

Session IV

GENE THERAPY: CONSIDERATIONS FOR LONG TERM PATIENT FOLLOW- UP

Exploring Novel Clinical Trial Designs for Gene Therapies

National Academies of
Sciences, Engineering, and Medicine

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Outline

- Long-Term Follow-Up (LTFU)
 - General considerations
 - Risks of gene therapy (GT) products
 - Risk Assessment
- Preclinical Considerations
- Clinical Considerations
 - Goals of LTFU
 - Patient Population considerations
 - Duration of LTFU
 - LTFU protocol elements
 - Post-Marketing Considerations

Guidance for Industry

Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact the Office of Cellular, Tissues, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2006

November 2006

Long Term Follow-Up After Administration of Human Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Revision

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018

July 2018

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products>

LTFU for Gene Therapy Products

- Monitoring for adverse events for an extended period of time
 - For subjects in clinical studies following protocol specified active follow-up period
 - For patients receiving GT therapy products post-licensure
- Not all GT products will require LTFU

Why is LTFU Needed?

- Gene Therapy products
 - Designed to achieve prolonged or permanent therapeutic effects
- Long-term exposure may result in
 - Undesirable or unpredictable adverse outcomes that may occur past the period of active monitoring
- Potential risks
 - Malignancy
 - Impairment of gene function
 - Autoimmune-like reactions
 - Reactivation of latency and infection
 - Persistent infections

Considerations for Risk Assessment for Delayed Adverse Events

- Product characteristics
- Target cell/tissue/organ
- Preclinical information
- Clinical information (e.g. prior clinical experience)
- Patient-related factors
 - Age
 - Immune status
 - Risk of mortality
- Relevant disease characteristics

Characteristics of Gene Therapy Products: Increased Risk of Delayed Adverse Events

- Integration activity
- Genome editing activity
- Prolonged expression of transgene
- Latency
- Establishment of persistent infections

Table 1. Propensity of Commonly Used Gene Therapy Products/Vectors to Modify the Host Genome



Product/Vector Type	Propensity to Modify Genome¹	Long Term Follow-up Observations²
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno-associated virus ³	No	Product specific (2-5 years)
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT) ⁴	No, but may persist and undergo reactivation	Product specific
Genome editing products	Yes; permanent changes to the host genome	Yes

Note:
Excerpted from Draft Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (July 2018)

¹ Based on product design (i.e., lack of any known mechanism to facilitate integration or genome editing), as well as cumulative preclinical and clinical evidence suggesting that a GT product does not integrate into or edit the genome or integrates in/modifies the genome at very low frequencies.

² Specific circumstances that indicate persistent expression of the transgene, in the absence of integration or genome editing, may be the basis for a conclusion that LTFU observations are recommended to mitigate long term risks to subjects receiving these vectors. This would depend on additional criteria, such as the transgene expressed or clinical indication, as described in this section.

³ Replication-negative vectors only.

GT Products with Potential Delayed Risks

- Integrating vectors, including:
 - Gammaretrovirus
 - Lentivirus
 - Foamy virus
- Herpes virus capable of latency-reactivation
- Genome editing products

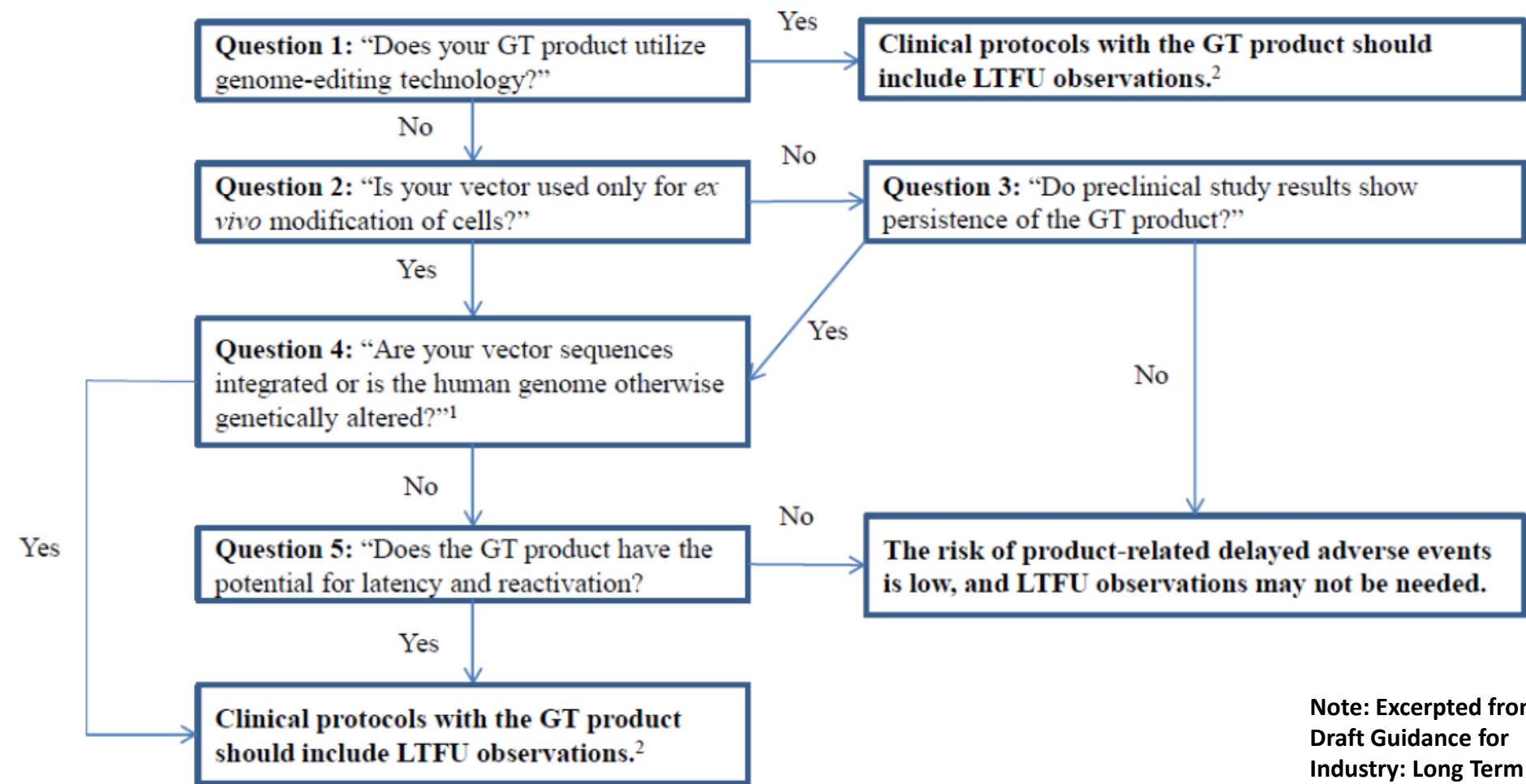
GT Products with Generally Low Risk of Delayed Adverse Events



- *Plasmids
- Poxvirus
- Adenovirus
- Adeno-associated virus (AAV)

*Note that plasmids that carry genetic elements capable of genome integration/modification are considered high risk

Figure 1. Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events



¹ If you have evidence that suggests that the product may integrate or if the product was intentionally designed to facilitate integration (please refer to Table 1, section IV.C of this document); the answer is “yes.”

² See section V. of the text for recommendations on how to perform clinical LTFU observations.

Preclinical Considerations

General



- Preclinical studies to assess
 - GT product localization/distribution and persistence
 - On-target and off-target effects
- Animal study considerations
 - Use intended GT clinical formulation and route of administration
 - Evaluate both sexes
 - Biodistribution assessment in vehicle control group and group of animals using maximum feasible or clinical dose
 - Correlation of product presence and/or persistence to adverse events
 - Characterization of kinetics of GT product; sacrifice at peak GT product detection and at later timepoints for clearance

Preclinical Considerations

Tissue Collection and Analysis

- Minimum tissue panel analysis
 - Blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, spleen
 - Additional tissues dependent on product, vector type and tropism, route of administration
- Assay methodology
 - Quantitative, sensitive assay, e.g. PCR
 - Should be able to detect vector sequence in both animal and human tissue

Clinical Considerations

- Goals of LTFU
- Clinical Trial Population
- Duration of LTFU
- Elements of LTFU
- Informed Consent in trials with LTFU
- Special considerations for
 - Integrating vectors and genome editing

Goals of LTFU



- Identify long term risks to patients receiving GT products
- Mitigate the risks
- Understand persistence of GT products

LTFU Population

- All subjects enrolled in the clinical trial who receive GT
- Characteristics of patient population need to be considered when designing a LTFU protocol
 - Life expectancy
 - Multiple co-morbidities
 - Exposure to other agents
 - Radiation
 - chemotherapy

Duration of LTFU



- Sufficient to detect delayed adverse events(AEs) based on
 - Product characteristics
 - Observed duration of *in vivo* product persistence
 - Observed duration of transgene expression
 - *In vivo* product characteristics
 - Nature of exposure
 - Route of administration
 - Anticipated time of occurrence of delayed AEs; consider
 - Expected survival rates and known background rates in study population

Duration of LTFU

- 15 years
 - Integrating vectors
 - Gammaretroviral and lentiviral vectors
 - Transposon elements
 - Genome editing products
- Up to 5 years
 - AAV vectors
- Risk-based approach considerations
 - for vectors capable of latency (e.g., Herpesvirus) or
 - long term expression without integration

Dedicated Clinical LTFU Protocol



- Detailed patient visit schedules
- Sampling plan for test samples, to include blood sampling
- Methodology for monitoring tests
 - Persistent vector sequences
- Clinical events of interest that will be monitored
- Health Care Provider template for non-investigator caregivers
- Accurate case histories

Elements of LTFU

- Detection of AE and Data Collection
- IND Safety Reports
- Annual Reports
- Clinical Protocol amendments
- Scheduled Physical Examinations
- GT Product Persistence

LTFU Procedures

First 5 Years

- Detailed plan for scheduled visits noting information to be collected (e.g. history, physical exam, labs, reporting of adverse events, etc.)
- Detailed case histories
 - Record of exposure to mutagenic agents
 - Record of emergence of new medical conditions of interest
 - New malignancy(ies)
 - New or worsening of pre-existing neurologic or rheumatologic disorder
 - New hematologic disorder

Subsequent 10 Years

- Contact subjects at a minimum of once a year
 - Telephone
 - written questionnaire or
 - office visit with health care provider as appropriate

Note: FDA strongly recommends sponsors make every effort to prevent patient loss to follow-up to the extent feasible for completion of LTFU observations

Detection of Adverse Events

Considerations



- Identification of suitable HCPs to collect AEs
- Consideration of tools to facilitate AE capture
- Assessment of causality of GT product and AE
 - Collection of tissue samples for follow up analysis
 - Biopsies and autopsies (informed consent required)
 - Preservation of tissues/samples
 - Specification of tests to enable causality assessment
 - Blood tests, cytogenetic and histological analyses, PCR, HLA typing or deep sequencing

Assessment of GT Product Persistence

- Test study subjects at least annually for persistent vector sequences until they are undetectable
 - Assay should be sensitive to detect vector sequences
 - Sample the likely population of transduced cells
 - Consider surrogate indicative of vector persistence
 - If invasive procedure is needed to sample transduced cells
 - Example: level of transgene product
- Note: consider modification of LTFU based on waning persistence of vector in context of risks

Informed Consent for LTFU



- Purpose of LTFU and expected participation and procedures, scheduled study visits, data collection
- Foreseeable risks
 - Adverse reactions associated with GT product
 - Delayed adverse reactions: e.g.: malignancy, autoimmunity, etc.
- Collection and storage of blood and tissue samples for future testing
- Autopsy may be requested to:
 - Test vector persistence, transgene expression, and related adverse reactions at molecular, cellular or tissue level

Post-Marketing Monitoring Considerations



- Pharmacovigilance plan requested at time of BLA submission
 - Routine surveillance
 - Submission of reports for serious, life-threatening and unexpected AEs
 - Registry system
 - Required post-marketing observational clinical trial
 - Risk Evaluation and Mitigation Strategy (REMS)



Thank you

Contact Information

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- **Regulatory Questions:**
 - OTAT Main Line – 240 402 8190**
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- **OTAT Learn Webinar Series:**
 - <http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
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