A-CELL WEBINAR SERIES

Generation of QTPP, Risk Assessment, and CQA Identification
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Q: Some of these Drug Product Quality attributes are linked to CQAs – how do you define identity, potency and safety early before you have undergone CQA risk assessment?

A: Identity testing is detection and quantitation of the active molecule that is providing the biological function of the product. In autologous cell therapies, CAR or TCR expression can be used for identity testing. At early clinical stages, CAR or TCR expression can also be used as a surrogate for potency. However, functional readout-based potency assays may be expected by Phase 2 or Pivotal by regulatory agencies.

For safety, certain compendial tests such as sterility, endotoxin and mycoplasma are expected from the start of clinical studies. For genetically modified products, Replication Competent Lentivirus (RCL) and Vector Copy Number (VCN) are also expected from start of clinical studies.

Q: When should we perform the first CQA risk assessment and at what points do you revisit the risk assessment?

A: First risk assessment can be performed as soon as the quality attributes that may impact efficacy or safety are defined. Stage 1 of the Validation Lifecycle is the best time to perform the CQA risk assessment. The risk assessment can be revised as information that can impact the assessment rankings, such as process or clinical experience, becomes available.

Q: Do these documents (TPPs, QTPPs) get submitted to FDA? At what stage?

A: These documents are not submitted to the FDA or other regulatory agencies but can be used as a basis for writing certain sections of the regulatory documentation. As stated in the presentation, CQAs can serve as the basis for the comparability assessment during process changes.

Q: Do regulatory agencies expect to see justification for the ranking of each attribute?

A: As the QTPP and CQA risk assessments are not submitted to regulatory agencies, there is no expectation for these justifications to be given to regulatory agencies. However, these rankings and the subsequent CQAs can be used to support certain sections such as comparability study design in regulatory documents. There may be questions from regulatory agencies to justify the statements in these sections. Thus, justifications of rankings should be captured as thoroughly as possible during the risk assessments.

Q: Do you envision the need for viral adventitious screening of cells, especially for autologous products?

A: Raw materials for cell therapy manufacturing are screened for adventitious viruses, where applicable. For autologous products certain virus screening is also performed at the apheresis step. As the patient related material (apheresis) is initiated from the same patient the product is given to, the developers do not need to screen for adventitious viruses at the Drug Product Step.

Q: Can you please share some insights on how to best establish control strategies given the different performances between patient materials and healthy donors?

A: It is important to account for differences in performance between patient materials and healthy donors. If possible, with the consent of the patient, patient material should be included in the development.

Q: As you indicated the A-cell document was written for autologous products. However, for allogeneic products where we are filling multiple vials, I don't see much guidance for demonstrating product uniformity across dosage units for a cell suspension. Are people simply using USP 905?

A: For allogenic products, the concepts in USP 905 are still relevant. Validation of a Fill/Finish System that can achieve consistent and fast filling of the batch while keeping the cells in suspension is important.

Q: When is potency assay required?

A: Ability to measure potency is fundamentally related to product characterization. Thus, potency assay development should be initiated as early as possible during the product development. If possible, having a potency assay in development will help to obtain as much product information as possible during preclinical and early clinical studies. Regulatory authorities do not require a fully validated potency assay until the end of pivotal Phase III clinical trials.

Q: Does the severity ranking of your quality attributes change with implementation of control strategy?

A: Severity ranking will remain the same as it is independent from the occurrence or detection of the impact. However, as the control strategy is defined and Normal Operating Range for process parameters are determined, the occurrence of the severe impact can be much less and detection via certain analytical testing can be implemented. Thus overall, the risk to efficacy or risk to patient safety is reduced.