Table 3: Release vs Characterization Tests

Scope

In the design of a control strategy, the first step involves the characterization of Drug Substance and Drug product to identify CQA (Critical Quality Attributes). Some of these CQA are directly controlled through release testing. The considerations to implement a test as part of the release specification include the need to confirm the CQA for each batch (e.g. to control potency, content, identity, or specific impurities). Other considerations are the suitability of an assay as a release test (e.g. assay variability, robustness, and other aspects relating to suitability for QC environment) and the potential impact of process steps on the functional activity based on process characterization.

While for a Marketing authorization, the release tests are required to be validated, in the clinical phase these assays are expected to be suitable and qualified. The results of the clinical batches will have to be taken into account when setting acceptance criteria for the release tests.

In this session, we will discuss the following questions:

- How to design appropriate and practical potency release assays to ensure biological functionality?

- Which criteria should release assays meet?

- Which considerations apply to the design of a suitable assay to be used in clinical studies?

- To what extent would process evaluation and validation be sufficient to allow omitting release assays?

Discussion Notes

We started discussing characterisation studies for potency. One of the characterization methods could be SPR (surface plasmon resonance) and it was mentioned that SPR does show (high) variability but still can be used as release assay if you use a proper reference. This also requires proper historical trending and monitoring variance (as you need to do for any release assay).

We discussed the methods development if you move from preclinical phase to clinical phase. We mentioned that you need a characterisation package and then develop control strategy and define release strategy based on the outcome of the extensive characterization and the identification of CQAs.

We discussed product-related impurities and their testing. If a molecule does have the desired biological activity but is (slightly) different from the active substance it is classified as a product-related substance and not as an impurity. If it does not have that activity it is considered an impurity.

We discussed HCP measuring using MS. Currently there no validated MS based HCP test as approved release assay. Only ELISA's for registered products. MS can be used in the

For clinical studies the analytical methods need to be qualified. During further development the methods need to mature and be validated by Phase 3 clinical study. Continuous monitoring of the methods results should be in place to control for changes in manufacturing process, but also to control method performance. Monitoring of the Ref standard results is suited for the latter. Batch consistency can only be confirmed it the analytical method performs consistently.

Further it was noted that tew peak detection is the most difficult for the method validation and that CQAs for molecules have to be defined in advance, albeit based on the characterization study.