

Roundtable Discussions Session 1 and 2 - Table 4 and Table 2 Respectively: Process Development of a Cell or Gene Therapy - Speed to a Phase 1 FIH Clinical Supply - Best Practices or Lessons Learned

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Abstract:

Gene and cell therapy offer transformative treatments by addressing genetic and cellular abnormalities, providing long-lasting effects and personalized care for patients with previously untreatable conditions. Improving the speed of process development for gene and cell therapy offers several benefits. First, it enables faster translation of promising therapies from the laboratory to clinical trials, expediting the development timeline. This, in turn, can accelerate patient access to potentially life-saving treatments. Second, faster process development leads to reduced costs, as it minimizes the time and resources required for development activities. Third, speedier process development enhances the commercial viability of gene and cell therapies, attracting more investment and industry interest. This, in turn, supports the growth and sustainability of the field. Moreover, faster development allows for timely submission of regulatory filings and expedites the path towards regulatory approvals. Ultimately, improving the speed of process development benefits patients by ensuring that innovative gene and cell therapies reach them more quickly, offering the potential for improved health outcomes and quality of life.

Questions:

1. How can we optimize process development in the early stages to streamline timelines and identify critical process parameters?
2. What strategies can be implemented to enable parallel processing and accelerate data generation and decision-making?
3. How can we leverage automation and high-throughput screening technologies to expedite process optimization and data collection?
4. What approaches can be used to prioritize critical process attributes based on risk and focus efforts on areas with the most significant impact on product quality and patient safety?
5. What process analytical technology (PAT) tools and real-time monitoring techniques can be implemented to enhance process understanding, enable rapid adjustments, and support continuous improvement?

Discussion Notes:

Tuesday, June 27th

What type of challenges have sponsors faced when the manufacturing process has been transferred from one facility to another?

- For CMOs and CDMOs, the facility should be fit for purpose and suit the needs of the sponsor's unique product-candidate. It is important on the part of the sponsor to select a CDMO which is a good fit for the sponsor's unique product and commercialization goals. All CDMOs cannot be everything to everybody. This assessment should be done in advance of selecting an appropriate

CMO/ CDMO partner. Not only should CMOs/ CDMOs be receptive to the sponsor's needs, but the sponsor should also be able to rely and lean on the manufacturing and validation expertise of the CMO/CDMO. The CMO/ CDMO may have significant manufacturing expertise with other sponsors with similar processes, and this information is invaluable to a sponsor. Ignoring or dismissing the expertise of the CDMO can be damaging to the relationship.

- Academic manufacturing facilities may face additional challenges particularly around commercial knowledge and the requirements for GMP manufacturing. However, academic manufacturing facilities may be more agreeable to changes and exhibit greater flexibility as compared to CMOs/ CDMOs.
- The greatest obstacle to overcome with any manufacturing arrangement centers around communication across all parties and stakeholders. It is critical to have expectation setting conversations upfront and agree upon critical boundaries to smoothly progress with any outsourced manufacturing. CMOs are servicing multiple clients with different needs and requirements so communication is critical for success. Having a solid escalation pathway, agreed upon, documented and signed by all stakeholders, in place upfront will greatly assist when issues and challenges arise.
- Larger CMOs understand that the voice of the customer/ sponsor is important and have well established systems and processes in place to manage the challenges that arise. Smaller and younger CMOs can be more agile and flexible but may be less experienced. As such, finding the best partner for the commercialization goals of the sponsor is an exercise in and of itself and is not one size fits all. Additionally, it is imperative that the sponsors themselves be well educated in terms of their wants, needs and requirements of their CMO and have a thorough understanding of their own manufacturing process.
- Having well-constructed and thoughtful timelines and milestones agreed upon by all stakeholders upfront is critical.
- What is the minimum package to provide to the CDMO to have a successful tech transfer?
- CDMOs may have a tech transfer checklist but this is not always the case. Having a healthy master plan upfront (starting runs, tech transfer, success criteria, not just a Gantt chart) is key and upfront planning is critical to success.
- Having a target candidate profile is helpful to have in place to work backwards from.
- Laying out a detailed and technical oriented draft of the manufacturing process is critical; providing as much detail as possible will aid in a successful tech transfer; anything that could impact the tech transfer needs to be communicated to the CDMO.
- Discussion around GMP expectations for the CDMO needs to take place, especially around the raw materials. Similar raw materials may be difficult to source across countries and this should be examined. It is also important to rank the criticality of some raw materials upfront as there could be lot to lot variability with larger molecule raw materials.
- 3 to 4 runs of reproducibility is important with a critical eye to the analytics.
- Assay development is also a critical area of concern and specifically around the potency specification. The potency specification should not be too wide. Additionally, attention should be paid to viral safety assays.
- What CMC approaches could be examined to speed up the process (from preclinical to clinical)?
- For gene therapy products, conduct preclinical tox studies with material that is representative of the clinical trial material. Also, it is helpful to examine the CMC strategy early on at FIH and what is anticipated to come after in subsequent phases.

- In the oncology space, there could be a relationship between potency and clinical efficacy. Each sponsor may receive different regulators' feedback around the potency assay. As such, closely examining the potency assay early on is critical.
- What are some other CDMO tech transfer points to consider?
- It is imperative and critical that the sponsor identifies good constructs for their product-candidate. This is not the role of the CDMO to sort out. Additionally, the CDMO cannot solve all the issues and challenges faced and be expected to solve everything.
- If there is anything that can be done in parallel, such as order multiple plasmids and have one vector across multiple processes, that will greatly speed progress. Also, having GMP grade reagents and a good analytical control strategy early on is important.
- Consider using the engineering run as reference material and spell out in the IND.
- Examine and invest assay development early on.

Wednesday, June 28th

How can we optimize process development to streamline timelines and identify CQAs? What approaches can be used to prioritize the critical process attributes? How to prioritize CPPs/ CQAs?

- Process optimization is a timely endeavor and planning in Phase 1 is important. The appropriate resources need to be in place early to help overcome the development challenges and really understand the manufacturing process and tech transfer.
- Consider the use of GMP material in the conduct of the tox studies and treat the engineering or tox lot like a GMP-like lot. This will assist with comparability down the line. Or manufacture the tox batch outside of GMP, then do tech transfer, and proceed with a FIH batch at the CDMO. Perform extensive comparability testing to create a reference point.
- The sponsor needs to have a clear vision of the path forward and what the study results will be used to support.
- Consider the use of established analytical methods across similar products so as not to have to continuously develop and validate new methods.
- More Phase 1 clinical trials are placed on hold due to CMC issues. This could be due to a wide specification range for the potency assay, lack of viral safety assay(s), or the non-clinical batch and clinical batch are not representative of each other or other reasons.
- For CQA identification, examine the potential impact to patient safety and viral clearance is always an initial focus.
- For IPCs in early phase, only file limits for the safety measurements (sterility, endotoxin, bioburden) and monitor other attributes and add a target. Other regulators may have a different perspective on this, however.
- Consider including Germany/ PEI in Phase 1 to receive initial, critical feedback upfront in development.

What strategies can be implemented to enable parallel processes/ instead of sequential events? How is this navigated? What kind of data is needed to enable this?

- Placing the pilot/ development batches on stability has been a practice accepted by the US FDA.
- Having another batch that is manufactured to invest in the technology and understand the process is helpful (as the clinical trial will not enroll enough patients to run through all of the clinical trial material).
- Spend time upgrading the raw materials to GMP grade