Roundtable Session 1 – Table 6 - Creative Approaches to Stability Assessment for Frozen Products

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Abstract:

Stability for cell and gene therapy products have unique challenges compared to other modalities. Not only are studies designed to accommodate small batch sizes, but the drug product is typically frozen at <-60C. This roundtable will focus on novel stability study designs and statistical analyses that are being used to overcome some of the challenges of assessing stability with small batch size frozen drug product.

Discussion Questions:

1. What are your biggest challenges with frozen drug substance or drug product stability?

2. What type of stability study designs do you employ to deal with small batch size frozen drug substance or product?

3. Do you employ any novel statistical analysis tools to stressed or accelerated arms of your studies to assign shelf life to your frozen drug substance or product?

4. What are your typical stressed and accelerated conditions for frozen drug substance or product.

5. Are freeze/thaw studies part of your strategy for bridging between frozen and accelerated conditions?

Notes:

Challenges due to "small batch size"

- Adapt CCIT testing: use vendor data for Phase I, use formulation buffer instead of filled vials for later phases, CCIT method depends on the type of the container (work with the vendor for potential use of non-destructive methods)
- Number of sterility samples needed each year?
- Assessment of newer low volume technologies to replace high volume requirement technologies for tests such as particulates.

Individualized therapies
- Use separate process to generate material for multiple timepoints
- Establish scale-down model for some attributes
- Duration of stability study can be much shorter (less stability timepoints)
- Healthy patient donor often used to model stability.

Scale-down model:
- Optimize freezing process (needs to match)
- Assess "comparability" of the two containers (use e.g. paired t-test)
- Use same material for the primary container

Drug Substance stability:

- Run stability on DS as well, perform DS hold time studies

Drug Product stability:

- Bracketing/ matrixing approaches can be used to cover different vial sizes

Challenges with frozen DS/DP

- Yield from patients is variable
- Do frozen products ever degrade?
  Examples from the table: Stability for AAV shown for up to 5 years → no degradation; cell therapies stable for 2 years
- For cells, -80°C storage could differ from liquid nitrogen storage
- AAVs: same capsid, different transgene GC content: varying stability possible
- Cell therapies: different stability possible for different cell lines

Accelerated stability/ stress stability

- Stress conditions for AAV: temperature, light exposure
- Important to cover temperature excursions (shipping, comparability assessments)
- Glass transition temperature important (mirror what can happen during manufacturing/ transportation)
- Cover CO_2 exposure (CO_2 could ingress via vial/ bag)

Stability studies

- Methods could be removed if it was shown that they are not stability indicating
- Add multiple (potential) assays already in Phase 1
- Acceptance criteria: specification for Phase 1 (report result for early phase, trending can still be done)

Novel statistical analysis tools used?

- No
- Shelf-life claim can be made by modelling from stress stability data, but this is a new / novel approach not well accepted. Using Baysian models etc. to predict RT data.

Number of DP batches for stability

- Early phase: e.g., 1 technical batch plus 1 GMP batch
- Commercial: three DP batches (PPQ) plus annual stability

Sampling for stability

- Use worst cases (e.g., surface/volume ratio)
- Justify study design

Additional considerations

- Extractables/ leachables studies: use formulation buffer
- Plastic containers: consider label/ glue as a source of leachables.