Table 7: Developing Process Analytical Technologies (PAT) to Support Advances in Cell Therapy Manufacturing

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Scope:

Process Analytical Technologies (PAT) are necessary to identify critical quality attributes (CQAs) and critical product parameters (CPPs), and in cell therapies novel and complex technologies are needed to meet the complexity of the manufacturing process. PAT has a significant role as it is a system that analyzes and controls manufacturing through in-processing or at-process monitoring of CQAs and CPPs, ensuring final product quality is met. Identifying and implementing CQAs and CPPs for a complex cell therapy manufacturing process is challenging and many developers rely on a conventional approach to PAT, which is insufficient. PAT also plays an important role in enabling Quality by Design (QbD), which is also challenging due to the complexities of cell therapies manufacturing. When developing PAT, understanding of the process and taking a risk-based approach is also critical. Health authorities also view PAT as a system to enhance our understanding and control of our manufacturing process, and specific requirements are expected for validating and controlling a manufacturing process. The agencies encourage meaningful communications through the form of meetings or informal communications to obtain feedback on PAT. Without the appropriate PAT, developers can face challenges such as inappropriate definition of CQAs and CPPs, high product cost, delays in product commercialization and overall challenges in the manufacturing setting.

Questions for Discussion:

1. What PAT challenges have you encountered due to the manufacturing complexities of cell therapies?
2. What experience do you have with the use of multiplex systems to monitor multiple parameters, and specific cell therapy parameters?
3. What is your experience with Health Authority interactions and PAT discussions? How soon did you engage in these communications?

Discussion Notes:

1. What PAT challenges have you encountered due to manufacturing complexities of cell therapies
   Multiple level of challenges involved:

- Assessing CQAs:
  a) Products are not well characterized/analyzed
  b) Most of these are rare diseases hence a limited dataset available for a robust CQA
- Assessing comparability
  a) A risk based approach is the way to go
  b) Genetic stability remains same however differentiation events may need to be monitored
- Assessing product monitoring
  a) Change in critical reagents – eg: as change in a cell line or cell type or CQA could result in a new product hence it could lead to a new filing
  b) Challenges could be faced in post commercial change if there is a change in the middle of commercial. There will be a need to assess product quality at every stage of change in PAT
- Manufacturing Consistency
  a) Spec Setting -Criteria may not be tighter at early phases but then re-evaluate when more datasets available to justify the AC
  b) Sample size is small, it leads to a challenge for analytical technology transfer
- Method Complexities
  a) Many of the in process methods are not QC friendly : eg RNA seq, TAT of these methods are slow
  b) Low stability of the products leads to method challenges
  c) A high cost involved with many methods – Transferring to CMO is a challenge as these technologies are associated with high budget costs
  d) A need for revolutionary development is required as traditional PAT does not apply to cell therapies- maybe we should contact academic partners for these new therapies as traditional mab methods do not work

2. What is your experience with Health Authority interactions and PAT discussions? How soon did you engage in these communication
   - Can we start with Q12?
     a) File a comparability plan
     b) Type C submission?
     c) Talk to regulators early on and engage in discussions with specific PAT related enquiries
     d) Set up a pre-IND meeting

   - In country registration
     a) Engage with health authorities requesting for method waivers due to inherent method complexities and challenges in analytical transfers

- Comparability draft guidance and CAR-T draft guidance are the key to follow and engage discussions accordingly
- CMC strategy needed for early submission and discussions at the early phases