KEY DRUG PRODUCT CONSIDERATIONS FOR iPSC-DERIVED NK CELL THERAPIES

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The field of autologous CAR-T cell therapy has evolved over the last few years as demonstrated by several marketed products including Kymriah, Yescarta, Tecartus, and Abecma. The model of each patient representing a new manufacturing lot results in source cell and batch-to-batch variability, which poses a challenge from a processing, quality control, and cost perspective. Given these challenges, the field of immunotherapy is moving from autologous to allogeneic cell therapies to gain several advantages, including reduced cost of goods, the ability to generate off-the shelf products, and process scalability.

In the case of differentiation to and expansion of iPSC-derived NK cells (iNK), there is a scalability challenge during the final stage of the manufacturing process to wash, formulate, and fill a large batch size within a reasonable time frame. In regard to batch size for allogeneic cell therapy products, the need for control over the fill and freeze process becomes more relevant for consistency when hundreds of vials have to be filled per batch. Further, as the scale of the process increases from Phase 1 and beyond, more efficient methods for filling and visual inspection need to be considered. To address one of the key process steps to control the quality of iNK drug product, we focus on the cryopreservation unit operation. While cell health, phenotype, and potency are generally preserved with fresh cells over relatively short periods of time, cryopreservation and storage of drug product is an essential supply chain requirement to control the delivery of allogeneic product to a larger number of patients.

Here, we will present case studies covering the following aspects of iPSC-derived allogeneic cell therapy development:

- Given the sensitivity of iNK cells during fill and cryopreservation in DMSO-containing solutions, a strong understanding of the key process parameters in these unit operations is required to generate a drug product with desired quality attributes. To support flexibility in manufacturing, we will show data to justify in-process hold times, while establishing an edge of failure.

- As part of process development, the work presented will demonstrate the need for an optimized cryopreservation profile based on the drug product presentation, as well as the batch size. As part of increasing our understanding of this unit operation, we assess the impact of cryopreservation on DP quality attributes.

- As part of drug product formulation development, the work presented will highlight the impact of formulation, specifically DMSO content, on cryopreservation of the cells and post-thaw drug product stability, as well as its limit from a clinical tolerance perspective.

- A key aspect of developing high-quality cell therapy products involves feedback from analytical readouts, which include release as well as characterization assays. Since the field of iPSC-derived cell therapy products is under development, a large effort to develop robust analytical assays to capture identity, safety, phenotype, and potency is underway. In this work, we will also highlight a subset of the cell therapy analytical tools which are used to characterize the quality and stability of iPSC-derived cell therapy drug product.