Table 6: Qualifications and Validations of Mass Spectrometry-Based Methods

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Key Words: Qualification, Validation, Lifecycle Management

Table Scope:

Mass spectrometry (MS) is one of the emerging techniques in the biopharmaceutical industry. As MS-based methods have gradually become powerful analytical approaches for product characterization and process understanding during discovery and development, there is a growing need to introduce these methods into GMP space and/or across lifecycle of a biopharmaceutical product to ensure regulatory success and more importantly, bring medicines to patients. During this process, challenges may arise from different aspects, such as sample preparation, instrumentation, data analysis, and compliance. In this roundtable, we will discuss best practices on method development, qualification, and validation under different laboratory settings across various phases of product discovery, development, and clinical/commercial release.

Discussion Notes:

There was limited discussion regarding PK/PD during the roundtable due to lack of interests/experiences. Common industry trend towards MAM, and there was more emphasis towards modalities other than monoclonal antibodies. In addition, there is a trend to move towards GMP compliance environment

- Method
  - **Qualitative (e.g., analysis of intact proteins or subunits)**
    - For ID only
    - ICH requirements are limited
    - Precision, robustness, method fit-for-purpose are the main parameters to be assessed
    - Typically rely on reference standard only for system suitability
    - Some attendance has experience of qualifying a DAR method for an ADC product, but might not use it in QC environment because it is a native MS method, probably go to RP-LC/MS to simplify. However, DAR should be a quantitative method. Hence, the sponsor generated a series of ADC product with a range of DAR values to demonstrated that the MS method is fit-for-purpose. On the other hand, it is more difficult to establish this method as a method platform due to drastically different linker chemistry
  - **Quantitative (e.g., peptide mapping)**
    - Example: MAM
    - In general, the field is moving towards MAM, either the multi-attribute method (peptide mapping with or without NPD) or multi-attribute monitoring (intact, subunit, and/or peptide mapping)

- Take oxidation quantitation for example, QE plus vs QE may provide different levels, and peptide standards spike-in. Some attendees have proposed normalization of levels among different instruments/vendors but it is a difficult route. Questions around if the regulatory agencies will accept the strategy
- Question came about regarding the strategy for validating an MAM-based method. Does the analyst need to validate every attribute one-by-one?
- Some attendees have experience with adjusting in-source fragmentation on certain instruments. However, it is a hassle as the users need to re-qualify the instrument when a new instrument is implemented. Alternatively, a bridging study is warranted.
- Robustness can be hard to prove for peptide mapping
- Major concern: how to train QC team effectively or do we ask vendors to make instruments and software more user-friendly
- Bottom line: AD and QC groups have different mindsets since QC is trained to not deviate from the written procedures. MAM-based method MUST have some level of flexibility, which need to be captured during the validation process.
- Suggestion: start with a simple, single-attribute related methods, and add redundancy to allow QC team to gain experience and confidence
- Risk of starting a complicated MAM-based method at the beginning of a project: resources can be wasted if the project gets cancelled or product gets re-engineered significantly

- **Instrumentation**
  - How much variability can be accepted between different instruments? Streamlining transferability at the beginning of the process is crucial
    - For example, validate a method on a Q-ToF and then transfer it to an orbitrap will be difficult
    - Even different Q-ToF instruments provide different responses
  - Ideal scenario: different users, different labs, and the capacity of 2 different mass spec instruments during validation process
  - Vendors has been aware of the trend of moving MS into QC and started to make commitment on instrument lifecycle management plan