Table 32: Reference Standards for Cell & Gene Therapy Products - Best Practices for Autologous Therapies

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Key Words:

Reference Standards, Cell and Gene Therapy

Scope:

Reference standards are a critical component of process control strategies for therapeutic proteins. They are particularly important when dosing and potency are critical parameters for patient safety and product efficacy. 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.

Reference standard (RS) material is vital to ensure product quality for each batch production. The biggest challenges for Cell and Gene Therapy autologous therapies is material limitation.

In this roundtable, we discussed opportunities of Drug Substance (DS) and Drug Product (DP) RS material and management. DP RS are commonly sourced from human cells; some companies use healthy individual patients to generate this material by combining multiple productions runs. Each run is separately characterized prior to pooling for large homogenous lot. The general understanding is that the RS must be representative of the commercial process.

Vectors could be utilized as DS as they are considered to be a critical manufacturing component. Additionally, some assay methods could use analytical standards in lieu of a reference material during development. Example of this would be a cytokine material for a cytokine related potency assay.

Assay controls may be another suitable alternative to a RS for some assays. A watchout for any commercially acquired material is to ensure thorough extended characterization (ie CE-SDS, electron microscopy, AEX).

Key understanding to how good is the Reference Standard is assessed through extended characterization. Characterization of an alternative analytical standards and a comprehensive comparability with proposed RS is also needed should a assay use analytical standards.

Stability protocol should push boundaries of required testing needed. The table discussion included a company's successful experience of HA acceptance to test potency purity, etc. while omitting pH and ID. Temperature range in a stability protocol may only require one target as most RS is stored in LN and it can be risk-ranked out (-140C vs -60C). It was also noted that acceptance criteria of the stability protocol

and its capability to see if there are changes in product (ie. Change in structure) which could pose a risk. Overall, there is a consensus agreement that the HA is still learning about CGT products.

Additional comments from the table included the USPs involvement in drafting a chapter for AAV, plasmid DNA, and Lenti virus.