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**
- Somatic cell genome editing

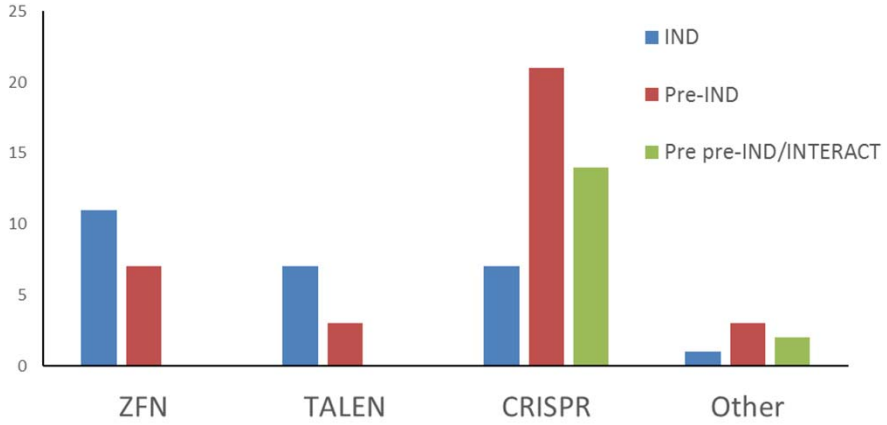
Consensus Study

- National Academy of Medicine International Consensus Study on gene editing technologies
  - FDA/CBER co-sponsored report
  - Initiated December 2015, Released February 2017

- Framework based on fundamental, underlying principles that may be adapted and adopted by any nation that is considering the development of guidelines

Regulation of Genome Editing Products

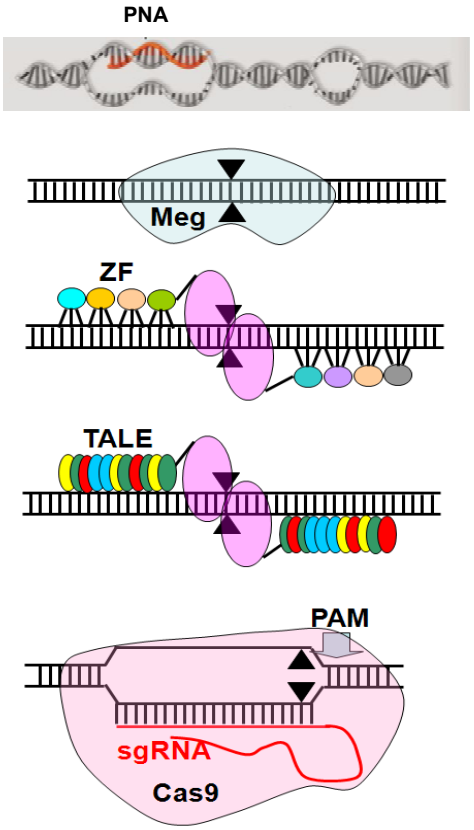
- CBER received the first submissions for genome editing products in 2008
- Currently,
  - 26 INDs
  - 34 Pre-INDs
  - 16 Pre-pre-INDs/INTERACT



- Science-based approach
- Benefit-Risk analyses
  - Potential to correct genetic causes or disease
  - Risk of unintended genome modification
  - Unknown long term effects of on- or off-target genome editing

Considerations for Developing Human Genome Editing Products

- Type & extent of modification
- Editing platform
- Optimization of targeting elements
- Delivery method
  - Viral vectors, nanoparticles, plasmid DNA, mRNA, protein (RNP)
  - Direct administration
  - Modification of cells ex vivo



Considerations for Developing Human Genome Editing Products

- Safety and efficacy
  - Optimize genome editing component expression
  - Verify Target
    - What models are available/appropriate?
    - What will you monitor – sequence, expression, function?
  - Design clinical trial
    - Patient monitoring, long-term follow-up

Human Genome Editing Product/CMC Considerations

- Genome editing components (e.g., nuclease, targeting elements, donor template) are considered critical for the manufacture of gene therapies utilizing genome editing
  - Provide details on how the components were designed, manufactured and tested in your IND
    - cGMPs should be followed
      - CGMP for Phase 1 Investigational Drugs Guidance
    - Components should be tested appropriately based on their manufacturing process (identity, purity, activity)
    - Specifications should be determined based on manufacturing experience
  - If components are modified during the product life cycle, comparability studies may be necessary

Human Genome Editing Product/CMC Considerations

- Delivered directly or as *ex vivo* modified cells
  - Test for sterility, identity, purity, potency, and residuals based on the manufacturing process
  - Set specifications based on manufacturing experience and what has been shown to be safe and effective in the clinical studies
    - The need to test each batch for off-target modifications, translocations, etc. will be considered on a case by case basis
    - Allogenic cell product Master Cell Banks need thorough characterization
- Characterize your product as much as possible early in product development

Human Genome Editing Safety Concerns

- Off-target genome editing
  - Type and 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

- Selection of appropriate 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

Method	Description	Examples	Concern
In silico	Identifies areas of homology to targeting sequence	BowTie2 BFAST Cas-Off-Finder	Platforms are based on different algorithms and often give different results
Cellular	Sequencing of tagged, edited sequences	Guide-seq BLESS/BLISS IDLV Capture	Off-target editing events may be cell type specific
Biochemical	Sequencing of edited, fragmented DNA	SELEX Circle-seq DiGenome-seq SITE-seq	May give rise to many false positive hits
Whole Genome sequencing	Next generation sequencing	Illumia	helpful in clonal populations but has difficulty identifying sites that are cleaved at low frequencies in bulk cell populations

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)

Assessing the Safety of Human Genome Editing Products

- 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 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

- INTERACT meetings
  - INTERACT - INitial Targeted Engagement for Regulatory Advice on CBER producTs https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
  - Non-binding, informal scientific discussions between CBER/OTAT nonclinical review disciplines (P/T & CMC) and the sponsor
  - Initial targeted discussion of specific issues after obtaining preliminary data from pilot studies but prior to conducting extensive animal studies
  - Requests should be sent to INTERACT@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
  - Genome editing components are considered to be critical for these products
  - Comprehensive product characterization is key to product development and understanding product risk
    - On-target editing efficiency
    - Off-target editing effects
    - Delivery method
  - Preclinical evaluation should be adapted to the specific product and level of perceived risk
    - Appropriate and informative models
    - Multiple orthogonal methods

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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