Updates on the FDA's Efforts to Accelerate Advances in Cell and Gene Therapy

Peter Marks, MD, PhD

ARM Cell & Gene State of the Industry Briefing

January 13, 2025

Agenda

- Progress in product approvals
- Advancing the regenerative medicine framework
- Expediting gene therapy development
- Looking forward toward in vivo genome editing

Regenerative Medicine Therapy 2024

- Amtagvi
  - Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor
- Symvess
  - Acellular tissue engineered vessel indicated for use in adults as a vascular conduit for extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible
- Ryoncil
  - For the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients 2 months of age and older

U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Lyfgenia (2023)
- Casgevy (2023, 2024)
- Lenmeldy (2024)
- Beqvez (2024)
- Tecelra (2024)
- Aucatzyl (2024)
- Kebilidi (2024)

Stem cell T cell Directly administered

Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/Ps)

HCT/Ps – Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient (§ 1271.3(d))

HCT/P	Not an HCT/P
Musculoskeletal tissue	Vascularized human organs for transplant
Cardiovascular tissue	Whole blood or blood components
Skin	Human milk
Dura mater	Human collagen
Ocular tissue	Nonhuman cells, tissues, or organs
Reproductive cells & tissues	In vitro diagnostic products as defined in 809.3(a)
Placenta/amnion	Blood vessels recovered with an organ (42 CFR 121.2) that are intended for use in organ transplantation
Cellular-derived therapeutic products (e.g., pancreatic islets, mesenchymal stem/stromal cells, fibroblasts)	Minimally manipulated bone marrow for homologous use and not combined with another article (except as described in 1271.3(d)(4))
HPCs derived from peripheral or umbilical cord blood	Vascular composite allografts

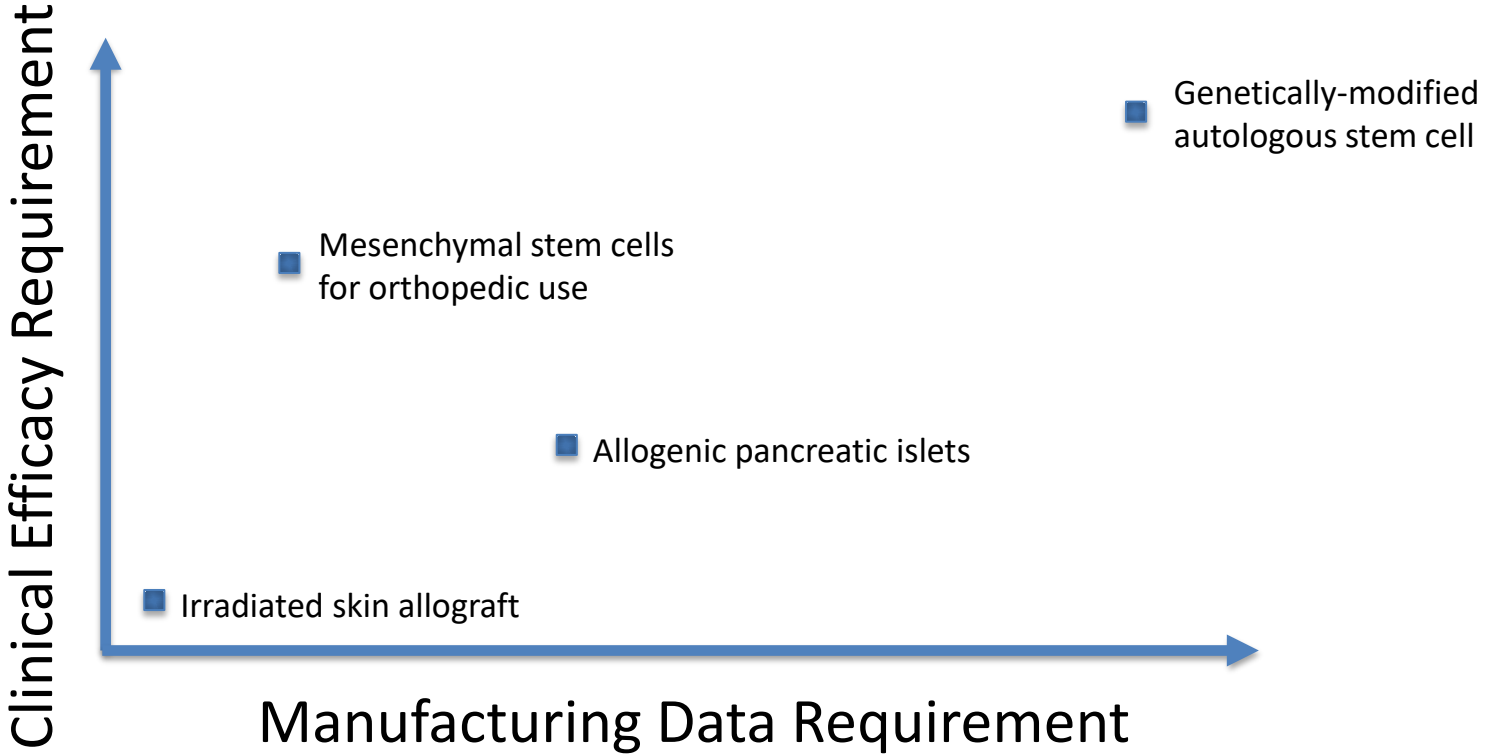
Two Regulatory Tiers for HCT/Ps

1. Drugs, devices, biological products (351 HCT/Ps)
   - Regulated under authority of section 361 and section 351 of Public Health Service Act and/or the Federal Food, Drug, & Cosmetic Act
2. 361 HCT/P (meet criteria to be kicked down)
   - Regulated solely under authority of section 361
   - Subject to "Tissue Regulations" (21 CFR Part 1271)
   - **Premarket review and approval not required**

Suite of Regenerative Medicine Final Guidance Documents

1. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception
2. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (updated July 2020)
3. Evaluation of Devices Used with Regenerative Medicine Advanced Therapies
4. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

A Broad Array of Products



Current Challenges

- Given the broad spectrum of cell therapy products, it is not surprising that some do not fit neatly into the current regulatory framework
- The current regulatory framework allowing self-designation as a product not requiring premarket review is open to misuse

Exploring Solutions

- Potential for risk-adapted framework based on carefully considered variable manufacturing and clinical data requirements
- FDA Scientific Workshop on February 25, 2025
  - Cell Therapies and Tissue-based Products: A Public Workshop on Generating Scientific Evidence to Facilitate Development

Advancing Rare Disease Products

- Rare Disease Hub established and operating
- Work to more clearly define the use of accelerated approval for cell and gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Communication pilot for rare diseases
- Application of platform technology provision

Rare Disease Hub

- Collaboration between CBER and CDER enhancing collaboration and consistency across FDA to address common scientific, clinical and policy issues related to rare disease product development, including relevant cross disciplinary approaches related to product review
- Staff has been assigned from CBER and CDER and the Hub Director of Strategic Programs has been brought onboard
- A strategic plan for the coming year is in the has been developed and will be released soon. The plan focuses on 5C's: communication, community, coordination, creativity, and cooperation

Leveraging Accelerated Approval

- The science inherent in the development of many gene therapies potentially facilitates the use of biomarkers as endpoints that are *reasonably likely* to predict clinical outcomes
  - Enzyme activity levels, structural protein levels can be measured and correlated with clinical endpoints in model systems or even in humans

Connecting Biomarkers with Gene Therapy Clinical Outcomes

Animal Models

- Disease model reflects aspects of human pathology
- Administration of therapy associated with achievement of a specific protein level ameliorates disease

Human Observations

- Disease state is associated with protein levels above or below a certain range
- Certain protein levels are associated with disease absence or minimal disease

Demonstrate that equivalent protein levels can be achieved in humans affected by the disease

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Pilot to facilitate coordinated and consolidated regulatory review
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot

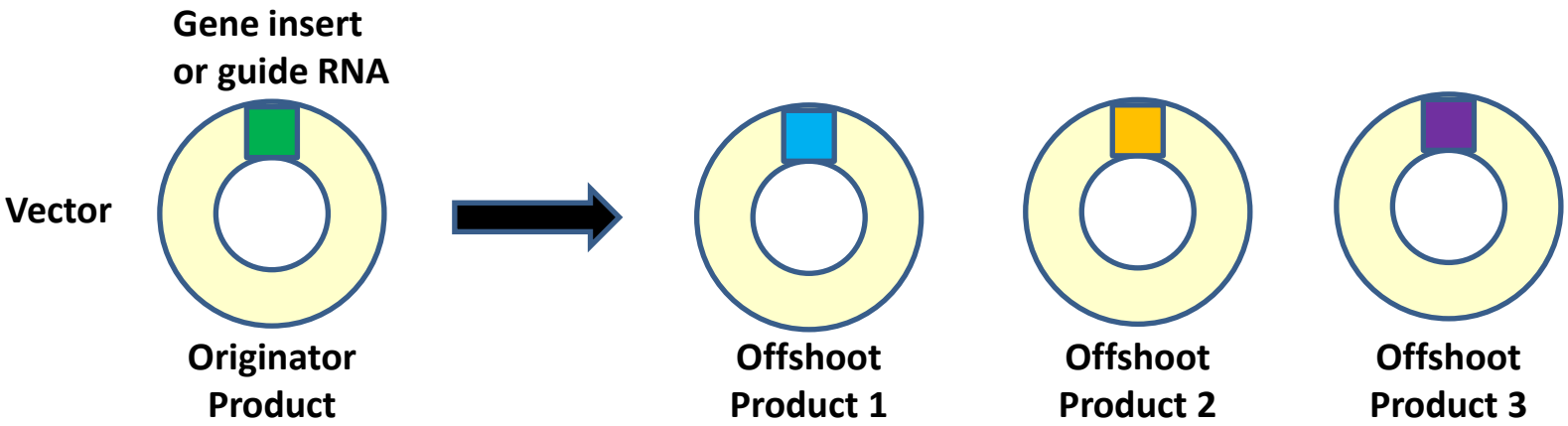
- Further accelerate pace of development for products intended to address unmet medical needs in rare conditions likely to lead to significant disability or death
- Four CBER eligible products selected initially to receive enhanced communications when selected for the pilot
  - An initial meeting to review features of the pilot program
  - Additional ad hoc email or live interactions on an as needed bases

https://www.federalregister.gov/documents/2023/10/02/2023-21235/support-for-clinical-trials-advancing-rare-disease-therapeutics-pilot-program-program-announcement

START Programs Selected

- NGLY1 deficiency - Grace Science LLC (AAV9)
  - Loss of function of NGLY1, cytosolic enzyme deglycosylating other proteins
  - Intellectual disability, movement disorder, transaminitis, hypoalacrima, polyneuropathy
- Rett syndrome - Neurogene, Inc (AAV9)
  - Caused mainly by mutation in methyl CpG binding protein 2 (MECP2), a transcription factor
  - Intellectual disability, seizures, loss of motor function
- Canavan Disease - Myrtelle, Inc (AAV)
  - Mutation in ASPA gene for aspartoacylase which metabolizes N-acetyl-L-aspartate in myelin
  - Intellectual disability, hypotonia
- Methylmalonic Acidemia - Moderna TX (mRNA)
  - About 60% caused by mutations in MUT gene for methylmalonyl-CoA mutase
  - Intellectual disability, movement disorders, lethargy, hepatomegaly

Platform Technologies



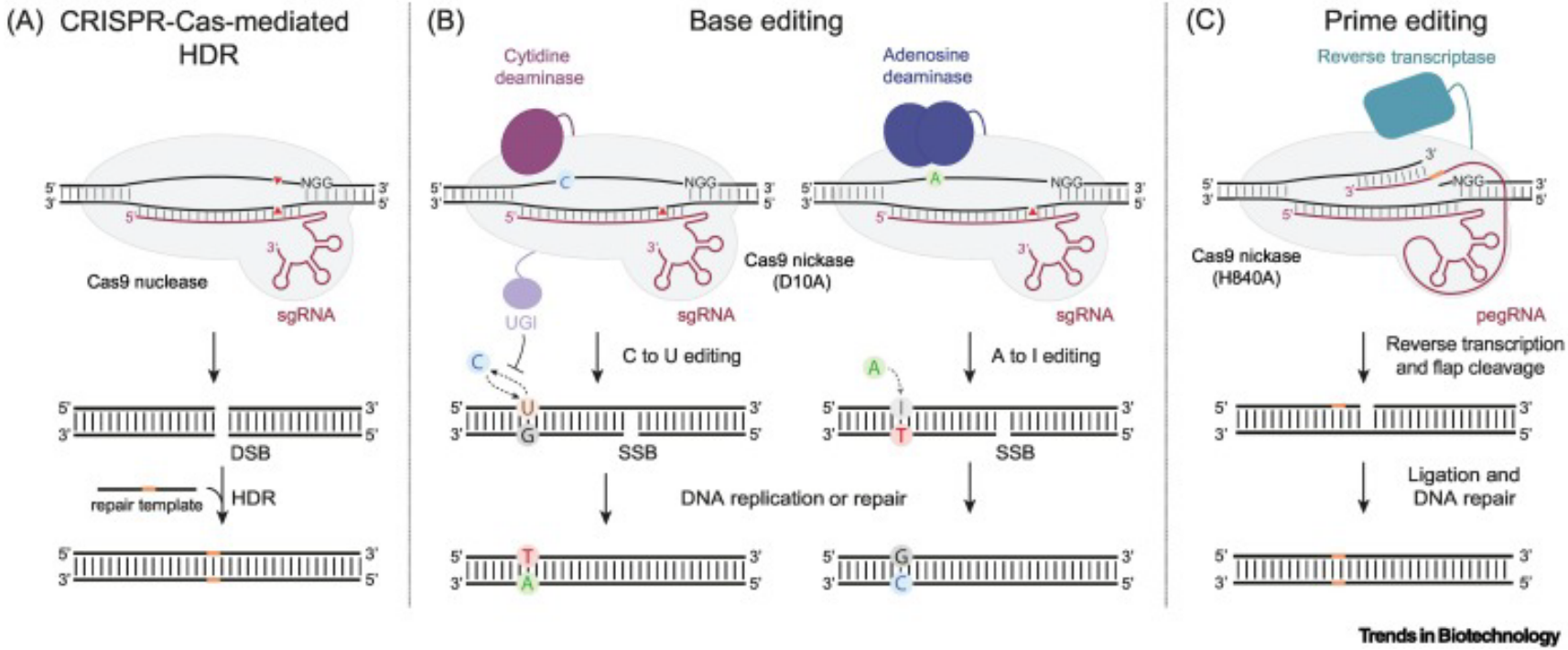
Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Omnibus Appropriations Act of 2023

- Section 2503. Platform Technologies
  - Sponsors may also “reference or rely upon data and information” from a previous application for a drug or biological product that incorporates or uses the same platform technology
  - Data must be submitted by the same sponsor or the sponsor relying on the data received permission from the sponsor who originally submitted the data
  - FDA will issue guidance relating to the program

CRISPR: Poster Child of a Platform

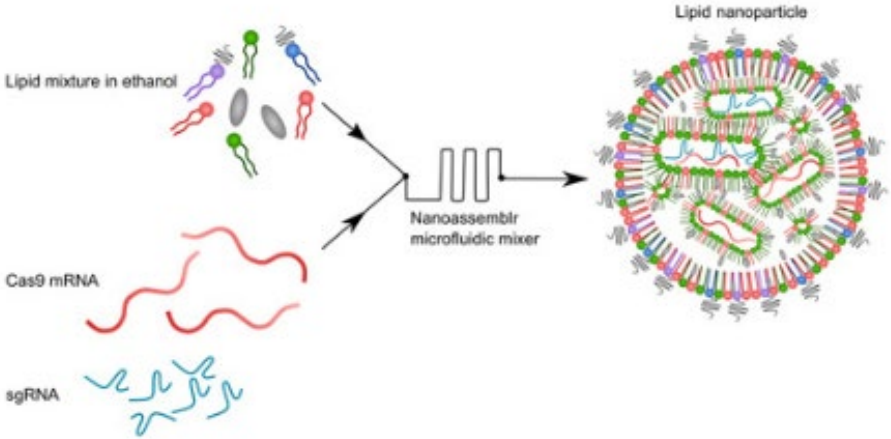


From: Zhao et al. Trends in Biotechnology. 2023; 41:1000-1012

Delivering In Vivo Genome Editing

- Non-targeted lipid nanoparticles go to the liver
- Use of cell surface molecules (CD antigens) to target T cells
  - Hamilton et al. Nature Biotechnology. 2024 ;42:1684–1692
- Use of specific lipids and crosslinking to target bone marrow
  - Lian et al. Nature Nanotechnology. 2024; 19:1409-17

Promise of the mRNA Platform



From: Rosenblum et al., Sci. Adv. 2020; 6:eabc9450.

A Powerful Quartet

- Delivery vehicle
- Advanced manufacturing technology
- Artificial intelligence applied in development
- Application of a regulatory platform

Summary

- The Center for Biologics Evaluation and Research will continue to actively advance the science and regulatory framework for gene therapy as well as expedite the review process to help bring the promise of genetic therapies to the broadest number of people globally


FDA
U.S. FOOD & DRUG
ADMINISTRATION