ESTABLISHING SUCCESSFUL COMMERCIAL CAR T MANUFACTURING ON A SHORT TIMELINE: A PROCESS DEVELOPMENT PERSPECTIVE

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The transformational impact of CAR T cell therapies on serious diseases enables a rapid path to licensure. Although many challenges of reliably delivering autologous CAR T therapies have been managed at clinical scale and quality, the transition to commercial scale and widespread availability to desperate patients presents many additional challenges. The process development contribution of pragmatic and engineering-based operations science with respect to facility fit, scale-out, and patient variability is essential to the success of this transition.

Whether adapting an existing facility or constructing a new one, GMP workspace design requires detailed process evaluation. In addition to maximizing efficient use of space, equipment, and labor, addressing facility impact on process is critical. For example, the scale or layout of a large commercial facility can increase the time necessary to perform a process step. As a result, the process runs within a different range of the parameter space within the facility. We describe time-related process characterization data and closed-system solutions to facility fit challenges along with the process expertise which contributes to successful technology transfer to new facilities. The task of facility fitting becomes increasingly complex as multiple facilities are implemented, as it is desirable to minimize facility-to-facility process variation.

A dramatic increase in scale (number of patient-batches) is associated with establishment of commercial manufacturing. Due to an individual batch being performed for each patient, an increase in the necessary facilities, equipment, and staff accompanies the scale increase. As new manufacturing, QC, and QA talent ramps up the workforce, a robust training program that imparts both process instruction and understanding is critical. Further, process design and batch record clarity must be improved to minimize process variability. We describe process and batch record improvements that address rapid workforce expansion and training. Autologous cell therapies present patient variability, which results in variable process performance and product characteristics. As the number of patient-batches increases, the number of occurrences uncommon process phenotypes also increases. This requires extensive instructions on how to consistently adjust the process for patient variability as well as process design that minimizes the effect of patient variability on performance while ensuring a consistent, high quality product. In addition, process performance data must be monitored to assess process performance and variability. We discuss examples of patient variability, troubleshooting, and batch history data.