Regulatory Framework for Gene Therapies Incorporating Human Genome Editing
A CBER Perspective

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Gene Therapy & Genome Editing

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

- Human genome editing is a process by which DNA is inserted, deleted, or replaced in the human genome using engineered site-specific nucleases and is therefore regulated as a gene therapy

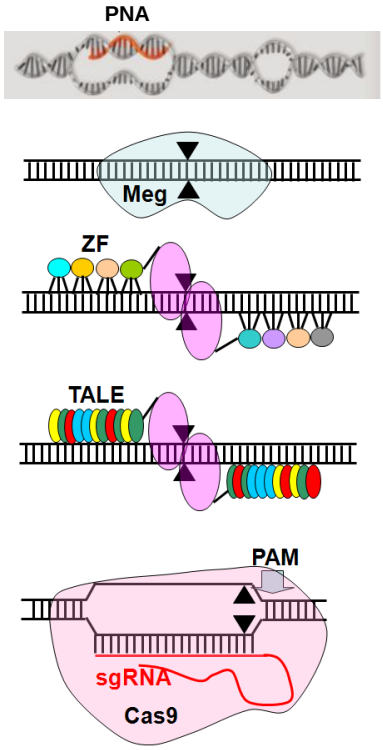
Regulation of Genome Editing Products

- CBER received the first submissions for genome editing products in 2008
  - 14 INDs
  - 8 Pre-INDs
  - 8 Pre-pre-INDs

- Science-based approach

- Benefit-Risk analyses
  - Potential to correct or remove defective genes
  - Risk of off-target genome modification, genome instability
  - Unknown long term effects of on- or off-target genome editing

Considerations for Developing Human Genome Editing Products



- Type & degree of modification needed
- Nuclease design
- Optimization of targeting elements
- Delivery method
  - Viral vectors, plasmid DNA, mRNA, protein (RNP)
    - Direct administration
    - Modification of cells ex vivo

Considerations for Developing Human Genome Editing Products

- Safety and efficacy
  - Optimization of genome editing component expression
  - Target validation studies
  - Preclinical studies
    - What models are available/appropriate?
    - What will you monitor – sequence, expression, function?
  - Clinical trial design, patient monitoring, long-term follow-up

Human Genome Editing Safety Concerns

- Off-target genome editing
  - Sensitivity of off-target screening methods
- Unintended biological consequences of on-target editing
  - Mutagenesis as a result of imprecise DNA repair following on-target editing
- Additional adverse effects due to genomic DNA cleavage at on- and off-target sites
  - Chromosomal translocations, inversions, etc.
- Immunogenicity
- Adverse impact of the delivery system
- In the case of *in vivo* genome editing, off-target cell/tissue editing

Challenges to Addressing Human Genome Editing Safety Concerns

- Multiple methods for predicting and identifying intra-chromosomal off-target and inter-chromosomal genomic modifications
- Accounting for genomic variation between individual human subjects
- Not all off-target genomic modifications will necessarily lead to adverse biological consequences
- Possible limitations of animal models for evaluation of safety and activity

Methods for Identifying Intra-Chromosomal Off-Target Modifications

- *In silico* methods
  - Computational methods identifying areas of homology to targeting sequence (e.g. BowTie2, BFAST, Cas-Off-Finder)
  - Platforms are based on different algorithms and often give different results
- Cellular methods
  - PCR amplification of tagged sequences allows identification of edited sites (e.g. Guide Seq, BLESS/BLISS, IDLV Capture)
  - Off-target editing events may be cell type specific
- Biochemical Methods
  - Sequencing of edited, fragmented DNA (e.g. SELEX, Circle Seq, DiGenome Seq)
  - May give rise to many false positive hits

Methods for Identifying Inter-Chromosomal Modifications

- In silico modeling
- Cellular approaches
  - Unidirectional sequencing (e.g. HTGTS, AMP-seq, UDiTaS)
  - Imaging based genome analysis (e.g. BioNano, FISH, karyotyping)
- Whole genome sequencing

Assessing the Safety of Human Genome Editing Products

- How are genome editing components produced and tested?
- How is on-target editing activity being evaluated?
- What are the kinetics of editing activity?
- Has there been thorough evaluation of potential off-target sites?
  - Types & frequency
  - Downstream consequences
  - Ratio of cleavage at on- versus off-target sites

Assessing the Safety of Human Genome Editing Products

- What models have been used to assess safety and activity?
  - Have *in vitro* and *in vivo* studies been performed?
  - Are genome editing components active in the models?
  - Are models informative for effects of on- and off-target editing?
  - Has safety of delivery vector been assessed?
  - In the case of *in vivo* genome editing, have off-target cells/tissues been characterized?
  - Has data been generated to inform the design of long term follow-up of potential study subjects?

Clinical Monitoring Considerations

- Clinical safety monitoring should be guided by:
  - Findings from preclinical studies
  - Features of the underlying disease
  - Anticipated disease-product interactions
- Safety reporting requirements (21 CFR 312)
  - Systematic observations of patients should be performed
    - Clinical, Radiological (if appropriate), Laboratory
  - Defined timed intervals for observations
- Long term follow-up studies

Early Communication with CBER/OTAT

- Pre-pre-IND interactions
  - Non-binding, informal scientific discussions between CBER/OTAT nonclinical review disciplines (P/T & CMC) and the sponsor
  - Initial targeted discussion of specific issues
  - Primary contact: Mercedes Serabian mercedes.serabian@fda.hhs.gov

- Pre-IND meetings
  - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  - Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population
  - Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf

Summary

- Gene therapies based on genome editing technologies are regulated using a science based approach, with consideration of the benefits and risks of each product
  - Comprehensive product characterization is key to understanding product risk
    - On-target editing efficiency
    - Off-target editing effects
    - Delivery method
    - Immunogenicity
  - Preclinical evaluation should be adapted to the specific product and level of perceived risk
    - Appropriate and informative models
    - Multiple orthogonal methods

CBER Contact Information

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- **Regulatory Questions:**
  Contact the Regulatory Management Staff in OTAT at CBEROCTGTRMS@fda.hhs.gov
  or Lori.Tull@fda.hhs.gov

- **References for the regulatory process for OTAT**
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- **OTAT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm