A User's Guide to FDA's Draft Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events

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This presentation will answer:

- What are the key events that led to development of this guidance?
- What are the scientific bases for long-term risks?
- How does one determine whether long-term observations should be performed in a particular clinical trial?
- What is meant by “observing participants for delayed adverse events”?

Key Events in Development of Guidance Document

- 1993, Letter to sponsors of retroviral vectors
  - Life-long surveillance of subjects
  - Guidance document published 2000
- March 6, 2000, "Gene Therapy Letter" – lack of good study conduct monitoring, including lack of long-term follow-up of subjects of retroviral vector-mediated gene therapy
- BRMAC Meetings*:
  - November 17, 2000
  - April 5, 2001
  - October 24, 2001

*Transcripts, www.fda.gov/cber/advisory/ctgt/ctgtmain.htm

Key Events in Development of Guidance Document (Cont'd)

- 2001, Implementation of recommendation to perform long-term follow-up of subjects in ALL clinical trials, regardless of vector

- June, 2004, Workshop on Long-term Follow-up of Participants in Human Gene Transfer Research
  - Lack of scientific basis for 2001 recommendations
  - Lack of details for how to perform long-term surveillance
  - Legal consequences for long-term surveillance

Properties of Gene Transfer Systems with Potential to Cause Delayed Events

- Persistence of Vector Sequences
  - Integration
  - Reactivation/Latency
- Transgene-specific effects

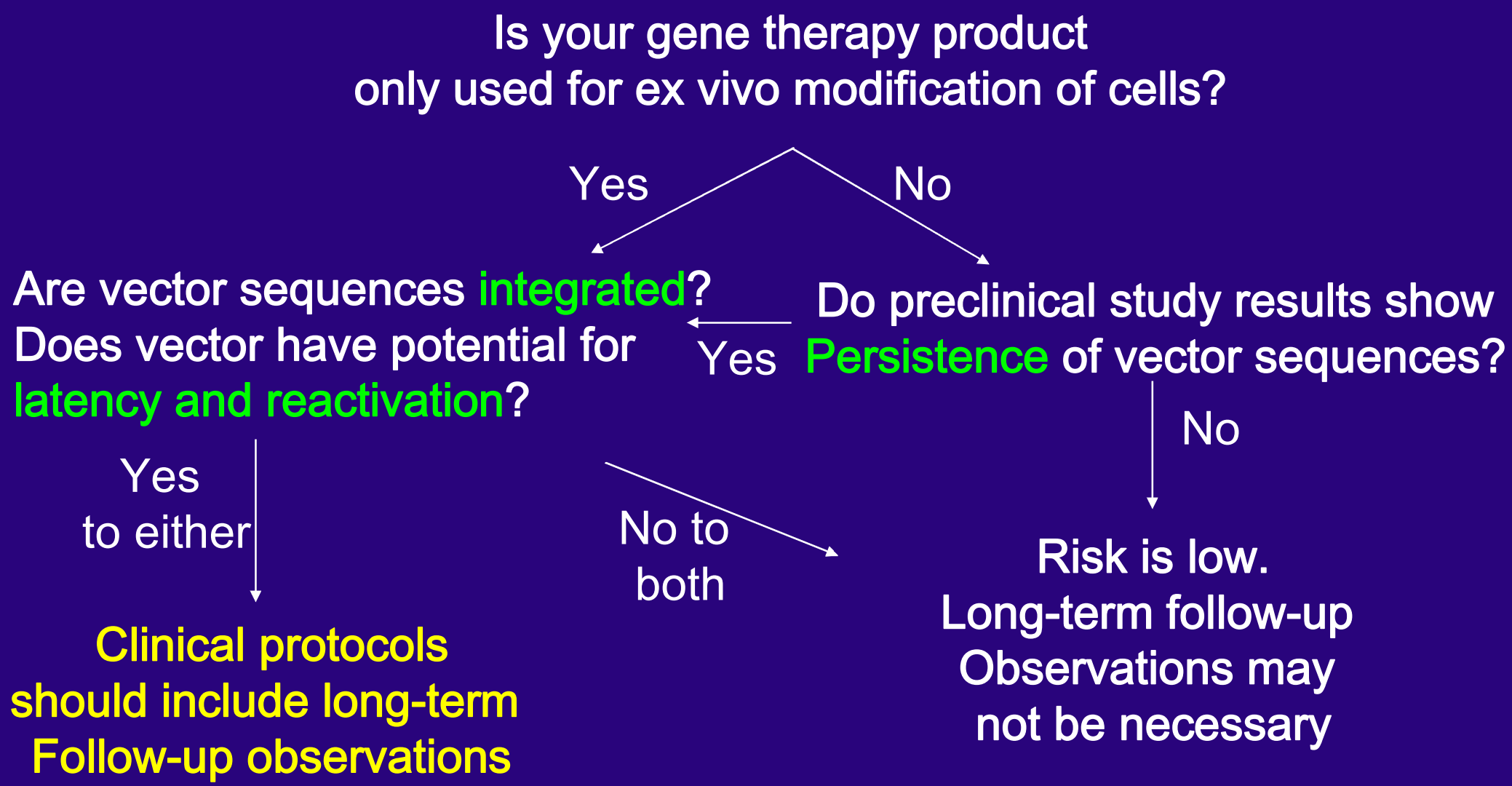
Persistence of Vector Sequences

- Long-term risk of persistence will be influenced by
  - Mechanism of persistence
    - Ex, integration of vector (Potential for Insertional Mutagenesis)
  - Latency and potential for reactivation
    - Ex, Reactivation of herpesvirus carries risk of encephalitis
  - Immune status of subject
    - Ex, immune response or lack thereof may influence outcome relative to long-term risks

Transgene-Specific Effects

- Tumorigenic effects of transgene itself
- Transgene expression may induce autoimmune disease in genetic disorders
- Constitutive expression may induce unexpected effects when endogenous gene is tightly regulated (e.g., metabolic pathways)
- Ectopic gene expression

Criteria to Assess Potential Delayed Risks of Gene Therapy



How to Determine Persistence

- Biodistribution Study with multiple time points
- Vector is defined to persist if detectable levels of vector are present throughout all time points of the study without any downward trend over several time points.

Integration/Latency

- Can perform as part of the persistence study to identify whether vector integrates

Or

- Refer to Table 1 Propensity to Integrate

Or

- If integration occurs or cannot be defined, perform long-term observations

Vector Type	Propensity to Integrate	LTFU
Plasmid	No	No
Poxvirus	No	No
Adenovirus	No	No
AAV	No	No
Herpesvirus	No, but latency with reactive potential	Yes
Retrovirus	Yes	Yes

Exceptions

- Evidence for persistence of transgene expression without integration: preclinical studies show potential for long-term toxicity.
- Evidence for potential long-term toxicity due to specific transgene; potential for autoimmune response
- Alterations to “non-integrating” vectors to change that property

Use of Retroviral Vectors: Special Considerations

- *When*
  - Used to Transduce Target Cells with High Replicative Capacity and Long Survival
- *If*
  - Surrogate is accessible for assay
- Test for vector sequences every 6 months first 5 years; yearly next ten years; or until no vector is detected.
- Recommended Points to Include in Informed Consent: accurately reflect risk of cancer

Retroviral Vectors, Continued

- When at least 1% of surrogate cells have detectable vector (by PCR, or other sensitive method)
  - Assess the pattern of vector integration sites.
    - If oligoclonal or clonal, identify integration site
    - Compare to human genome; determine whether oncogene
    - Monitor for signs of malignancy

Clinical Long-Term Studies

- Should be performed if
  - Criteria suggest that vector/gene therapy is associated with a high or uncertain risk
  - Information about product, taken as a whole, shows a need for long-term follow up
- Need not be performed if
  - Clinical considerations determine that studies would have no scientific value

Determination of Scientific Value of Follow Up

- Population characteristics with predicted low scientific value to perform long-term observations:
  - Short life expectancy
  - Multiple morbidities
  - Exposure to other agents

Duration of Follow Up

- Duration of in vivo vector persistence
- Duration of in vivo transgene expression
- Exposures of study population
- Expected survival rates
- Other relevant factors

Elements of Observation: First 5 Years

- Systematic case histories, baseline information
- Detect gene therapy related events
- Record exposures to mutagens
- Visit health care provider annually
- Record new malignancy, neurologic disorder, rheumatologic or autoimmune disorder, hematologic disorder
- Elicit cooperation from study participants in reporting events

Observations: 6 – 15 years

- Contact annually, specific screening if indicated
- Continue appropriate follow up as indicated by results from previous years

Other considerations

- Report to FDA, expedite if serious
- File annual reports with FDA
- Examine as indicated by emergence of adverse events
- Test for vector sequences at least annually, if technically feasible

Reminder: NCRR Support Available for Academic Studies

- Support for subject visits to General Clinical Research Center (GCRC)
- Blood sample storage available through NGVL at no cost to NIH-funded studies
- Clonality analysis by NGVL for retroviral vector studies, when FDA required

http://grants.nih.gov/grants/guide/notice-files/NOT-RR-04-005.html

Submit Comments by November 21

Written Comments:

Division of Dockets Management, HFA-305

FDA, 5630 Fishers Lane, Rm 1061

Rockville, MD 20852

Electronic comments:

http://www.fda.gov/dockets/ecomments

Additional Questions?

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