Table 3: Multi-Attribute Method (MAM) in Development vs. MAM in QC

Facilitator: Zhenjiu Liu, Pfizer, Inc.

Scribe: Chen-Chun Chen, *Eli Lilly and Company*

Key Words: Multi-Attribute Method (MAM), Development, QC

Table Scope:

The multi-attribute method (MAM), a technique based on liquid chromatography-mass spectrometry peptide mapping, can provide targeted site-specific quantitation of multiple product quality attributes (PQAs) simultaneously, as well as a purity assessment via new peak detection.

Although MAM has been widely implemented as an analytical procedure for biotherapeutic proteins to support product and process development, challenges remain for implementing the procedure in QC laboratories. This round table will discuss the considerations, challenges, and strategies of the application of the technology in development vs QC. The goal is to improve the implementation of this technology to be more efficient and robust.

Questions for Discussion:

1. What is the general MAM strategy workflow? When is MAM implemented for a project? How are the attributes selected?What instrument, software and report format are used for MAM? What is the frequency of MAM testing in development? Is MAM out-sourced or in-sourced? What type of MAM has been implemented in development and QC? Peptide-map based or intact or subunit MAM? What is the MAM training practice like?

2. What are the challenges of MAM in development? Where are the bottlenecks: Analyst, instrument, software, or data analysis? How often are manual peak integration involved? Is MAM a parallel assay or replacement of traditional assay? Which assays are replaced and at what stage? How is new peak detection utilized in this? Is it fairly automated or does it require frequent investigation of the data by trained mass spectrometrists? What risk assessment and bridging are done for traditional assay replacement? How does the MAM workload and turnaround time compare to conventional assays? How do organizations ensure quality for the MAM assay?

3. What are the challenges of MAM in QC? Are there any differences in instrument, analyst and software compared to development? What are in the considerations for method validation?

Discussion Notes:

1. Discussion on Strategy:

   • Implementation Time: Start planning as soon as possible. It would be great to align the method right after candidate selection, ensuring a streamlined workflow setup.
   • Training: The consensus was that a two-week period is feasible for the personnel training, considering the automatic sample preparation is set up. Extensive discussion was held regarding the QC scientists training, emphasizing the need for making the MS-based method more accessible and acceptable to a larger number of QC scientists.

• Software and Tools: Discussed the diverse range of software and tools currently being used in various settings. GMP compliance software is required for QC.

2. FDA Approval and Industry Acceptance:

   • Discussed the challenges in persuading industry stakeholders to embrace the newer method.
   • Explored the potential benefits of integrating MAM in QC and manufacturing stages, following the utilization of conventional methods during the development stage.

3. Comparative Analysis of MAM:
   • Identified that MAM could potentially replace four conventional methods: rCE-SDS, CEX-HPLC, glycan map, and immunoassay.
   • Encouraged further exploration and substantiation of these findings.

4. Suggestions for Implementing MAM in New Modalities:
   • Offered suggestions for entities interested in incorporating MAM into their laboratories, highlighting the necessity of technical expertise. From evaluating system validation/robustness, MAM implementation also required qualitative and quantitative validation and personnel training. More valuable details can be found in USP chapter <1060>: Mass Spectrometry-Based Multi-Attribute Method for Therapeutic Proteins.

5. Survey and Feedback on the MAM application in Development and QC
   Handouts were distributed to survey to gather more insights into current workflow setups. The survey results showed most labs use MS2 peptide mapping, intact mass or subunit mass analysis for MAM in development, while MS1 peptide mapping and/or intact mass in QC. Hardware and software are mostly from Thermo and Waters. NPD is challenging, not implemented in QC yet.

Participants:
Diverse group (12 people in total) including representatives from:
1. Labs with MAM implementation
2. Labs without MAM implementation
3. CRO, Biopharma Companies
4. Data Scientists
5. Mass Spectrometrists

Conclusion:

• Recognized the potential advantages of the MAM method while acknowledging the barriers to its widespread acceptance, primarily due to technical complexity.
• Underlined the need to streamline the process to facilitate easier adoption in the industry.
• Emphasized the importance of following the FDA's guidelines and suggestions to align with industry trends and regulatory compliance.

Future perspectives:

"No assay is perfect, so there is always room for improvement."

1. Facilitating workshops and training sessions for analytical scientists to foster wider acceptance and implementation of MAM.
2. Engaging with regulatory authorities to garner support and foster a collaborative approach to MAM integration in the industry.