FDA Perspectives on the use of Adenoviral Reference Material

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Background/History

- 1999 Development of RAC AdSAT working group
- 1999 RAC Safety Symposium
- Oct. 5th Williamsburg BioProcessing Foundation meeting
- Federal Register Notice 2/1/01
- Development of ARMWG

Recommendations of RAC AdSAT Working Group

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

Leveraging Agreements

- Feb 1 meeting Co-Sponsorship agreement
  - Allowed for public discussion and input
- WBF-CBER Partnership Agreement
  - Allowed for partnership between FDA/WBF/industry/Academia
    - Identify relevant criteria in production, and distribution of adenoviral reference material
    - Improve ability to evaluate safety of adenoviral GT products

Perspectives/Issues

- Concern over precision and accuracy of adenoviral titers
  - particle counts (multiple methods used)
  - infectious units (inconsistency between assays)
- 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/Contamination concerns
  - RCA: how much is present
  - toxicity of vector particle

Approaches

- Reference Material Development
  - physical: particle counts
  - biological: infectious particle titer
  - procedural: development of SOPs

FDA's Role in ARMWG

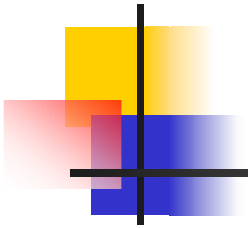
- Review Proposals for vector production
- Make recommendation for selection of appropriate group(s) to manufacture, characterize and distribute reference material.
- Set testing qualifications for reference material
- Collate data from reference material testing
- Provide guidance to WG

Importance of Reference Material

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

Current FDA Recommendations

- Clinical dosing by viral particle number
- RCA levels <1RCA in 3 x 10e10 vp
- Infectious units:vp ratio <30vp/1iu
- Complete sequence of all vectors <40kb.



Where Do We Go From Here ?

Recommended Use of Adenoviral Reference Material

- Used to validate an internal reference
- Used to define infectious unit and virus particle for adenoviral GT vectors
- Analytical methods can be validated against ARM-although limited quantity of ARM available
- Will allow for analysis of safety and efficacy based on similar unit measurements
  - RCA
  - Dosing

What is Not Expected

- Standardization of specific assay methods
- Endorsement of specific production, purification methods
- Duplicate ARM titer & particle values
  - Values were based on statistical analysis
  - Individual values based on statistically significant number of assays run against internal reference

Proposed Regulatory "Phase In"

- Public outreach describing methodology and analysis
  - Publications in journals
  - Information on WBF website-www.wilbio.com
- Allow for generation of internal reference
- Allow for assay validation using internal reference
  - Optimization of internal assay methods
  - Implementing new assay procedures

Proposed Regulatory "Phase In" (cont.)

- Recommend new IND sponsors use validated internal reference or ARM in titer, particle & RCA determination
- Recommend existing IND sponsors perform Retrospective analysis
  - RCA levels
  - VP/IU ratio
- Complete "phase in" time expected to take no longer than a year

Conclusions

- Use of ARM will allow comparison of data from different studies using different adenoviral vectors
  - Improve precision of assays - titer, particle & RCA
- Use of ARM will improve safety and efficacy
  - Control of clinical doses
  - Comparability between clinical trials
  - Comparability between preclinical trials
- Result in policy development

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Questions & Information

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