- Development of qualitative, quantitative vector standards - Adenovirus
  - determine particle number
  - determine infectious titer
- Allow comparison of toxicities observed in different studies
  - preclinical
  - clinical



Perspectives/Issues

- Concern over precision and accuracy of adenoviral titers
  - particle counts (multiple methods used)
  - infectious units (best 30% imprecision)
- Sharp threshold effect in dose/toxicity curve

Perspectives/Issue (cont.)

- Consistency in clinical dosing
  - dose control
    - closer approach to maximum tolerated dose
    - smaller dose increments
  - analysis of dose related adverse events
- Safety concerns
  - RCA: how much is safe?
  - toxicity of vector particle

Approaches

- Standards Development
  - physical: particle counts
  - biological: infectious particle titer
  - procedural: development of SOPs
- Precedent
  - RCR standard
    - CBER/ATCC /industry/academia collaboration

FDA Initiatives

- Collaboration with industry and academia to develop standard
  - Participation in adenoviral standardization working group
- Adenovirus research group

Collaboration with Industry/Academia

- Oct. 5, 2000 Ad vector conference
  - organized by WBF in conjunction with FDA/industry/Academia
- Consensus to develop well characterized standard
- FDA take lead using a working group approach

Leveraging

- Working with others outside CBER to meet public health responsibilities
- Investing resources in collaboration with others
- Allows for flexibility and more rapid movement
- http://intranet.fda.gov/leveraging/

Leveraging Agreements

- Feb 1 meeting Co-Sponsorship agreement
  - Allows for public discussion and input
- WBF-FDA Partnership Agreement
  - Allows for partnership between FDA/WBF/industry
    - Participation of FDA in development of a voluntary industry standard
    - Identify relevant criteria in production, and distribution of adenoviral standard
    - Improve ability to evaluate safety of adenoviral GT products

FDA's Role in Working Group

- Responsible for leading process to evaluate and select group(s) to manufacture, characterize, and distribute the standard
- Agreement with WBP Foundation
  - serve as "facilitating entity" for WG and FDA
  - post RFAs, announcements, meeting minutes
  - oversee the performance of each contractor

FDA's Role in Working Group (cont.)

- Review Proposals for vector production
- Make recommendation for selection of appropriate group(s) to manufacture, characterize and distribute standard.
- Set testing qualifications for standard
- collate data from standard testing
- provide guidance to WG

Adenovirus Production Scheme

Master Cell Bank

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Ad5 wt virus

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Master Viral Seed Stock

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Production of purified formulated bulk virus

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Characterization, safety testing

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Vialing, freezing, storage

Adenoviral Research Initiative

- Interaction of human and murine adenoviral vectors with viral receptors
- effect of receptor interaction on viral tropism and pathogenesis

What will be Accomplished by Standard Development

- Production of more consistent, safer, quality adenoviral vectors
- Allow comparability between preclinical studies
- Allow comparability between clinical studies
- Development of regulatory policy