Table 6: Setting and Revision of Specifications - Regulatory Considerations/expectations; New Challenges, Interplay Between Analytical Test Results, Clinical Testing and Regulatory Expectations (Identification of CQAs)

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Scope:

Specifications are defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described (ICHQ6B). According to the guideline, specifications are one part of a total control strategy designed to ensure product quality and consistency. Specifications for drug substance and drug product focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

Specifications are established based on data and are strongly related to product and process understanding. Challenges arise from limited datasets, from adequate choice of data for specification setting, from representativeness of data for specification setting or from inherent (process and analytical) variability of data.

Questions for Discussion:

1. Discussion on setting adequate specifications should cover:
1. Relevance of clinical results for specification setting
   a. How to derive clinical experience
   b. Limited number of batches available
   c. Are the results of clinical batches representative of the product / for specification (analytical and process variability)
   d. How to link specification acceptance criteria to clinical experience
2. Relevance of supporting statistics
   e. At which stage of development are statistics considered useful
   f. How can the use of statistics support the justification of acceptance criteria
3. Relevance of biological activity tests for clinical efficacy
   g. How well does the potency assay mimic clinical efficacy
   h. Which types of tests are considered acceptable for commercial control system (i.e. enzymatic activity test, binding activity, cell-based potency....)
4. Release and shelf life specifications for drug substance and drug product
   i. How to distribute the "budget" between drug substance (release and shelf life) and drug product (release and shelf life)
   j. How to justify different release acceptance criteria compared to end of shelf life criteria

Discussion Notes:

- Special challenge exists when the variability of available clinical supply batches is low. Especially in case where limited (1-3) batches are only available to define the specifications. Variability of clinical batches may not reflect at scale manufacturing variability which could represent to a risk for product supply.

- In this case use prior knowledge on attributes, data from preclinical studies, or available animal models can support the setting of specifications.

- Stability modelling or prediction tools can be used to support the end of shelf life acceptance criteria.

- In general it is important to identify the CQAs for the product and to understand their impact on product performance.

- In an enhanced development identification and assessment of CQA's is following an risk based approach which may include the evaluation of the potential impact of the CQA on potency (as evaluated by the QC potency assay as well as additional functional characterization assays as applicable), pK- and pD-behavior, immunogenicity and safety. This leads to a better understanding of the criticality of the CQA's and informs the testing strategy as well a setting of specifications acceptance criteria. Specification acceptance criteria for high risk CQA's should be based on clinical history whereas acceptance criteria for medium and low impact CQAs may be expanded beyond clinical history with appropriate justification provided.

- In general analytical variability should not be used as the sole reason to expand specifications acceptance criteria if it is reflected in the manufacturing history.

- Most of the attendees use statistical tool to support setting of specification acceptance criteria.

- Ensuring the potency plays and important role in setting specifications and acceptance criteria not only for the potency assay itself but also for those attributes which have an impact on potency as shown during CQA assessment.

- Due to the higher variability of the potency assay applicants often propose broader acceptance criteria for the potency specification. The suitability of a potency specification of 50 to 150 % to control the biological activity of a commercial product was challenged.

- Clear link between potency assay and the expected clinical MoA is important. Additional surrogate assays might be required to mitigate the fact that potency assay used is not adequately reflecting the mode of action.

- It was also reported that after having established a clear correlation between the readout of a surrogate assay and the potency assay, a company could successfully replace the potency assay with a surrogate assay for a smaller protein.

- In dependence of the molecule and the mode of action the glycosylation pattern may need to be controlled as part of the specification.

- The concept of release and shelf life specifications for drug substance and drug product and how to distribute the "budget" between drug substance (release and shelf life and drug product (release and shelf life) was discussed. While a common approach was to start from the drug substance manufacturing history consider DP manufacturing impact and storage there seems to be a trend to start with having the Drug product end of shelf life limit in mind and distributing the budget backwards to the drug substance release limit.