Roundtable Discussion Session 1 and 2 – Table 9: CQA Risk Assessments for Cell and Gene Therapies

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Abstract:

Per ICH Q8: Critical quality attributes (CQAs) are physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality for cell and gene therapies. The development of analytical testing strategies for CQAs is an important part of product development. The approach for development of the analytical testing strategy will focus on assessing potential CQAs for a particular product. A risk-based approach can be used to assess the criticality of quality attributes across all categories. The risk-based approach can include an assessment and ranking of impact and uncertainty categories for each quality attribute.

The impact ranking is based on current processes and product knowledge, product characterization, nonclinical and clinical development experience, regulatory guidance, and published literature. The impact ranking of a quality attribute is based on the magnitude effect on the drug product attributes that have known clinical safety and/or efficacy correlation.

The uncertainty ranking is based on the amount of knowledge and experience with a specific attribute.

This roundtable will discuss the scoring strategy associated with the risk-based approach described above as well as alternative strategies for CQA risk assessments.

Questions:

1. How should the scoring strategy be set up for the risk-based approach described in the abstract?
2. What are the cut-offs for CQA, potential CQAs (pCQA), and Non-CQAs?
3. Should pCQAs be monitored with characterization methods?
4. What are examples of attributes that fall into CQAs, pCQAs, or Non-CQAs?
5. What are alternative strategies for CQA risk assessment?

Discussion Notes:

Most participants were familiar with the risk-based approach described in the abstract. The commonly used risk-based approach to support the determination of CQAs uses criteria for impact and uncertainty compared in a matrix to identify parameters to be measured as CQAs. Criteria for impact are related to

the potential effect on product safety and efficacy. Criteria for uncertainty are tied to the knowledge, experience, and/or evidence for the specific attribute.

Uncertainty and Impact are compared using a matrix similar to those shown below. This matrix can be qualitative or semi-qualitative:

Qualitative is a red, yellow, and green coding approach

		Impact		
		Low	**Medium**	**High**
Uncertainty	**High**	**pCQA**	**CQA**	**CQA**
	Medium	**pCQA**	**pCQA**	**CQA**
	Low	non-CQA	non-CQA	pCQA

- Semi-quantitative assigns numerical values to each impact and uncertainty level, which is multiplied, and the final value is used to help determine CQAs

		Impact		
		Low (1)	**Medium (3)**	**High (5)**
Uncertainty	**High (5)**	pCQA (5)	CQA (15)	CQA (25)
	Medium (2)	Non-CQA (2)	pCQA (6)	CQA (10)
	Low (1)	non-CQA (1)	non-CQA (3)	pCQA (5)

The distribution of the matrix to support the determination of non-CQAs, preliminary/potential CQAs, and CQAs may vary from one organization to another relative to the product and the individual organization's risk tolerance.

The current model of determining CQAs is built on products for well-understood diseases and simple products. This structure is not as well suited for start up ATMPs. Cell and gene therapy products may not follow the typical process of TPP to QTPP to CQA. CQAs may need to be developed before the QTPP is completed.

Round participants discussed attributes that may fall into the ranges of high impact and high uncertainty. These may include, but are not limited to:

- Viability of the cellular donor material
- Characterization of donor material
- Cellular impurities
- Comparability of donor material, specifically for allogeneic products

If a product does not meet an identified CQA, but a risk-benefit analysis determines the product should still be released for patient use, limits for the CQA are maintained. Caution should be used when changing the limits for a CQA based on product data, as a trend of failures may indicate a manufacturing issue or change. Patient experience should also be tracked when a product is released with an out-of-specification CQA.

Patent acceptance criteria may also have CQAs, as many cell and gene therapy products are dependent on the patient.

Use of the risk-based approach for CQAs should be conducted by a team to ensure objective evaluation. Team makeup will vary based on the stage of the product. One or two individuals with manufacturing and scientific process knowledge can assess products in the development stage. Assessment of products at the pivotal stage should have a more comprehensive team, including but not limited to those with knowledge about:

- Manufacturing robustness
- Regulatory requirements and filings
- Clinical data and outcomes
- Toxicity
- Efficacy

Similarly, the formality of the execution and documentation of the assessment process should align with the product stage. The initial assessment conducted in the pre-clinical stage could be documented in a memo or simple report, stating the process used and the outcome. Execution of the process at the pivotal stage should be document in a more formal report, maintained and approved in the validated quality system, ideally using a current effective procedure that details the assessment mythology.

This assessment tool works best when completed early in product stages, the assessment is then updated as the product moves through the development and approval stages. Early execution of the assessment can help determine where the most uncertainty lies and what additional data needs to be collected. Identifying uncertainties can help identify information that is needed to complete the TPP or QTTP if those are not yet completed.

The frequency of assessment execution can vary based on the organization and product development speed. Some organizations perform the assessment only at pivotal for inclusion in the BLA, some execute it once at clinical and again at pivotal. Organizations would be best served with more frequent updates as information is gathered about products. This can help prioritize next steps for data gathering, method development, and validation. How these points for review are determined can be set based on the organization's priorities and product development plans. For example, the review can be based on:

- Clinical stage – executed before/after each stage
- Project/manufacturing Milestone associated with the generation of meaningful data
- Time-based – such as every 3 or 6 months
- Regulatory milestones such as submissions, pre-IND meetings with regulators, or other engagement with regulators
- Business milestones such as following decisions to move forward to the next stage of the product development process.

Outstanding questions:

- How to manage potential CQAs that may not be in the release panel? Cell and gene therapies is the only space in which not all CQAs are in the release panel, as the level of analysis doesn’t allow for inclusion on release.
- When using CQAs how or other parameters for comparability, how is it determined if differences in the outputs are meaningful vs. related to the inherent variability in the process/product