Manufacturing of Cell-Based Therapies
November 9, 2022

Q: What is the acceptable requirement to show comparability of small-scale models and large-scale models?

A: As it was also discussed in A-Cell's first seminar (Generation of Quality Target Product Profile, Risk Assessment and Critical Quality Attribute Identification), the standard approach to Cell Therapy development starts from the definition of a Quality Target Product Profile (QTPP), from which Critical Quality Attributes (CQAs) and Critical Process Parameters CPPs) are derived, which are then finally used as the basis for defining a control strategy. This applies to both large-scale and small-scale process development.

Under such light, comparability assessment between two different processing schemes, including comparability of large- versus small-scale versions of a single protocol, requires an assessment of whether CQAs and CPPs are preserved between the two methods. As CQAs refer to the final drug product, there should be no difference in CQA measurements across the two methods.

Conversely, as CPP are process-specific, there might be subset of CPPs that apply to one method but not to the other: for example, rocking rate might be a CPP for a large-scale process, whilst not being applicable to a potential small-scale equivalent process that – while yielding the same CQAs- utilizes G-Rex static flasks for which rocking rate is not a CPP. As such, CPP comparability assessment should be limited to the subset of CPPs that are applicable to both methods, while always ensuring that all CQAs are preserved and comparable.

It might also be worth considering analytical testing elements and understanding the biological impact of a potential scale process change on the product. Traditionally, there have not been good 1:1 scale down models for typical T cell expansion vessels (with the G-Rex being a possible exception). Thus, one should consider impacts in scale or other associated "known knowns" when developing the testing plan. For example, shortening a CART process from 14 days to 7 days is likely to have obvious impacts on yield (e.g., fewer active cell doublings). It might also impact the "fitness" of the resulting T cell population at harvest, which could have impacts on phenotype, potency, etc. This should be considered when designing a comparability plan from start and one should prepare a narrative to speak to expected analytical changes that are detected as part of the models employed.

Q: What MES and LIMS solutions would you recommend for CGMP application??

A: The choice of electronic systems comes down to several factors. The key elements that should be considered are as follows:

- 21CRF Part 11 compliance
- The inter-operability and compatibility with other existing software programs (e.g., ERP or inventory management solutions, Learning and Document management, Quality systems, as well as implementation of chain of identity (COI) and chain of custody (COC) control, etc)
- IT considerations at site (e.g., on-premise vs. cloud-based requirements)

- Ease of use, training and user requirements (e.g., are there licensing considerations that might how you intend to use these software solutions)
- From the A-Cell chapter, the most notable MESs in the life sciences space include Körber Pharma (formerly Werum IT Solutions) PAS-X, POMSnet Aquila from POMS, Emerson Syncade, and Rockwell FactoryTalk Pharma Suite

Q: Are the individual graphics/tables/schematics/diagrams/illustrations in the A-Cell document and webinars available for download and cited use?

Yes

Q: The selection reagent is often carried through and used as the activation reagent (beads). If possible, would there be an advantage of using a different selection vs activation reagent?

A: There are several manufacturing approaches in which cell selection reagents are not utilized as activation methods. As an example, one approach might involve the use of antibody-bound nano-magnetic beads for cell selection (e.g., CD3+ enrichment via MACS), followed by activation via soluble antibodies (e.g., OKT3, TransAct). Such methods are discussed in A-Cell Chapter 8, including their advantages and drawbacks. A potential advantage of soluble activation reagents is the elimination of a bead-removal step at harvest, which can be associated with significant cell loss and additional processing time/failure rates.

Q: What are the options for automated filling of formulated DP into cryobags for allogeneic products?

At the moment, there are limited options here. Most fill/finish solutions have been targeted towards either bags (e.g, Terumo Finia), or multi-use products, such as the Aseptic Technologies (M1 or L1) fillers or AST GENiSYS lab solutions). Other options are emerging, but as with this entire space, the technology is new and not broadly adopted yet. It should be noted that identifying solution for many therapies seems premature for Phase 1 studies where dose escalation may require a broad range of volumes and cell numbers, making it challenging for a single fill/finish solution to cover all possible needs.

Q: What is your advice on how to mitigate particulates arising in the process, especially those that may arise from single-use plastics?

A: This is a challenging space, as there are a number of “new” products with product contact being developed and introduced in this space (thus limited experience exists). To mitigate this, there are at least 2 solutions. 1) Consider your commercial supply agreement as an opportunity to partner with the supplier to complete an assessment on particulate mitigation strategies (for their product and their suppliers), and 2) Utilize very high quality starting materials and utilize in-line filters or strainers, where possible as part of the process (or prior to dosing).

Q: What are some key factors and considerations to keep in mind when it comes to purchasing freezers? Given the current market environment, what are your suggestions for customers that need to be more prudent with capex?

A: There are several ways to approach this question. One could identify less expensive options (e.g., lesser-known brands, discounted units, etc.), join industry associations, such as Bio, NC Biosciences,

Biocom, etc., which can provide early guidance and often substantial discounts on equipment and lab supplies. Aside from the purchase of the equipment, your storage protocols become critical. Consider what you are storing and where these samples would impact your program, customers, or company livelihood should something go wrong. I think we can all picture a freezer packed full of boxes with samples that are poorly labeled and without a clear catalog of what's available. I would suggest a thoughtful approach to the storage location and duration of retention for samples. Identify the amount of time in which they need to be retained and be diligent about reviewing and discarding the samples on a routine schedule.