Table 25: Reference Standards for Cell & Gene Therapy Products: Best Practices for Autologous Therapies

Facilitators –

Kirsten Kramer Jakobsen, *Novo Nordisk*

Helena Madden, *bluebird bio, Inc.*

Scope:

Reference standards are a critical component of process control strategies for therapeutic proteins. Although some international or national standard materials are available for C&GT products, most manufacturers are developing their own product-specific internal reference standards for product development and commercialization. For this unique class of products templated approaches to reference standards should be feasible for accelerating development. This roundtable will discuss the challenges in C&GT standardization and best practices for establishing, characterizing, and qualifying in-house primary reference material and working reference materials for C&GT products.

Questions for Discussion:

1. What are the challenges for C&GT reference standards you are facing?
2. What are your thoughts on reference standards limited to specific products versus industry-wide standards for specific product classes?
3. What are your thoughts on best practices for development of reference materials for C&GT programs and autologous therapies?
4. What materials are used as reference standards during the different phases of product development?
5. How are you envisioning bridging to a new reference material during product development? What statistical assessments are performed to justify difference between PRS and WRS?
6. What are the challenges and strategies for assigning potency for bioassay reference standards? What type of testing and acceptance criteria do you apply to prevent potency drift during product lifecycle?
7. Are there any unique considerations for evaluating stability of C&GT reference standards? How are acceptance criteria established?

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

The major challenges for C&GT reference standards are:

- Material limitations – might only have 1 DS/vector to use as Reference Standard (RS), DS/vector batches are small, variance from batch to batch seen in development. Pool batches that are representative. Larger quantities are needed for PRS.
- Don't know much about CQAs, not sure which attribute are important for RS qualification, Increased testing is needed since not much is known
- Cannot evaluate several batches and choose the best candidate RS as done for Mab RS
- No clear guidance from regulators → no consistency in approach across industry for CGT products
- Cannot use 1 Viral Vector (VV) RS if you have different VV serotypes for delivery of a transgene
- Differences in EMA vs FDA considerations for viral vector (critical material vs DS)
- Since FDA requires functional potency assay(s) for DS a potency assay for RS is needed

Discussion on the use of international Reference Material vs product-specific RS:

- International reference materials (RM) cannot be used for all CQAs (e.g. AAV RM for titer, AAV RM for particles)
- Disagree with titer method used for international RM, prefer to use product-specific titer method
- Tests performed on international RM are not specific for sponsor product
- Hard to predict & manage long-term supply for international RM vs managing in-house RS supply
- Aliquot size of in-house RS might be advantage over international RM aliquot size
- EU Pharmacopoeia is adding a monograph for GT
- Internal reference standard should be used for impurity measure
- HCP std, 20-30 years horizon, kit and reagents one for each product
- Suggestion – establish RM for empty capsids

Best practices for development of reference materials for C&GT products:

- The principle of bridging all WRSs to a PRS may not be used due to lack of knowledge or lack of material for both PRS and WRS
- One company is bridging candidate WRS to PRS, other RT attendees not at this point of product development yet
- Rejected lot may be used for RS candidate if it's representative and rationale can be scientifically justified
- Pooling batches to be used as RS increases supply & decreases testing/stability requirements

- Consider the purpose of the RS. Use RS for Identity and Potency, but not as an 'assay control'

Materials used for RS during the different product development:

- Interim RS used at early stage, Using tox material as Interim RS
- Split 1st Ph3 campaign into PRS/WRS, aim for 5 years stock.
- WRS should be representative to clinical batch. PRS/WRS from PPQ batch later on use a GMP batch

Considerations for bridging to a new reference material include:

- Test candidate WRS vs PRS & compare to historical lot test results
- Use narrower RS acceptance criteria for key assays (vs. release test acceptance criteria) or use narrower criterial for selection of RS candidate material
- Statistical assessment might not be feasible due to limited data
- Bridging is only relevant for Potency

Challenges and strategies for assigning potency for bioassay reference standards:

- More than 1 potency method exists (infectivity, expression of gene of interest, functional potency test
- Method applied is important (e.g. using TCID-50 for infectivity vs ddPCR for delivery of infectious material)
- Many ask (or plan to ask) Health Authority for advice
- Cannot test significant number of samples for potency determination, most are using 3 independent tests
- Would like AC to be less than specification, but don't want to reject lot as WRS unnecessarily
- Not sure if, when, & how to apply a correction factor if potency of candidate WRS is different from PRS. A correction factor is NOT recommended.
- Do more independent replicates to narrow SD
- Potency assignment of biotherapeutic reference standards by Paul Faya, Matthew W. Borer, Kristi L. Griffiths, and Bhavin S. Parekh. Journal of Pharmaceutical and Biomedical Analysis 191 (2020) 113577

Testing and acceptance criteria applied to prevent potency drift during product lifecycle:

- Don't have enough data for statistical comparison, may use Tolerance Interval or Std Deviation
- Measure 'strength' as amount (particle per ml) and compare to 'units' activity

Stability testing of C&GT reference standards:

- All RS are put on stability testing (annual), narrower AC than release AC may give warning & time to replace an unstable RS