Safety Considerations for Gene Editing and Other Gene Therapy Products: An FDA Perspective

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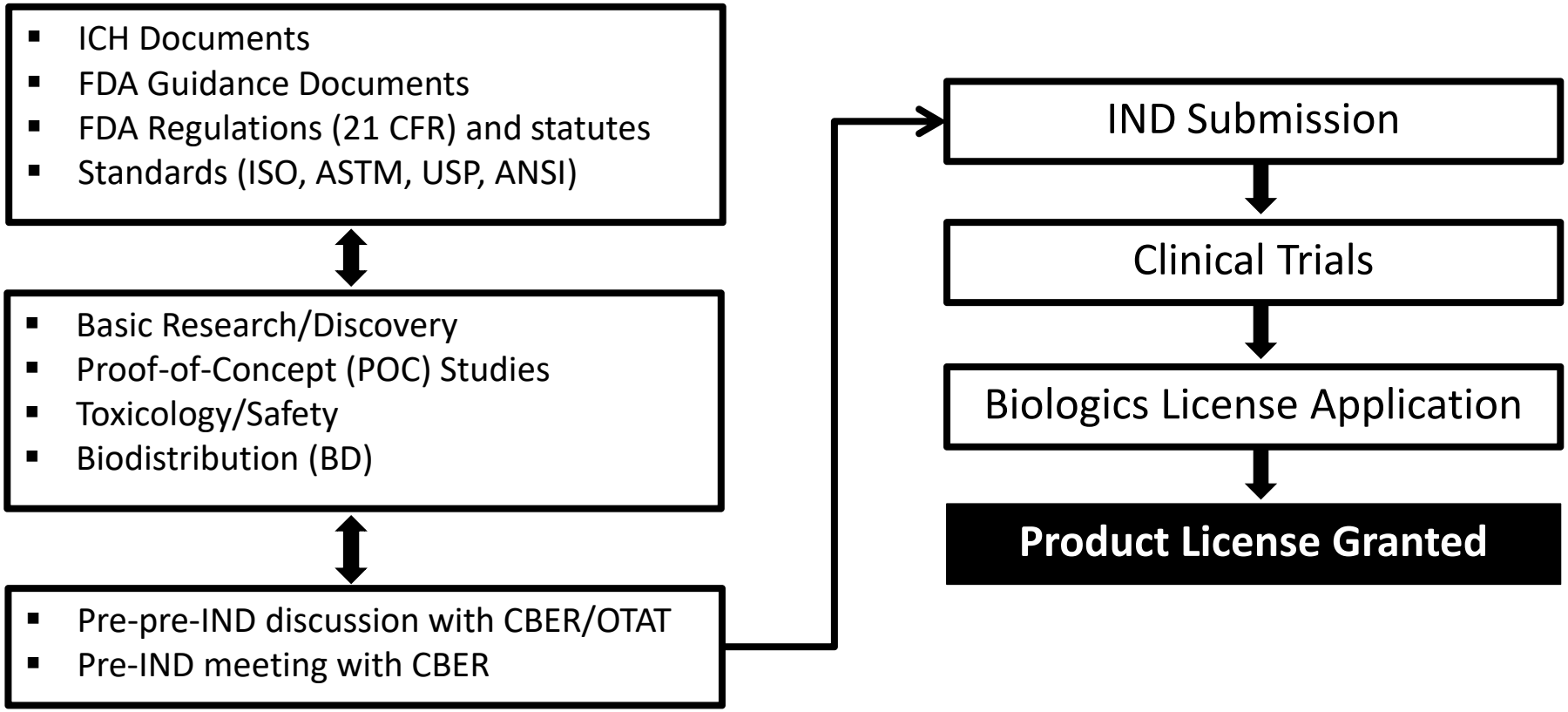
Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **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)
- **Products for xenotransplantation**

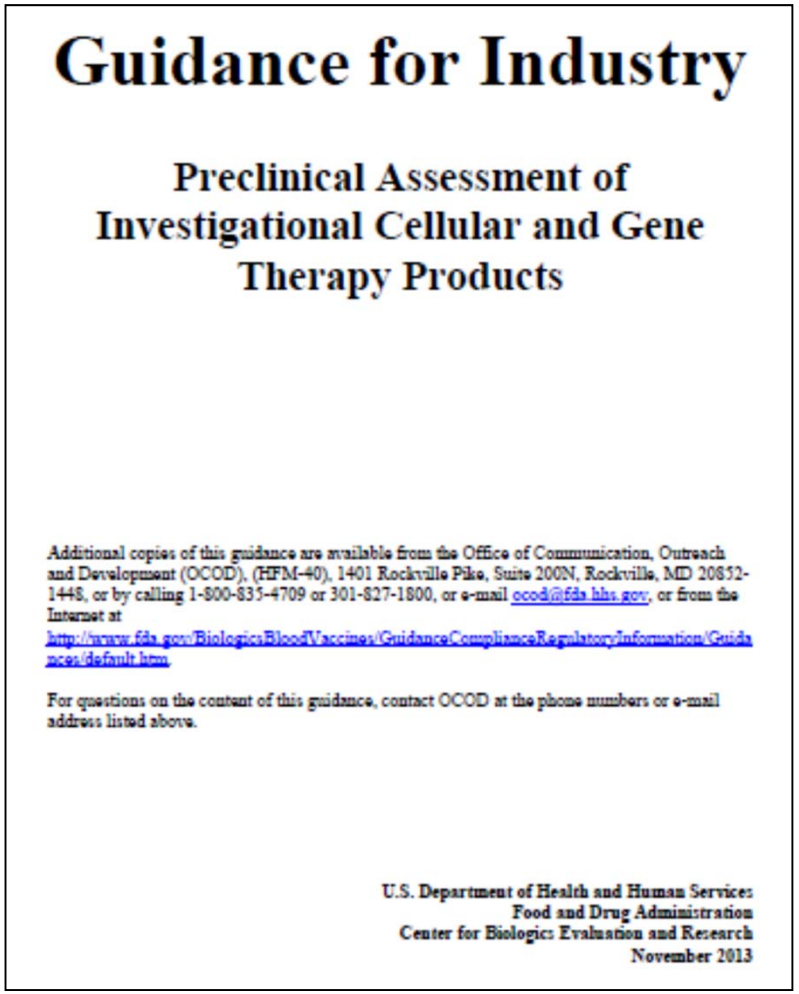
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Snake venom antisera
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

Translational Development for Gene Therapy (GT) Products



General Considerations for Preclinical Testing Programs

- Preclinical study considerations
  - Objectives
  - General program design
- Recommendations for assessment of cell therapy, gene therapy, and therapeutic vaccines
- Explicitly incorporates the 3R's of animal testing
  - **R**educe, **R**efine, **R**eplace



Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

Preclinical Program Objectives

- Support the rationale for the clinical trial
- Make recommendations regarding clinical trial design
  - Dose (e.g., initial safe starting dose level, dose-escalation scheme, dosing schedule)
  - Eligibility criteria / patient population
  - Clinical route of administration
  - Clinical monitoring (e.g., safety, activity, duration of follow-up)
- Support the assessment of benefit:risk profile for subjects

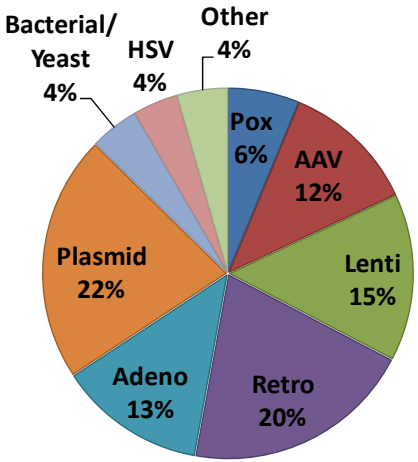
Safety Assessment in Animals for GT Products

- Goal - employ study designs that address safety and the scientific basis for conducting a clinical trial
  - Robust study designs based on product characteristics and risks
- Study Designs:
  - Pharmacology / proof-of-concept (POC) studies in relevant animal model(s) of disease / injury, as feasible
  - Toxicology (T) studies in healthy animals
  - Hybrid pharmacology-toxicology study design (POC + T)
  - Vector biodistribution
  - Additional studies for specific safety considerations

Gene Editing and Gene Therapy

- Gene therapy products mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences

- Common gene therapy products:
  - Plasmids
  - Viral / bacterial vectors
  - *Ex vivo* genetically modified cells
  - Gene edited (GE) products



Examples of Therapeutic Applications for GT Products

- Hematologic disorders
- Neuromuscular disorders
- Ocular diseases
- Skin diseases
- Lysosomal storage disorders
- Viral infections
- Cancer

GT Products in CBER

- First gene therapy Investigational New Drug (IND) submitted in 1989
- Nearly 600 active GT INDs in CBER (~1000 INDs submitted)
- First gene editing IND submitted in 2008
- 13 gene editing INDs in CBER

Unique Aspects of Incorporating GE

- Process by which DNA is inserted, deleted, or replaced in the genome using engineered site-specific nucleases
- Nucleases create site-specific double strand breaks (DSBs) at desired locations in the genome
- Induced DSBs are repaired through non-homologous end-joining (NHEJ) or homology directed repair (HDR)
- This process results in targeted modification (edits)

Current GE Technologies

- Four families of engineered site specific nucleases:
  - Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas systems)
  - Mega nucleases
  - Transcription Activator-Like Effector Nucleases (TALENs)
  - Zinc Finger Nucleases (ZFNs)

- Delivery method
  - Viral vectors, plasmid DNA, mRNA, protein, ribonucleotide protein (RNP) complexes
    - Direct administration *in vivo*
    - Genetic modification of cells *ex vivo*

Regulatory Review for GT Products Incorporating GE

- Science-based approach
- Benefit-risk analysis
  - Potential to:
    - Correct or remove defective genes
    - Eliminate disease phenotype
    - Improve therapeutic effects
  - Risk of:
    - Off-target modifications in the genome
    - Genome instability caused by chromosomal translocations / rearrangements
  - Unknown long term outcomes from on- or off-target genome editing events or due to the delivery system (vector)

Safety Considerations (1)

- Genome modification specificity and characterization
  - Optimization of GE components and targeting elements (e.g. CRISPR / Cas9 / gRNA)
  - Type and degree of genome modifications involved
  - Minimizing off-target editing events
  - Appropriate insertion of the intended transgene in the genome

Safety Considerations (2)

- Potential adverse effects due to genomic DNA cleavage at on- and off-target sites
  - Off-target events related to oncogene activation and disruption of protein-encoding sequences, gene regulatory elements, microRNAs, etc.
  - On- and off-target events impacting on chromosomal structure, translocations, rearrangement
  - Impact on the 'landscape' surrounding on-target events

Safety Considerations (3)

- Adverse effects due to gene mutations introduced by the nuclease and the endogenous DNA repair activity
- Immunogenicity
  - GE components that are foreign to humans, (e.g. expressed nuclease, RNP)
  - Overexpression of the transgene product
  - Potential generation of undesired peptides / proteins from the edited genomes
- Adverse impact of the delivery system (e.g. insertional mutagenesis potential)

Assessing Safety (1)

- The testing strategy should:
  - Consider human relevance when selecting test systems
  - Incorporate *in vitro* and *in vivo* models, as appropriate
  - Address safety for the GE components and the proposed clinical delivery system
  - Consist of appropriate and informative assessments of both on- and off-target editing
    - Products that are species specific
    - *In vitro* studies with human cells
    - *In vivo* studies with animal surrogates
  - In the case of direct *in vivo* GE, both identification and characterization of off-target cells / tissues should be considered

Assessing Safety (2)

- Has there been a thorough evaluation of potential off-target sites using both biased and unbiased methods?
  - What types of off-target editing events are occurring?
  - What is the impact of these events?
- What is the percent cleavage at the on- versus the off-target sites?
- What are the kinetics of nuclease cleavage and the persistence of cleavage activity?
- How are the nucleases and donor sequences delivered?

Impediment to Addressing GE Safety Concerns

- No ‘gold standard’ for predicting and identifying off-target genomic modifications
- No ‘gold standard’ for evaluating large genomic modifications or genomic instability
- Possible limitations with use of various animal models / species for safety evaluation and subsequent identification of potential risks
- Not all off-target genomic modifications will necessarily lead to adverse biological consequences
- Accounting for genomic variation between individuals in humans

Current *In Vitro* Methods for GE Safety Assessment (1)

- "Small" (up to 100 bp) insertions and deletions (indels)
  - *In silico* prediction and deep sequencing of the predicted cleavage events (biased)
  - Biochemical approaches (non-cell based, unbiased)
  - Cellular approaches (cell-based, unbiased)

Current *In Vitro* Methods for GE Safety Assessment (2)

- "Large" changes (translocations, inversions, deletions, etc.) by cleavage that can occur inter- or intra-chromosomally
  - In silico prediction and molecular analysis
  - Cellular approaches (e.g. fluorescence *in situ* hybridization [FISH]; karyotyping, etc.)
  - Whole genome analysis by sequencing

Use of Animals for Assessing GE Safety

- There are significant differences in the genome between humans and animals that can make identifying the appropriate animal model / species challenging
- What is a relevant *in vivo* test system?
  - Can the clinical product be evaluated or should animal surrogates for the GE components be used? Are the animal surrogates representative of the clinical constructs?
  - For *ex vivo* modified cells, what cell source should be used? Is it patient-derived cells, healthy human donor cells, or animal-derived cells? Do they respond to GE in a manner similar to the clinical cell source?
  - For *in vivo* delivery, is the selected animal species suitable for assessing both the GE components and the delivery vector?

When to Engage CBER/OTAT

Pre-Pre-IND Interactions

- Non-binding, informal scientific discussions between CBER/OTAT nonclinical review disciplines (CMC and Pharm/Tox) and the sponsor
- Initial targeted discussion of specific issues
- Not a discussion on definitive safety studies
- Primary contact
  - Mercedes Serabian (mercedes.serabian@fda.hhs.gov)
    Chief, Pharmacology/Toxicology Branch 1 (PTB1)

When to Engage CBER/OTAT

Pre-IND Meetings

- Non-binding, but formal meeting between the FDA and sponsor
- Briefing package should include summary data and sound scientific principles to support use of a specific product in a specific patient population

Guidance for Industry
Formal Meetings Between the FDA and Sponsors or Applicants

Summary

- Comprehensive product characterization is key to understanding product risk
- The preclinical testing program may need to be adapted to the specific GT product and level of perceived risk
- New *in vitro* and *in vivo* test models should be considered as the science and technology advances
- The 3Rs should be applied to preclinical testing programs
- Communication with FDA at early stages of product development may be beneficial

References

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013) http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM329861.pdf

- Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (March 2015) https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015) http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf

- Human Genome Editing: Science, Ethics, and Governance; A Report of The National Academies of Sciences, Engineering and Medicine; The National Academy Press, Washington DC , 2017. https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

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FDA Headquarters

- **OCTGT Learn Webinar Series:**

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

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
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