Table 2: Cell and Gene Therapy Products - Manufacturing Control Strategy and CQAs

Facilitators –

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Scope:

While it is understood the principles of control strategy and CQA assignment for CGT are the same as other parenteral biological therapies, there are unique challenges with these newer modalities. For gene therapy, a challenge is material availability and relative novelty/lack of clarity on mechanism of action, which may impact the ability to perform structure – activity relationship (SAR) studies. Analytical methods are also relatively new or yet being developed for several attributes. For cell therapy, a major challenge is the variability intrinsic to the starting material, and the inability of determining the proven acceptable ranges (PAR). In this roundtable, we will discuss the phase appropriate controls for production, testing and distribution of CGT products.

Questions for Discussion:

1. Are there unique considerations for CQA identification and assessment for cell and gene therapy products, as compared with those used for established modalities (i.e., mAbs)?
2. Many attributes score as critical due to lack of understanding (high uncertainty). How do we address as an industry?
3. How can we incorporate/address the impact of starting material variability in the overall manufacturing control strategy?
4. How do we assess and demonstrate comparability of cell and gene therapy products during development and manufacturing?
5. How are forced degradation/stability studies utilized in establishing CQA and control strategy for CGT products, compared to biologics?

Discussion Notes:

January 25 and 27, February 2 and 4, *combined* –

Are there unique considerations for CQA identification and assessment for cell and gene therapy products, as compared with those used for established modalities (i.e., mAbs)?

The same principle on how to identify CQAs and scoring CQAs apply to CGT, with the following challenges:

- Control strategy is different for different types of therapies and increasingly complex:
- AAV: might be less complex as it can be platformed. A lot is known about AAVs from the vaccine world, however the challenge is applying the vaccine's standard on a completely different scale (25mL).
- Allogeneic cell therapy (e.g. iPS): could start from a bank so reducing the variability helps. However platform concept not really applicable. Also, the product is a cell and the complexity of the cell is larger than a biologics.
- Autologous cell therapy: there is a lot of variability from donor to donor. This increases the burden to CQAs.
- Uncertainty of the impact to potency and safety need to be evaluated from scratches, as not much platform knowledge available.
- Companies don't necessarily have a defined strategy for potency testing early on, but it is needed prior to pivotal clinical trials.
- It's important to demonstrate with the CGT product is intended to do early on, leveraging assays even in discovery if needed, to have understanding if any attribute is or is not a CQA
- Very limited in the materials that you can work with need to drive development of methods that can assess multiple attributes at the same time.
- MAM could be an opportunity; GXII another opportunity to measure DNA and protein components at the same time.
- GT such as AAV have two components in it, the protein part and the DNA part, and they both need to be addressed so the number of CQAs might be higher than a mAb.

Many attributes score as critical due to lack of understanding (high uncertainty). How do we address as an industry?

- In vitro studies/cell based bioassay is key. We need perhaps a matrix of assays to be able to confirm the potency of the material, and the impact that any change to CQA could have on potency. Animal studies could be used to branch out of the CMC-only space, and encouraged partnership with clinical with small PK/PD studies, or even just PK/PD measurements during an

already planned study. Development and Discovery work together to enhance CQA understanding.

- Cellular therapies are a personalized market and the critical attributes tend to focus on safety

- For gene therapies, a lot of discussion focused on the high importance of the potency assay. In early development stages, focus might be on titer and potency method. They are also important for structure-function studies. Some participants confirmed they are doing this advanced characterization. It is much more difficult if a good potency assay has not been developed.

- With development it is possible that more information is obtained to discharge an attribute from being considered a CQA. It is therefore important to be able to collect information on multiple tests methods on early phase to have a complete footprint of the material that went in the clinic. Sponsors should not be discouraged from using several characterization methods if they don't know how to set limits.

How can we incorporate/address the impact of starting material variability in the overall manufacturing control strategy?

- Because of the variability intrinsic in the starting material, we need to take the CQA assessment one level behind the DS manufacture and include also starting material manufacture in the assessment. A request from FDA was reported to track the starting material all the way through the DP.

- For CGT, it applies the principle "the process is the product" and the controls are moving on the consistency of the process performance rather than the release of the batch.

- Discussion occurred on how to what to define "acceptable" variability on products such as cell therapies, where the starting material is different for every batch. A mention was made to retrospective testing and analysis to establish boundaries

- Interactions with the FDA/agencies may be helpful

How do we assess and demonstrate comparability of cell and gene therapy products during development and manufacturing?

- Having good potency assay. (like a matrix, containing multiple steps, infection, expression, functional proteins, etc.)

- Reference standard is very important:

- given the limited amount of material, we should consider using external RS, such as a compendia, or an ATCC-made AAV of the correct serotype.

- Pooled different batches into one RS is an option too.

- Sequential comparability: A to B, B to C, C to D; then A to D.
- Use multiple test methods for a key attribute, such as DNA characterization methods: NGS and other orthogonal methods
- Need to tie to clinical relevance, where possible. Otherwise agency might defer to clinical experience as being needed.
- Highly likely in the recent cases that CMC and potentially comparability is the reason for delays in submission. Keep retains is mandatory by CFR but also highly recommended to be able to re-test clinical lots with more state-of the art methods, once developed

How are forced degradation/stability studies utilized in establishing CQA and control strategy for CGT products, compared to biologics?

- Force degradation studies are a must have. They are needed to validate the list of CQAs and identify what is the degradation profile of your asset.
- DNA and protein might need different stressors
- For a ultrafrozen product, could combine accelerated and stressed studies, or Freeze-thaw and stressed studies
- Stability studies are needed to support shelf life but perhaps there is room for brainstorming alternative ideas to the std ICH boundaries
- Could use bracketing approach or matrixing approach, such as testing few time points for each lot