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# Clinical Development of Gene Therapy: Safety Evaluation and Monitoring

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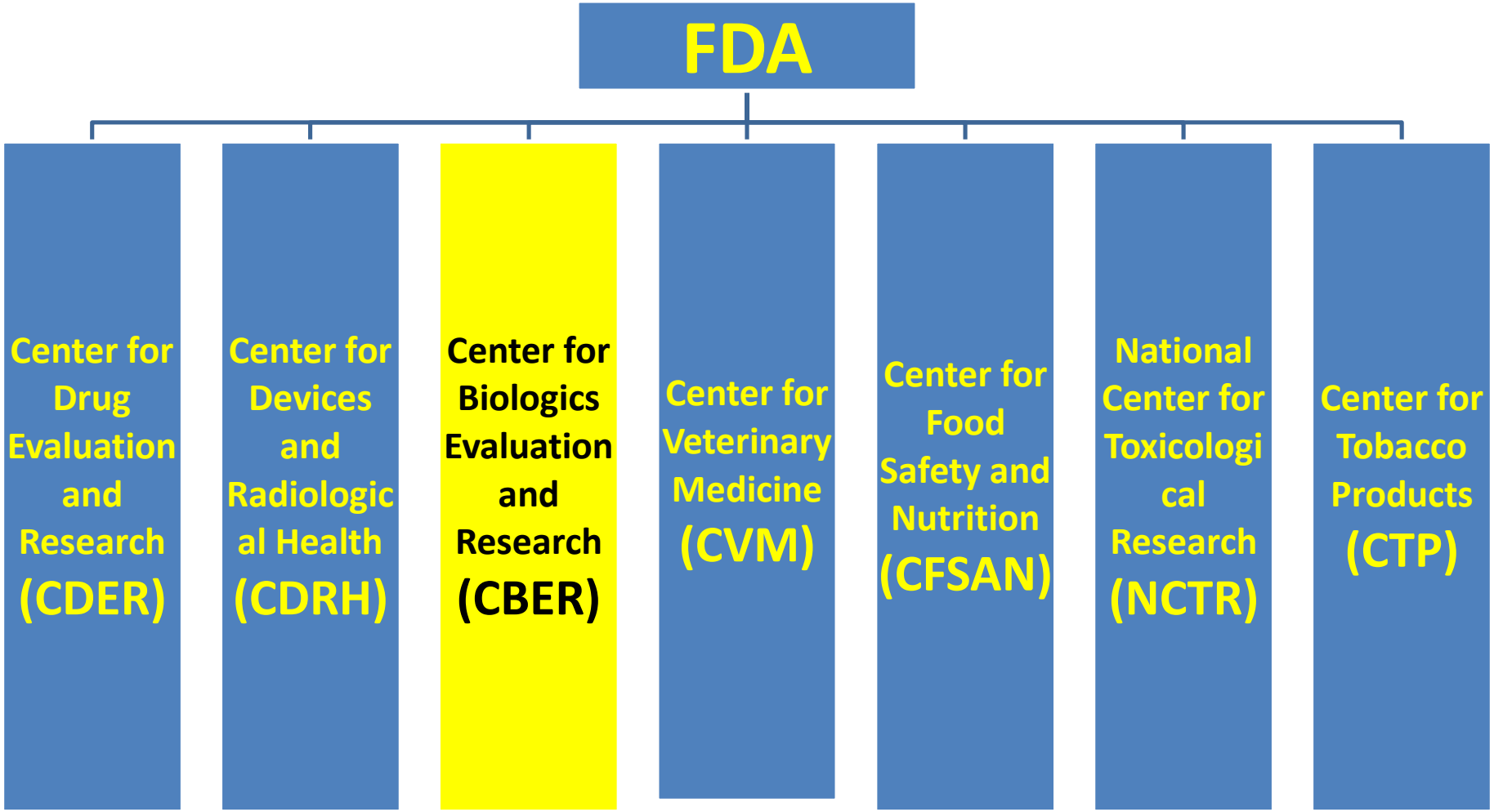
Center for Biologics Evaluation and Research (CBER), FDA

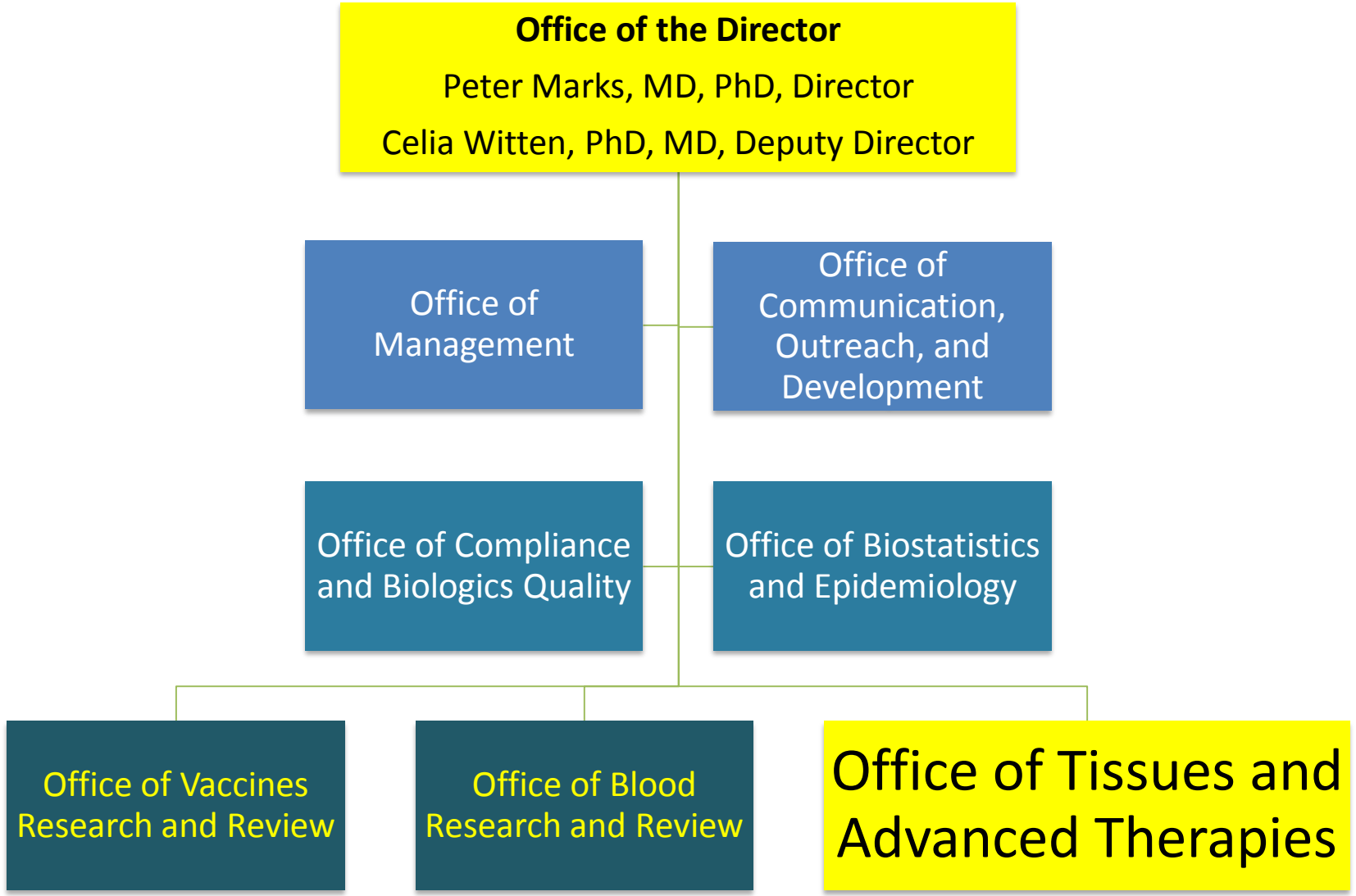
# Outline

- Overview of OTAT, CBER, FDA
- Potential safety concerns of gene therapy (GT) products
- Safety monitoring before and after approval
- OTAT experience from approved GT products

# FDA Organization



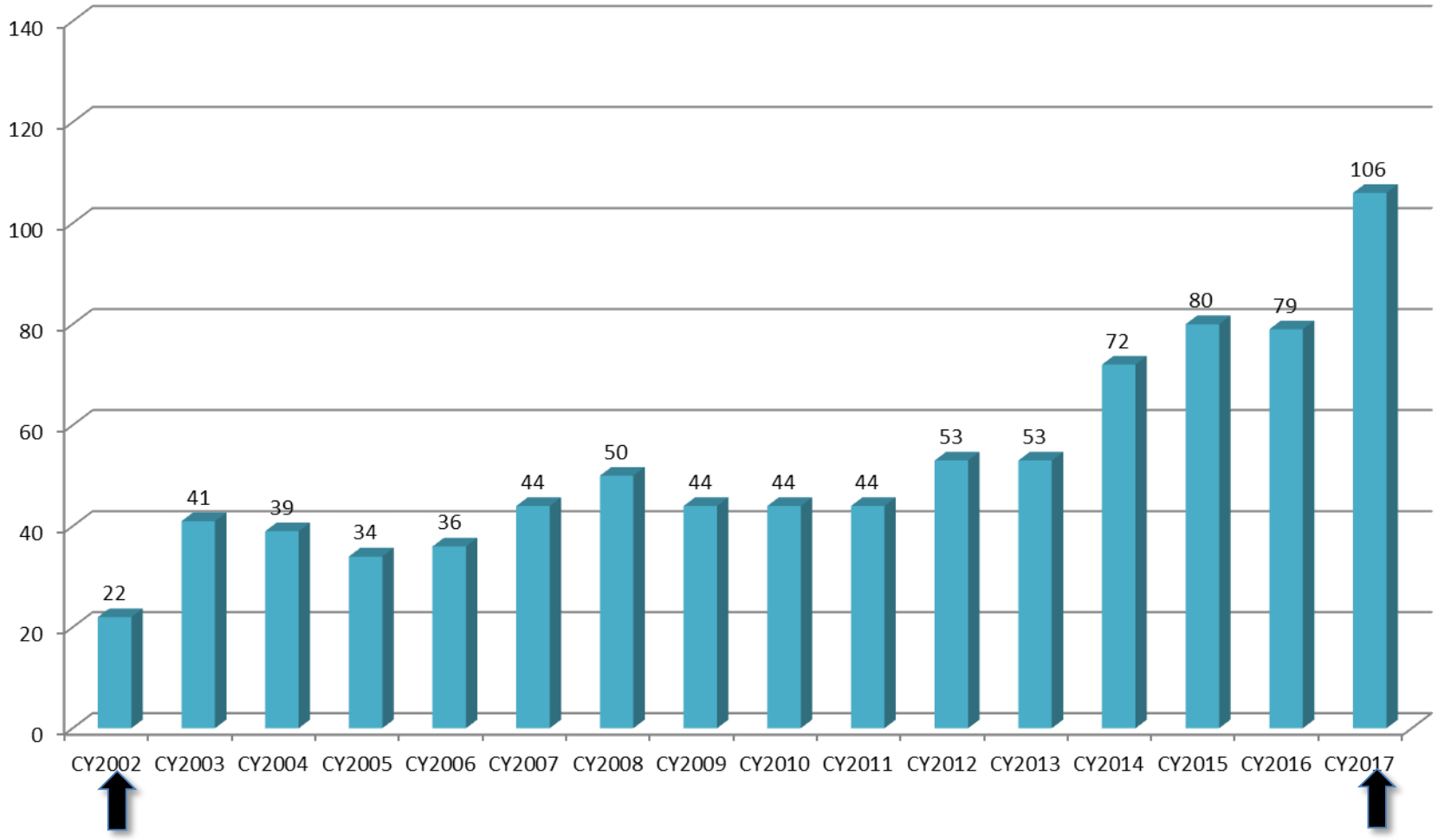
# Center for Biologics Evaluation and Research (CBER)



# Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Products for xenotransplantation**
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Snake venom antisera
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

# All IND Submissions with Gene Therapy Products, CY 2002-2017




**Gene Therapy IND increase by 34.2% from 2016 to 2017**

# Definitions of Human Gene Therapy and Human Gene Therapy Products

- Human Gene Therapy: It seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use

- Human Gene Therapy Product: All products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering human genetic sequence

# Examples of GT Products

- Genetically modified microorganisms
  - Replication-deficient viral vectors (e.g., adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., adenovirus)
  - Bacterial vectors (e.g., Listeria, Salmonella)
- Ex vivo genetically modified human cells
- Engineered site-specific nucleases used for human genome editing

# Unique Characteristics of GT Products

- Integration activity
  - Retroviral vectors known for integration event in the genome
  - Such integration not directed to specific sites
  - Potential disruption of critical host genes at the site of integration
  - Potential activation of proto-oncogenes near the integration site – malignancy
  - Leukemias: Reported in more than 1 trial where subjects received genetically-modified cells manufactured using gammaretroviral vectors

# Unique Characteristics of GT Products

- Genome editing activity
  - Genome editing based GT impart activity through site-specific changes in genome
  - Potential off-target effect on the genome
  - Potential undesirable changes in the genome,
    - e.g., malignancies and impairment of gene functions

# Unique Characteristics of GT Products

- Potential effects following transgene expression
  - Vascular endothelial growth factor: Potential for unregulated cell growth
  - Protein associated with cell division such as p53: Potential for malignancy

# Unique Characteristics of GT Products

- Latency
  - Potential for latency, e.g., herpesvirus
  - Potential for reactivation from latency
  - Risk of delayed adverse events related to a symptomatic infection

# Unique Characteristics of GT Products

- Establishment of persistent infection
  - GT product with replication competent viruses and bacteria, e.g., listeria-based bacterial vectors
  - Potential to establish persistent infections – particular concern in immunocompromised patients
  - Risk of delayed but serious infection

# Safety Monitoring

- Routine general safety monitoring to look for expected and unexpected safety issues
  - Recording of symptoms
  - Standard clinical measurements
    - Physical examinations
    - Routine labs
    - Other examinations appropriate for the condition being investigated
  - Specific monitoring program depending on
    - Nature and mechanism of action of the product
    - The study population
    - The results of animal studies
    - Any related human experience

# Safety Monitoring

- Special monitoring considerations
  - Immunogenicity, e.g., viral capsids
    - Monitoring for both cellular and humoral immune responses
    - Cryopreserving baseline and post-treatment blood / plasma, as appropriate for later evaluation if adequate assays not yet available
  - Duration of persistence of the product and its activity
    - Product persistence: Looking for evidence of the presence of vector in biological fluids or tissues
    - Activity: May be assessed by looking for physiologic effects, e.g., gene expression
    - Planning for possible postmortem studies if some deaths are expected to occur during the course of the trial

# Safety Monitoring

- Special monitoring considerations
  - Viral shedding
    - Address early in product development
    - FDA Draft Guidance: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (2014)
  - Integrating vectors: GT products integrating into the genome
    - Monitoring for clonal outgrowths when technically feasible
    - Performing assays to assess the pattern of vector integration sites in relevant surrogate cells
      - For example, determine whether cells carrying integrated vector sequences are polyclonal, or monoclonal,
      - FDA Draft Guidance: Long Term Follow-Up After Administration of Human Gene Therapy Products (2018)

# Safety Monitoring

- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on scientific and clinical knowledge, results of animal studies, and experience with related products
- Long-term follow-up (LTFU) may be required for certain GT products
  - Extended assessments that continue some of the scheduled observations of a clinical trial past the active follow-up period
  - An integral portion of the study of some investigational GT products
  - LTFU/surveillance plan(s) should also be put in place post-licensure for monitoring delayed AEs

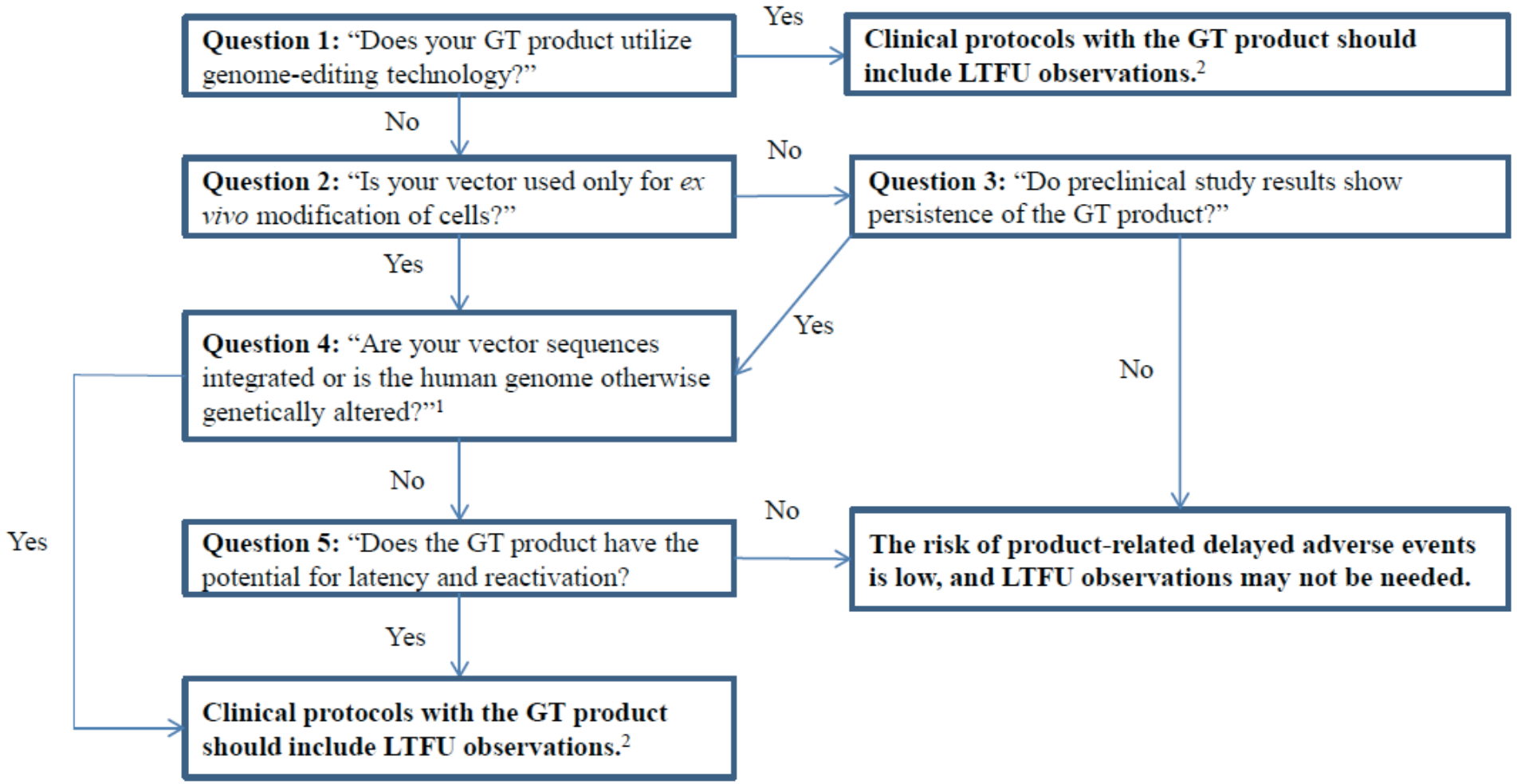
# Duration of Monitoring

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

### Draft Guidance for Industry

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

# Framework to Assess the Risk of GT-Related Delayed AEs and the Need of LTFU




*Long Term Follow-Up After Administration of Human Gene Therapy Products (draft) (2018)*

# LTFU Protocol: Clinical Considerations

- Perform all LTFU observations according to FDA regulations governing clinical trials
  - ICH E6 Good Clinical Practice: Consolidated Guidance (1996)
- Objective: Identify and mitigate the long term risks to the patients receiving a GT product
- Consider designing the protocol to assess the long term clinical efficacy and durability of the product
- Study population
  - All study subjects who received the GT product
  - Consider the characteristics of the patient population when designing the protocol
  - Informed consent document

# LTFU Protocol: Duration

- Sufficient to observe the subjects for risks that may be due to
  - The characteristics of the product
  - The nature of the exposure
  - The anticipated time of occurrence of delayed adverse events
- Elements to consider when determining the duration
  - The observed duration of *in vivo* product persistence
  - The observed duration of transgene expression
  - Product characteristics in *vivo*
  - Route of administration
  - The expected survival rates and the known background rates of the events of interest in the study population
  - Other factors: e.g., the durability of clinical effect

# LTFU Protocol: Duration

- Current General Recommendation of LTFU Duration

| GT Product Type | LTFU Duration (years) |
|---|---|
| Integrating vectors (e.g., gammaretroviral and lentiviral vectors, and transposon elements) | 15 |
| Genome editing products | Up to 15 |
| Adeno associated virus (AAV) vectors | Up to 5 |

  - Broadly based on GT product type
  - Consider previously discussed elements

# LTFU Protocol: Clinical Considerations

- Establish a dedicated clinical LTFU protocol detailing
  - Patient visit schedule
  - Sampling plan (e.g., blood samples for tests)
  - Monitoring tests
  - Clinical events of interest that will be monitored
- The investigator: Prepare and maintain adequate and accurate case histories that record all observations and other pertinent data on each subject
  - A baseline history prior to GT product exposure should be included

# LTFU Protocol: Clinical Considerations

- For the first 5 years
  - Maintain a detailed record of exposures to mutagenic agents and other medicinal products
  - Establish a method to record the emergence of new clinical conditions, such as
    - New malignancy(ies)
- For the subsequent 10 years (when applicable)
  - Contact patients at least annually
  - Cont. appropriate follow-up methods as indicated by previous test results

# LTFU Protocol: Clinical Considerations

- Detection of adverse events (AEs) and coordination of data collection
  - Identify suitable HCPs to facilitate detection of delayed AEs
  - Encourage patients to be proactive in reporting AEs
  - Propose a clinical program for follow-up procedures to determine the relationship between AEs and the GT product
- IND safety report (when applicable)
  - Follow applicable reporting requirements outlined in 21 CFR 312.332
  - Annual reports / Development Safety Update Report: Submit information obtained during the previous years' investigation under the Section of LTFU

# FDA-Approved Gene Therapy Products

- Tisagenlecleucel (Kymriah)
  - 1st cell-based gene therapy approved in the US
  - Autologous human T cells genetically modified with a lentiviral vector encoding a chimeric antigen receptor (CAR) targeting human CD19
  - B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse (≤ 25 years) and adults with relapsed or refractory (r/r) large B-cell lymphoma
- Axicabtagene ciloleucel (Yescarta):
  - Autologous human T cells transduced with a gammaretroviral vector encoding a CAR directed against human CD19.
  - Adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy
- Voretigene neparvovec-rzyl (Luxturna)
  - 1st FDA-approved direct gene therapy targeting a genetic disease due to single gene mutation
  - AAV serotype 2 vector expressing the *RPE65* gene, encoding human retinal pigment epithelium 65 kDa protein
  - Confirmed biallelic RPE65 mutation-associated retinal dystrophy

# Postmarketing Safety Monitoring

- Tisagenlecleucel (Kymriah)
  - Spontaneous postmarketing adverse events reporting not sufficient to identify a serious risk of secondary malignancies associated with the product
  - Post-Marketing Requirement (PMR)
    - Post-marketing, prospective, multi-center, observational study to assess the long-term safety of the product and the risk of all secondary malignancies occurring after treatment with tisagenlecleucel
    - The study will include at least 1000 pediatric and young adult patients with relapsed / refractory (r/r) B cell acute lymphoblastic leukemia and 1500 r/r large B-cell lymphoma patients
    - The enrolled patients will be followed for 15 years after the product administration

# Postmarketing Safety Monitoring

- Axicabtagene ciloleucel (Yescarta)
  - Spontaneous postmarketing adverse events reporting not sufficient to identify a serious risk of secondary malignancies associated with the product
  - Post-Marketing Requirement (PMR)
    - Post-marketing, prospective, multi-center, observational study to assess the long-term safety of the product and the risk of all secondary malignancies occurring after treatment with axicabtagene ciloleucel
    - The study will include at least 1500 adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy
    - The enrolled patients will be followed for 15 years after the product administration

# Postmarketing Safety Monitoring

- Voretigene neparvovec-rzyl (Luxturna)
  - Ongoing LTFU of clinical trial patients
  - Routine medical practice
  - Adequate Prescribing Information
  - Voluntary post-marketing plan by the applicant
    - Distribution and use of LUXTURNA through Centers of Excellence, and mitigating risks by training pharmacists and surgical staff
    - A prospective multi-center 5-year observational registry to collect safety information for patients treated with LUXTURNA
  - No PMR

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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