Roundtable Session 2 - Table 5 - Phase Appropriate Engineering Run Approaches (i.e. IND Enabling Runs for Filing and Stability)

Facilitator: Rashi Srivastava, AstraZeneca

Scribe: Gaël Debauve, UCB

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Abstract:

Cell and gene therapy products represent a significant advancement in the field of medicine, offering potential cures for various genetic and cellular disorders. However, the development and commercialization of these therapies require meticulous planning and execution of engineering runs, especially during the IND (Investigational New Drug) enabling phase. These engineering runs are critical to demonstrate product quality, consistency, and stability, which are essential for successful regulatory submissions and long-term viability.

Discussion Questions:

- What is the minimum number of engineering runs required for submission, and at what scale?

- Is there flexibility regarding the grade of reagents and the space (process development or GMP environment) in which the engineering runs should be conducted for early phase studies?

- How can the stability protocol/studies be performed during the IND enabling studies?

- Additional point proposed and agreed at the beginning of the discussion: How do these considerations evolve toward commercialization?

Notes:

Participants:

Mix of experts from Process Development (PD), MSAT, Analytics, and Regulatory Affairs

Modalities discussed:

- Autologous and allogeneic cell therapies
- AAV and lentiviral vectors

Note: No regulators were present—industry feedback only

Discussion Summary:

1. Minimum Number and Scale of Engineering Runs

- Number of engineering runs: Variable. From 1 (minimum) to 3.
    - In the 1 Eng run scenario, the participant confirmed that a pilot run (ahead of the engineering batch) was produced in Process Dev (PD) lab (non-GMP) at scale.
    - In the 3 Eng run scenario, the participant mentioned that 2 Eng batches were produced in PD (non-GMP) and 1 in GMP facility using same operators and reagents.
    - Flexibility: Prior knowledge and standardized platforms may reduce number of IND-supportive batches
- Scale: Feedback from participants is that engineering runs are produced at same scale than clinical material. No case reported where a different scale was used.
- Potential use of IND-supportive batches.
    - To generate data used to build the control strategy, evaluate the process performance/variability and to support specifications design/definition.
    - For GLP tox studies.
    - To generate reference standards.
    - For analytical method validation. Note: PD material at a different scale could also be considered for method validation as soon as it is deemed representative of the clinical material.

2. Stability Design

- Stability material: Early phase IND supportive stability batch can be conducted on PD material, not necessarily produced in a GMP facility, if scale and manufacturing process are representative to the clinical material.
- Shelf-life supporting stability conditions:
    - Must have: Intended storage and in-use.
    - Nice to have: Accelerated but some guidelines highlight the fact that temperature might affect the behavior of the product (e.g., viral vector). Therefore, accelerated stability data might not be appropriate for shelf-life determination *per se* but could support forced degradation studies.
- Cell therapy: Clinical material stability may not be required if stability has been demonstrated on representative non-clinical material.

3. Road to Commercialization

- Discussed approach for process characterization/validation:
    - 1 final confirmation run in PD (non-GMP) at scale with GMP-grade reagents followed by 1 GMP engineering batch at scale before PPQ
- Post-IND changes: In the case of significant changes (e.g. site changes), on top of the comparability assessment a new stability study is expected (also captured in ICH).
- Stability not part of comparability section but stability done. It seems to be an expectation from the guidelines.
- Stability expectations:
    - Allogeneic cell therapy: 3 PPQ batches in stability
    - Single PPQ batch programs: a reduced stability package may be possible (subject to approval by the appropriate Health Authority) and supported by hold studies.
    - Donor Considerations in Cell Therapy
        - Typical: 3 donors, 3 batches (1 per donor)
        - Stability design: Matrix design (stability design (timepoints) different for the different batches to cover more timepoints)
        - Possible reduction: 1 donor–1 batch upon Health Authority approval. Justification to be provided to mitigate the absence of donor-to-donor variability.

4. Regulatory and Guideline Updates

- ICH Q1: Stability Testing of Drug Substances & Products
    - Draft Guideline: On 11 April 2025, the ICH Expert Working Group endorsed an updated, consolidated ICH Q1 draft at Step 2b, integrating core stability chapters and three annexes—including one on ATMPs (Advanced Therapy Medicinal Products).
    - Public Consultation: The draft was released for public comment on 30 April 2025, with a comment deadline of 30 July.
- USP-NF 〈1067〉 Best Practices for the Manufacture and Quality Control of rAAV
    - Contains a section for stability on rAAV
    - Draft Chapter in public consultation through USP Pharmacopeial Forum (PF) 51 (3) updates USP Access Point Login