Navigating "DS vs. Critical Component" for Ex-Vivo Human Genome Editing Autologous Cell Therapy Drug Products

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The Regulatory Challenge

- For ex vivo cell therapies, gene editing (GE) components — sgRNA, Cas9, repair templates, and RNP complex — occupy an ambiguous regulatory space between Drug Substance (DS) and Critical Component.
- The 2024 FDA Guidance, e.g*: "When the GE components are expressed in vivo by directly administered plasmids or vectors, the plasmid or vector in its final formulation encoding the GE component is considered the DP. If used to modify cells ex vivo, the GE components are considered* ***critical components*** *for the manufacture of the final product because without these components, the resulting cell product would not have the same pharmacological activity."*

Why Gene Editing Components Classification is Important

Drug Substance (DS)

- **Regulatory framework**
  - Full commercial cGMP compliance
- **Stability strategy**
  - Extensive ICH-compliant stability programs
- **CTD documentation**
  - Dedicated CTD Module 3.2.S
- **Testing and release**
  - Validated assays for quantitative potency
- **Supplier oversight**
  - Managed within the sponsor's cGMP quality system

Critical Components

- **Regulatory framework**
  - Risk-managed material controls
- **Stability strategy**
  - Phase-appropriate stability profiles
- **CTD documentation**
  - Documented under CTD Module 3.2.S.2.3
- **Testing and release**
  - Certificate of Analysis (CoA) demonstrating functional performance
- **Supplier oversight**
  - Vendor qualification for GMP-grade sourcing

Overview of Autologous Cell Therapy Programs

Program A

- Engineered T-cells modified by CRISPR/Cas9 with site-specific integration of a DNA Repair Template encoding a neoantigen-specific TCR sequence
- Module 3: 4 Drug Substances
- GE Components as DS:
  - Repair Template
  - sgRNA
  - RNP Complex
  - DS Cells

Program B

- Platform manufacturing process derived from Program A
- Repair Template targets a different neoantigen-specific TCR sequence
- Module 3: 4 Drug Substances
- GE Components as DS:
  - Repair Template
  - sgRNA
  - RNP Complex
  - DS Cells

Program C

- Similar manufacturing process to Programs A & B
- Repair Template targets a different neoantigen-specific TCR sequence
- Module 3: 3 Drug Substances — leveraged 2024 FDA Final Guidance
- GE Components:
  - DS
    - Repair Template
    - RNP Complex
    - DS Cells
  - Critical Components
    - sgRNA

Regulatory Filings: GE Component Classification Outcomes Across Three Programs

Program A

- Strategy: Legacy — filed prior to 2024 Guidance
- Reclassification attempt: DECLINED— agency requested retention of current DS structure
- Early IND classification appears to be set for duration of program life-cycle and into pivotal

Program B

- Strategy: Platform from Program A — same 4-DS structure
- Reclassification attempt: DECLINED— agency cited ease of review
- Similar to Program A, IND classification locked in even at early phase

Program C

- Strategy: Leveraged 2024 Final Guidance
- Classification: sgRNA + Cas9 as Critical Components — AGREED
- Allowed for flexibility with a hybrid model for gene editing components as critical components and DS

Strategic Takeaways for FDA and the CGT Industry

- **Early FDA alignment on gene-editing (GE) components** can reduce regulatory burden across both early and late stages of cell therapy development.
- **Classify gene editing as Critical Components (CC)** where scientifically justified:
  - **Use risk-based assessments** in place of default Drug Substance (DS) expectations.
  - **Avoid prolonged negotiations** to obtain flexibility otherwise tied to DS framing.
- **Phase-appropriate flexibility for GE components in early development** supports program viability and enables efficient progression to late-stage development in cell therapy.
- **Sustain engagement with the FDA in late-stage platform programs** to re-evaluate evidence-based flexibility for GE components.

Thank you!

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