Regulatory Perspectives on Gene Therapies Incorporating Human Somatic Genome Editing

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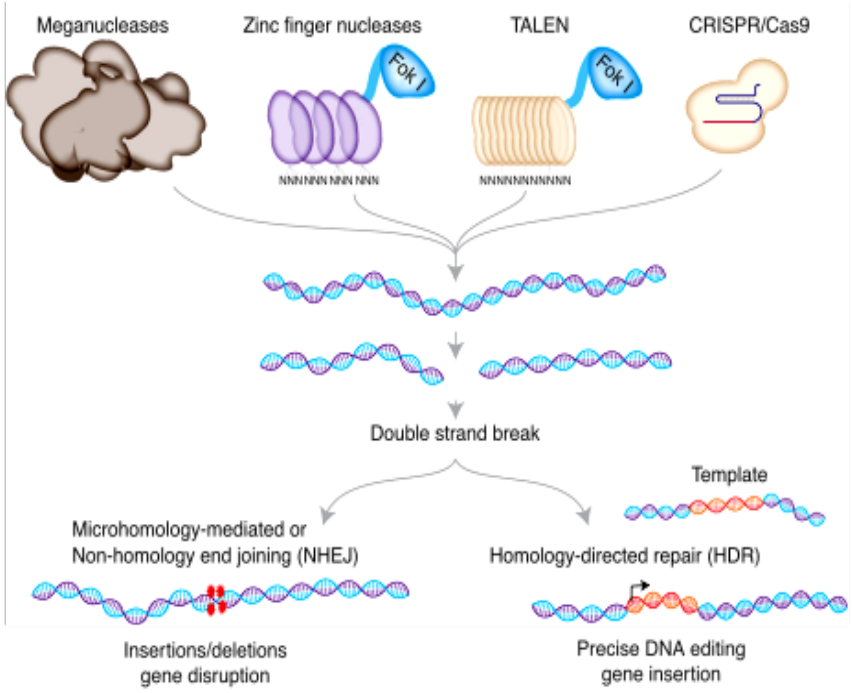
Gene Therapy & Genome Editing

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 sequences are added, deleted, altered or replaced at specified location(s) in the genome of human somatic cells, ex vivo or in vivo, using nuclease-dependent or nuclease-independent GE technologies.

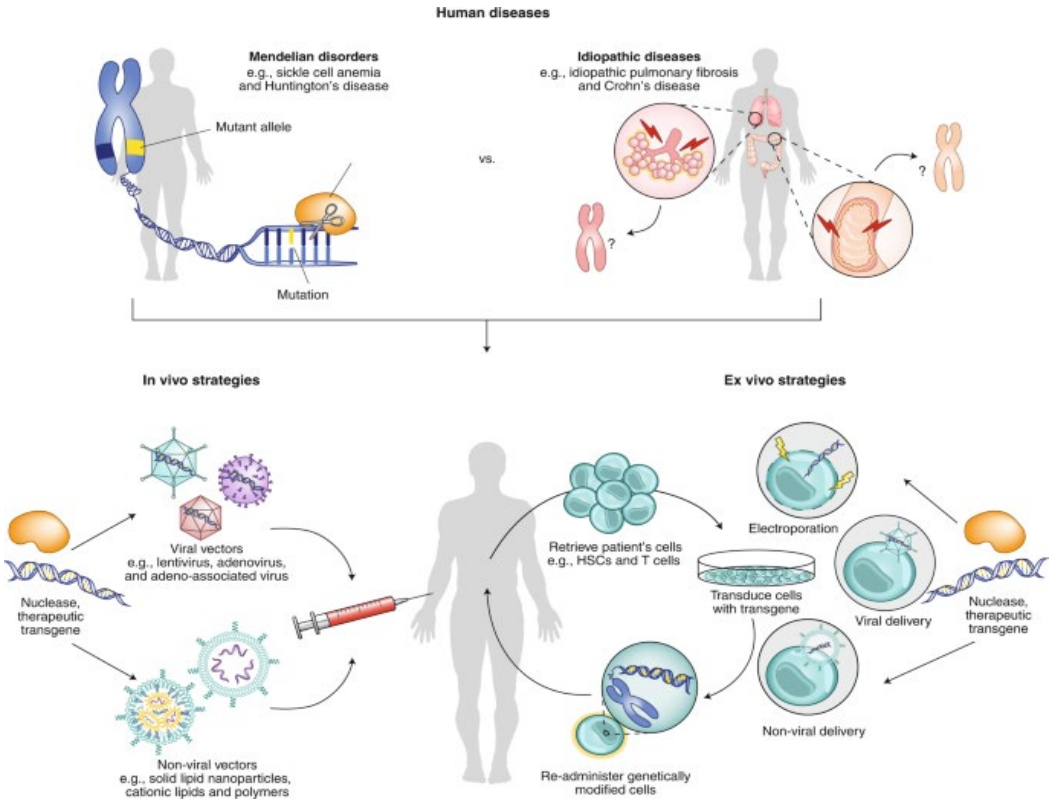


Mazhar Adli, Nature Communications, 2018

Genome Editing (GE) Products

GE products include:

- Directly administered, in vivo genome editing products
- Ex vivo genome edited cell products



van Haasteren, J., et al., Nature Biotechnolgy, 2020

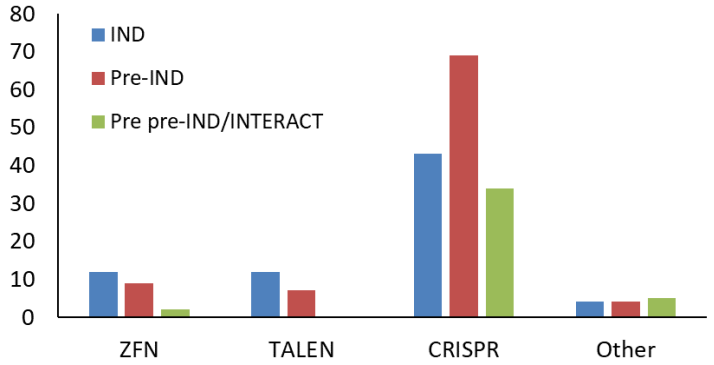
Regulation of GE Products

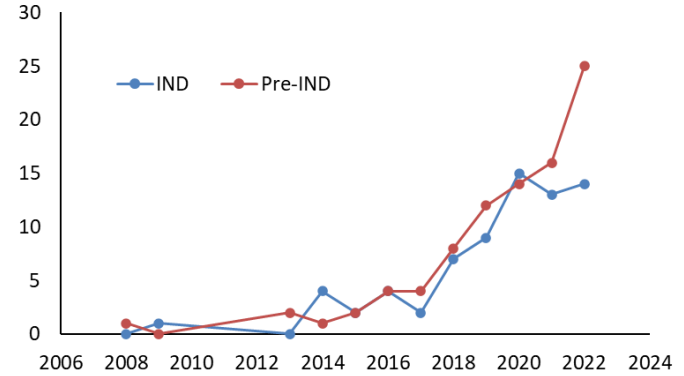
CBER received the first submissions for genome editing products in 2008

- 71 INDs
- 89 Pre-INDs
- 41 Pre-pre-INDs/INTERACTs

INDs

- 10% in vivo genome editing products
- 90% ex vivo genome edited cell products





Regulation of GE Products

Science-based approach

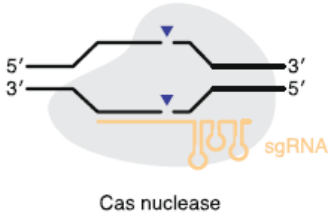
- Characterization of the product mechanism of action and safety attributes, using current knowledge and tools in the field

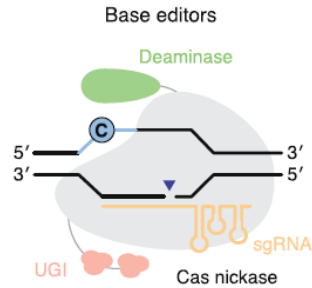
Benefit-risk analyses

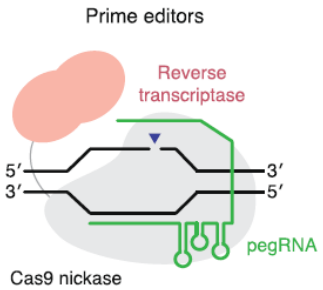
- Potential to correct genetic causes of disease
- Risk of unintended genome modification
- Unknown long-term effects of on- or off-target genome editing

Considerations for Developing GE Products

- Type & degree of modification needed
- Mechanism of DNA sequence change
- Product design and delivery method
  - In vivo versus ex vivo
  - Viral vectors, nanoparticles, plasmid DNA, mRNA, protein (RNP)
- Optimization of genome editing component expression
- On- and off-target verification studies
  - What assays and models are available/appropriate?
  - What will you monitor – sequence, expression, function?
- Clinical trial design, patient monitoring, long-term follow-up







Anzelone, Koblan, and Liu; Nature Biotechnolgy, 2020

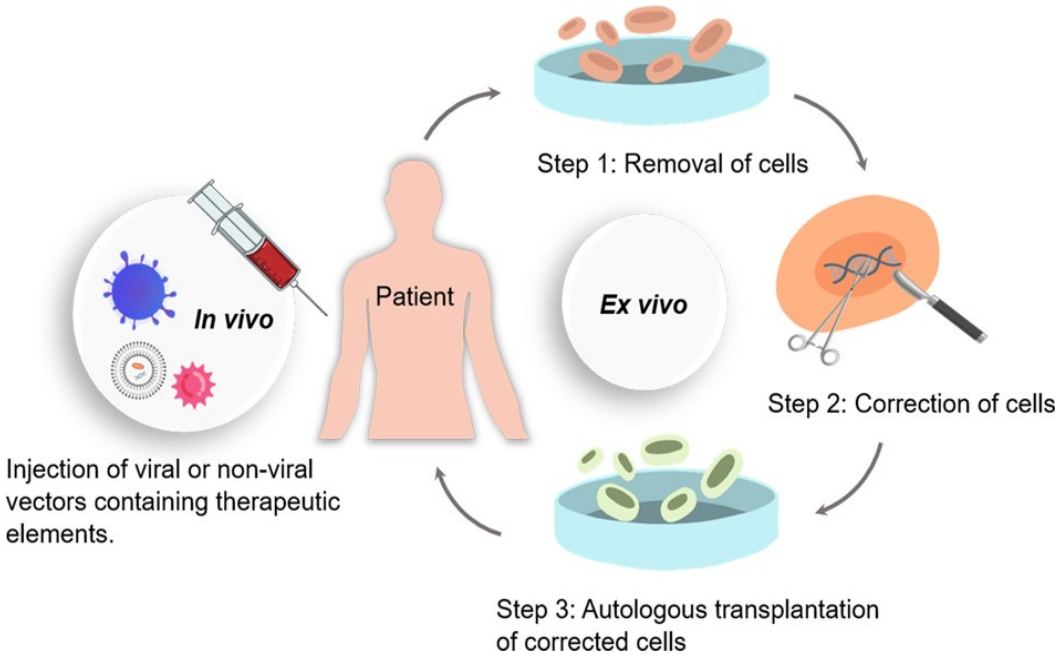
Ensuring GE Product Quality

- Suitable qualification of starting materials & components
- A well-defined process and process controls
- Appropriate product testing & characterization

GE Components

Genome editing components (e.g., nuclease, targeting elements, donor template) are considered:

- Drug substances when they are formulated into nanoparticles to produce the drug product that is directly administered to perform genome editing in vivo
- Critical components when they are used to perform genome editing in cells ex vivo and the autologous/allogeneic cells are the drug product



Li, H., et al.; Signal Transduction and Targeted Therapy, 2020

GE Component CMC Considerations

- Detailed descriptions of how the components are designed, manufactured, and tested should be included in an IND

- GE components that are used in routine product manufacture should be manufactured according to CGMPs
  - Phase 1: FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs
  - Full CGMPs are expected for BLA supporting trials and licensure

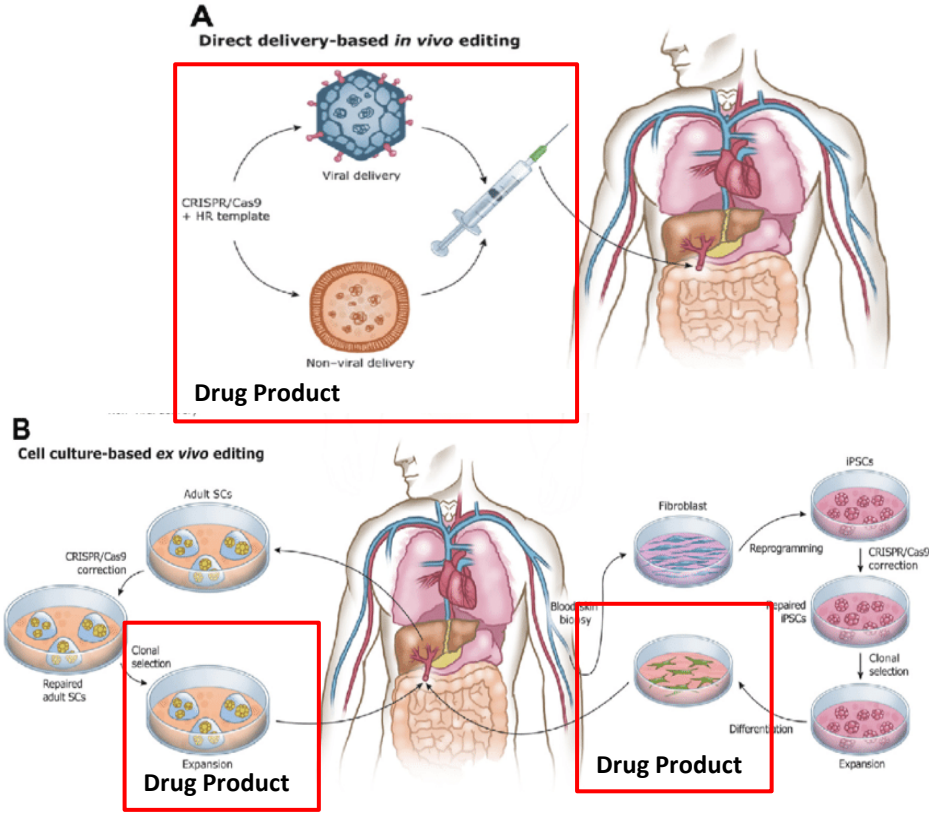
- GE components should be tested for safety, identity, purity, activity, and residuals based on their manufacturing process
  - Set acceptance criteria based on manufacturing experience and what has been shown to be safe and effective in preclinical/clinical studies

- Stability of GE components should be assessed

GE Drug Product Testing

- Test final product for safety, identity, purity, potency, and residuals based on the manufacturing process
  - Set acceptance criteria based on manufacturing experience and what has been shown to be safe and effective in preclinical/clinical studies

- For ex vivo modified cell products:
  - Characterize the presence of residual genome editing components
  - The need to test each batch for off-target modifications, translocations, etc. will be considered on a case-by-case basis
  - Allogenic cell products may need additional characterization to ensure safety
  - If drug product manufacture involves expansion/differentiation of a cell bank, it may be appropriate to perform certain testing on the cell bank



Nataša Savić & Gerald Schwank; Translational Research, 2015

Human Genome Editing Safety Concerns

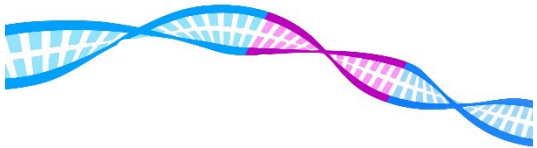
- Off-target genome editing
  - Type and sensitivity of off-target screening methods
  - In vivo: off-target cells/tissues
- Unintended biological consequences of on-target editing
  - Mutagenesis as a result of imprecise DNA repair following on-target editing
- Additional adverse effects due to genomic DNA cleavage at on- and off-target sites
  - Chromosomal translocations, inversions, etc.
- Immunogenicity
  - To GE components, editing outcome, or the delivery system

Challenges to Addressing Human Genome Editing Safety Concerns

- Selection of appropriate methods for predicting and identifying unintended genomic modifications
- Accounting for genomic variation between individual human subjects
- Determining the biological impact of identified unintended genomic modifications
- Possible limitations of animal models for evaluation of safety (and activity)
- Patient monitoring for genome editing-related adverse events

Assessing the Safety of Human GE Products

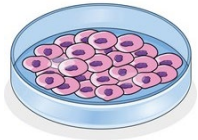
- How is on-target editing activity being evaluated?
  - Sequence change, change in protein production, biological change
  - Are methods capable of identifying large and small indels?
- What are the kinetics of editing activity?

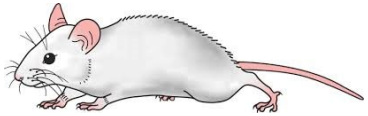


- Has there been thorough evaluation of potential off-target editing sites?
  - Types & frequency
  - Downstream biological consequences

Assessing the Safety of Human GE Products

- What models were 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 of effects of on- and off-target editing?
  - Has safety of delivery method been assessed?
  - In the case of *in vivo* genome editing, have off-target cells/tissues been identified and characterized?
  - Has data been generated to inform monitoring and 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 patient-product interactions
- Safety reporting requirements (21 CFR 312)
  - Systematic monitoring of patients at defined time intervals
- Long term follow-up studies: 15-year follow-up

Early Communication with CBER/OTP

INTERACT meetings

- INTERACT - INitial Targeted Engagement for Regulatory Advice on CBER producTs
- Non-binding, formal scientific discussions usually between CBER/OTP 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
- Additional information can be found at: OTAT INTERACT Meeting | FDA

Pre-IND meetings

- Non-binding, formal meeting between FDA and sponsor (with formal minutes generated)
- Meeting 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 of PDUFA Products (December 2017) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf

Summary

Gene therapies utilizing genome editing are regulated using a science-based approach, while considering the benefits and risks of each product

- Genome editing components are most often considered drug substances or critical components of these products
  - Detailed descriptions of how the components were designed, manufactured, and tested need to be provided
- Comprehensive product characterization is key to product development and understanding product risk
  - On-target editing efficiency
  - Off-target editing outcomes
  - Delivery method
- 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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- **References for the CBER/OTP regulatory process and interactions with CBER/OTP**
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
  https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-tissues-and-advanced-therapies

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