

Monitoring for Insertional Mutagenesis: FDA Recommendations

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Background

- FDA advisory committee meeting October 10, 2002
- Data presented regarding first patient that developed leukemia in French X-SCID trial
- Data from LAM-PCR revealed development of a clonal outgrowth months before clinical symptoms
- Committee recognized that these types of assays were not yet validated, but recommended analysis of vector integration sites as part of subject monitoring

Recommendations- where?

- Ultimately published as part of “Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events”, 2006
 - AKA: Long-Term Follow-Up (LTFU) Guidance
 - Specific subsection on “Special Considerations Regarding Integrating Vectors”
 - Specific sections on when LTFU is recommended will not be discussed in this presentation
 - LTFU typically needed for retroviral/lentiviral vectors

Key Events in Development of LTFU Guidance Document

- FDA Advisory Committee Meetings 2000-2001
 - Led to initial 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

LTFU- Duration of Monitoring

- 15 years of follow up recommended, but FDA will consider other factors to justify alternative duration
 - Duration of in vivo vector persistence
 - Duration of in vivo transgene expression
 - Exposures of study population
 - Expected survival rates
 - Other factors relevant to the feasibility and scientific value of conducting LTFU

Elements of Observation: 1-5 Years

- Systematic case histories, baseline information
- Annual physical evaluations by health care provider
 - Laboratory evaluations such as hematology profile
- Detection of gene therapy-related adverse events
 - Elicit cooperation from study participants and their health care providers in reporting events
 - Report SAEs in expedited reports
- Record exposures to mutagens
- Record new malignancy, neurologic disorder, rheumatologic or autoimmune disorder, hematologic disorder
- Test for vector persistence until undetectable

Elements of Observation: 6 – 15 years

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

LTFU: Special Considerations Regarding Integrating Vectors

- *When*
 - Used to Transduce Target Cells with High Replicative Capacity and Long Survival
- *If*
 - Surrogate is accessible for assay
 - e.g. If CD34+ cells are target for therapy, then PBMC serve as surrogate
- Test for vector sequences every 6 months for first 5 years; yearly next ten years; or until no vector is detected

Integrating 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
 - Method should be:
 - Shown to be specific, sensitive, reproducible
 - Based on data with appropriate positive and negative controls (i.e., target cells with known number and sites of vector copies integrated vs. target cells with no vector integrants)
 - LM-PCR and LAM-PCR have been typically used

Integrating Vectors, Continued

- If an integration analysis indicates development of a predominant clone or monoclonality, identify integration site
 - Compare to human genome; determine whether oncogene
 - Monitor for signs of malignancy
 - Perform additional analysis for clonality no more than three months later
 - Submit this essential information in an information amendment to the IND (21 CFR 312.31(a)) within 30 days

Integrating Vectors, Continued

- While oligo or monoclonality may not *a priori* result in malignancy, FDA recognizes that these observations increase the risk of developing a malignancy, and therefore recommend additional monitoring when
 - Persistent monoclonality
 - Clonal expansion (i.e., the % of cells positive for a particular vector integration site is shown to increase over multiple timepoints)
 - Evidence of vector integration near or within locus known to have oncogenic activity

Integrating Vectors, Continued

- To screen for specific disease entities, FDA recommends that sponsors/investigators use established methods and/or seek advice from clinicians with expertise in screening for the health care risks to which, according to available evidence, the subjects may be exposed.

Additional Recommendations Needed?

- Currently no specific defined criteria for development of a predominant clone or monoclonality
 - e.g., >20% gene modified population is derived from a single clone
- As methods such as high throughput sequencing have emerged, unclear as to the best methods to use for monitoring and the best methods for sample preparation
- Is there value in generating a reference material for international use?
 - Cell line with specified integrations

Additional Information

- Comments and Questions
 - daniel.takefman@fda.hhs.gov
- General information for OCTGT and related regulatory references (including LTFU Guidance)
 - <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>