Table 8: The Momentum of Multi-Attribute Method: Best Practices for Continued Success

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Scope:

The multi-attribute method (MAM) employs LC/MS–peptide mapping and automated data analysis to simultaneously monitor an array of product quality attributes. Analytical technologies may be implemented at various stages throughout a product lifecycle including process development, characterization, quality control, comparability, and biosimilarity. Appropriate implementation requires rigorous evaluation of performance metrics to demonstrate suitability for an intended purpose. MAM has reportedly been accepted for the first time as a replacement assay for conventional electrophoretic and chromatographic methods. This workshop aims to collectively identify the current deployment of MAM, challenges associated method development and/or validation, as well as develop next steps for more consistent implementation of MAM across the industry.

Questions for Discussion:

1. MAM has been implemented successfully as a replacement assay – what is the recipe for success from an industry point of view in terms of replacing conventional release assays with MAM, as well as using MAM in QC? What is the regulatory opinion and expectations for the use of MAM in product development and for batch release/ID/stability?
2. What are good examples of system suitability solutions and performance criteria for MAM? Is an industry-wide system suitability approach advantageous?
3. Is it appropriate to set a relative abundance threshold for monitoring trace-level PQAs – 0.5% has been proposed at numerous conference roundtables? What is acceptable MAM performance and what if CVs for MAM are higher than conventional release/ID/stability assays?
4. For "new peak detection" in MAM, what are acceptable thresholds and fold changes that constitute a new species? What actionable methods are being used to determine appropriate threshold setting to minimize risk associated with false negatives?
5. What are the best practices for incorporating MAM data and information in regulatory submissions? Would MAM allow for immediate simplification of regulatory submissions, or is data from all conventional analytical methods still expected in addition to MAM?

Discussion Notes:

- There were a total of 15 participants from Industry, University/Research and Government Agencies.
- Moderator Jason Rouse (JR) started the discussion with an overview of Multi-Attribute Method (MAM), current deployment of MAM, various challenges, and some potential next steps for evolving the method for increase consistency.
- MAM is an evolution of traditional peptide mapping – combing multiple attributes into a single assay with the goal replacing multiple assays.
- MAM is being attempted in the process development and QC. Most laboratories were currently implementing MAM as an additional rather than replacement assay. One laboratory suggested MAM was being used as a replacement assay in the QC environment.

- The method performance and validation needs are quite different and require attention when used in process development vs QC. The process development side and its utility have been demonstrated to a greater degree. More experience with the method in a QC environment will be valuable.
- New peak detection (NPD) can be challenging
    - Out of specification evaluations can be timely
    - Validation of this data processing approach is challenging (LOD/LOQ)
    - Identifying appropriate threshold settings can be challenging and software dependent
    - The question was posted as to how different vendors, instruments, etc. might be calibrated for response factors, etc.
- Is there a need for a widely accepted standard such as a synthetic peptide mix?
- Internal standard of some sort?
- Attribute Analytics and Specifications
    - Experience has been that specifications are set based on clinical relevance. MS-based LOD/LOQ for deamidation, for example, may be lower than a required clinically relevant specification. MS-based detection will likely have lower site-specific LOD than other assays such that clinically relevant limit specifications will likely be used as opposed to method LOD/LOQ.
    - Validation requirements must be fit-for-purpose. ICHQ2R1 is still a valuable asset in determining metrics for validation based on intended need (e.g. identity, purity, limit assay, etc.)
- System suitability
    - Elements such as mass accuracy, retention times, and reproducibility would be useful.
    - Synthetic peptides and full protein digests have been incorporated to various degrees.
    - Two-tier method control strategy is often preferred
- Instrument qualification standards such as a peptide mix
- True system suitability standard (reference standard protein) that incorporates entire method preparation, data acquisition, and data interpretation