Roundtable Session 1 – Table 7 – MAM in Development and in QC

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Abstract:

Multi-Attribute Method (MAM) represents a paradigm shift in the analytical characterization and quality control of protein therapeutics, leveraging high-resolution mass spectrometry to simultaneously monitor multiple critical quality attributes (CQAs) in a single analysis. By replacing multiple conventional assays with one comprehensive platform, MAM enables more efficient product development, enhanced detection of post-translational modifications, and improved monitoring of product variants throughout the biopharmaceutical lifecycle. This targeted approach provides unprecedented specificity for detecting and quantifying product-related impurities, while offering superior sensitivity compared to traditional methods like HPLC and ELISA.

Despite its transformative potential, MAM implementation faces challenges including significant capital investment, complex data analysis and highly trained personnel requirements, and regulatory uncertainties regarding method validation and acceptance criteria. However, opportunities abound as the biopharmaceutical industry increasingly embraces MAM for its ability to streamline analytical workflows, reduce development timelines, and enhance product understanding. As computational capabilities advance and regulatory frameworks evolve, MAM is positioned to become the cornerstone of next-generation quality control strategies.

Discussion Questions:

1. Questions about the general workflow, sample preparation automation, timing of implementation, attribute selection, and tools used (instruments, software, reporting).
2. Inquiries about testing frequency, in-house vs. outsourced testing, data storage and analysis (local drive or cloud) and training practices.
3. Exploration of bottlenecks in the MAM process (analyst, instrument, software, or data analysis).
4. Questions about MAM as a parallel or replacement assay, which traditional assays it replaces, and at what stages.
5. Inquiries about new peak detection, automation level, risk assessment, and bridging studies.
6. Capacity, comparison of MAM workload and turnaround time to conventional assays.
7. Challenges specific to new modalities (fusion proteins, multi-specifics etc.)
8. Questions about quality assurance for MAM.
9. Differences in instruments, analysts, and software compared to development.
10. Considerations for method validation in QC and regulatory acceptance

Notes:

Attendees included a diverse group from pharma, biotech, software and instrument vendors. MAM experiences ranged from exploratory to those who are already actively using MAM for analytical development.

Discussions on hardware and software used in MAM indicate a trend towards instrumentation providing improved robustness and consistency over improved sensitivity. High-resolution MS is necessary in the development lab space but in the QC lab, instrumentation that is easier for non-MS experts to use are preferred. Thermo and Waters instrumentation, with Chromeleon and Unifi software, respectively, combined with automated sample preparation (via Hamilton or Andrew instruments) were mentioned in MAM workflow implementation.

Discussions of the MAM development process included early identification of sequence liabilities via hotspot characterization to create a MAM library, ongoing discussions between analytics and project team with regards to the quality target product profile (QTPP), references to ICH Q8 (product quality attribute assessment), understanding of critical quality attributes (CQAs) and gradual refinement of the MAM workbook. There is a gap in software's ability to automate data processing without the need for manual intervention from the MS expert. There was an emphasis on MAM needing to reach a point where we can automate as much of the process as possible. Companies are primarily utilizing company cloud servers for data storage as opposed to local drives.

Most attendees are currently using MAM for information only and are monitoring for stability or comparability purposes, but not for release. Some companies are implementing MS in QC using intact level methods, which are simpler to execute and train non MS-experts on compared to the peptide-mapping based MAM. In-house MAM testing is practiced at larger companies, but smaller biotechs tend to out-source since they do not have the necessary instrumentation, trained staff, nor funding.

Although there are various MS methods in the QC space, "New Peak Detection" (NPD) is a feature of MAM that is still under-utilized. If a new peak that is not an attribute is detected, there needs to be a predefined approach on how to identify it and close the investigation under tight timelines. There have been developments in methodically evaluating false positive hits in NPD workflows, but additional work will be needed.

Bottlenecks in the MAM process are primarily attributed to complexity of instrumentation, since majority of users are using high-resolution Orbitrap-based mass spectrometers. The Qda mass detector is the simplest mass analyzer to operate, and is acceptable for QC labs. The more strategically simple the MS, the more approachable it is for non-MS experts in the QC space. Attendees currently working on MAM implementation also mention that the time and amount of training needed for non-MS experts to run MS is extensive and often exceeds the turnover rate in QC (2 – 3 years). There is also a need for a streamlined package or software platform.

Challenges with existing software for MAM data analysis are related to robustness issues. Workflows can be designed so that QC analysts can run the software and transfer results. When training non-MS experts, they can be self-sufficient if the workflow is working well. Issues arise when there is an invalid assay and troubleshooting is needed, since redevelopment and documentation will be needed to ensure the assay can continue on and any investigation can be closed quickly.

Additional discussions on challenges for MAM are related to regulatory agency requirements. MAM was intended to provide additional value by replacing multiple conventional assays. However, there is limited incentive for companies to adopt MAM if data from cheaper, simpler assays are sufficient for drug approval. There is an opportunity for MAM to be implemented in complex modalities, since conventional assays may be less robust for these new molecules. Bridging studies will be very important to help non-MS experts correlate MS data with conventional assay readouts (e.g. visual chromatograms).

For MAM to progress, we can broaden support for MAM beyond MS experts by making MAM more accessible in QC. Strategies include adopting simpler instrumentation, using automation, and streamlining the MAM development and implementation process.