Table 1: Qualification and Validation of MS Methods

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Scope:

With the increasing scope and complexity of biomolecules in the pharmaceutical pipeline, mass spectrometry (MS) based methods have been increasingly proposed for use in Quality Control (QC) laboratories to support drug substance/product release and stability testing. However, MS is still not commonly used in QC testing of therapeutic proteins due to MS method-specific challenges. The general regulatory expectations (e.g., ICH Q2(R1), ICH Q6B, the FDA Guidance on Validation of Chromatographic Methods, the FDA Guidance on Analytical Procedures and Methods Validation for Drugs and Biologics, 21 CFR 211.165(e) and 211.194(a)(2)) and considerations for MS are not different from other QC methods; however, MS-based methods are generally more complex than conventional chromatography-based or electrophoresis-based methods and their qualification and validation may warrant additional consideration. We will discuss these specific challenges (such as HRAM MS system related validation, setting up appropriate system suitability, etc.), drive a conversation around and share our experiences on the qualification and validation of MS methods, especially for therapeutic proteins.

Questions for Discussion:

1. What are the biggest challenges to qualify and validate MS methods?
2. What are the unique challenges to validate MS methods for biotechnology products using HRAM MS systems?
3. What are the drivers for the consideration and implementation of these MS methods in QC?
4. How do you set up system suitability/assay acceptance criteria for these MS methods? What MS parameters should we maintain in QC?
5. What MS platforms do you have in QC? Any potential improvements might be needed?
6. Any challenges during MS methods tech transfer? What is the compliance strategy for MS methods validation?

Discussion Notes:

Discussion during this session focused on the following key points:

- Groups have had issues with cross validating instruments and tech transfer between sites, particularly with low abundance quality attributes, whereas oxidation measurements by LC-UV were consistent.
    - Is there a better way than CV to report low level attributes?

        - CV is always going to be different close to LOQ
        - Reporting non-modified peaks instead of modified peaks would bring lower CVs, but is less representative of the actual attributes
        - Is there a way to justify the higher CV of lower intensity peaks?
        - Is the difference clinically relevant? Does it change efficacy or safety?
        - Is the Limit Testing method suitable for the low abundance quality attributes?

- Most groups have only started to qualify their methods but have not yet attempted full validation.
    - Can instrument vendors help with instrument and method validation?
        - Currently, it seems vendors don't understand what is involved in full scale and end-to-end QC method validation
        - It would be helpful to hold a session or training on what is required when validating an instrument.
    - Qualification should be designed around the limits of the specific system
    - SST and acceptance criteria are not only challenging for MS methods
    - For method validation, can reference FDA perspective paper – note that the risk assessment is critical, and it is important to pay attention to system and molecule
    - NPD validation is also important

- MS Instruments used included:
    - ESI-TOF, QExactive, MALDI, QDa, Vanquish, and Exactive+
    - Caveat – many of these have not yet been validated.

- Software used included:
    - Chromeleon, Empower, Genedata Expressionist
    - Vendor plays critical role in CFR 211 compliance