

Roundtable Session 1 - Table 9 - Multi-Attribute Method (MAM) in Development and QC

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Abstract

Multi-attribute method (MAM) most commonly refers to a peptide mapping-based LC-MS method that site-specifically monitors multiple product quality attributes in a single analysis, though intact- and subunit-level MAM have also been developed and applied. Its major appeals include attribute-specific resolution that conventional assays may not provide, the potential to consolidate several release and stability tests into one method, and a non-targeted new peak detection function that can serve as a purity test.

MAM has gained substantial momentum in the biopharmaceutical industry. A large body of MAM-related work has been published, regulators have engaged with MAM through emerging technology pathways, a USP general chapter has been issued, and industry consortia and position papers have articulated shared expectations. Applications now extend well beyond monoclonal antibodies into increasingly complex and emerging modalities.

Yet this momentum has not translated into broad adoption in the industry. Systematic use of MAM through development, and its implementation as a release method on specification in QC laboratories, remains concentrated in a relatively small number of programs and companies due to technical as well as practical challenges.

This roundtable aims to bring together practitioners in the industry to share real experience and to discuss the major challenges in implementing MAM in development and QC in GMP Settings.

Discussion Questions

1. Which therapeutic modalities benefit most from MAM?
2. Where across development activities does MAM add the most value, and where do conventional methods still win?
3. What does it take to keep MAM robust and consistent in a QC lab over the long term?

4. How should new peak detection criteria be set, justified, and acted on when a peak appears?
5. What hinders global regulatory acceptance of MAM as a release method, and what would it take to change that?

Notes

1. Which therapeutic modalities benefit most from MAM?

The discussion began by considering what qualifies as MAM. No single definition was identified as universally accepted. MAM most commonly refers to an LC-MS peptide-mapping method that monitors multiple product quality attributes, but intact-level and subunit-level MAM approaches are also available.

Monoclonal antibodies remain the classical application for MAM. However, participants emphasized that the value of MAM is not necessarily determined by therapeutic modality. The greatest benefit may instead come from situations in which one MAM assay can replace or consolidate several conventional methods, reduce turnaround time, and provide more specific information about product quality attributes.

Therapeutic enzymes were discussed as another relevant application. In this context, MAM can be used to monitor attributes such as glycosylation and methionine oxidation. MAM also has considerable value in characterization, where its ability to provide site-specific information can address ambiguities that may not be resolved by conventional assays. One example involved a peptide containing two methionine residues. A conventional result could indicate that oxidation was present but could not determine which methionine was modified. MS-based analysis could provide the site-specific information needed to distinguish between the two positions.

Vaccines and other products requiring a large number of release tests were also discussed as possible applications. For these products, the ability to consolidate multiple tests could provide substantial operational and economic benefits.

Participants generally agreed that modality alone should not determine whether MAM is valuable. The decision should be driven by the quality attributes that need to be monitored, the limitations of existing methods, and the potential time and cost savings from assay Consolidation.

2. Where across development activities does MAM add the most value, and where do conventional methods still win?

MAM can provide value across the product lifecycle, although participants described different implementation strategies. MAM is already useful for characterization and development activities, while the greatest operational payoff may ultimately come from commercial release testing through the consolidation of several assays.

One strategy discussed was to develop MAM early and transfer it through the entire development process into QC. However, this approach requires considerable work to be frontloaded early in development, when the final critical attributes and program needs may not yet be fully understood.

An alternative strategy is to work backward from the conventional assays that present the greatest challenges. Rather than attempting to replace every assay with MAM, organizations can identify assays with high failure rates, limited specificity, or long turnaround times and evaluate whether MAM offers a more effective solution. This focused approach may also be easier to introduce into QC laboratories where hesitation about adopting MS-based methods remains.

Participants noted an important difference between development and QC perspectives. Development scientists may want to examine as much information as possible, whereas QC laboratories generally need a focused method that provides clear and actionable results. A QC-oriented MAM method may therefore need to limit reporting to predefined, relevant attributes rather than present every feature detectable by MS.

Lower-resolution platforms, including single-quadrupole systems, were discussed as

potentially useful for targeted monitoring of predefined attributes. High-resolution platforms provide greater analytical flexibility and support new peak detection, but simpler instruments may offer advantages in cost, training, installation, maintenance, and method Transfer.

Conventional methods may remain preferable when they are already robust, inexpensive, easily transferred, and well accepted. MAM provides its clearest advantage where it adds site-specific information, replaces several separate assays, reduces testing time, or helps investigate unexpected results from conventional methods.

Economic considerations remain important. Even when an advanced MS platform provides superior analytical performance, its cost and limited availability may prevent laboratories from establishing sufficient capacity for routine release testing.

3. What does it take to keep MAM robust and consistent in a QC lab over the long term?

Long-term robustness requires control of sample preparation, chromatography, instrument performance, software, and laboratory conditions. Participants reported that established MAM methods can remain stable, although changes in instrument behavior, including time-of-flight drift, can create analytical challenges.

Consistent sample preparation is particularly important because preparation-related artifacts may be detected as apparent product changes or new peaks. Incomplete alkylation was discussed as an example of a preparation issue that could generate an unexpected signal. Detailed protocols, appropriate controls, effective analyst training, and clearly defined system-suitability and assay-acceptance criteria are therefore critical.

Participants noted that protocol instructions do not always transfer perfectly between analysts and laboratories. Experienced personnel should be involved in method transfer and co-validation, particularly during initial implementation at a new site.

Automated sample preparation can reduce variability and improve consistency. Although automated systems can also fail or introduce errors, participants generally viewed automation as less variable than repeated manual preparation. Automation may therefore improve both routine attribute monitoring and the reliability of new peak detection.

Laboratory conditions can also affect method performance. Examples included temperature differences that influenced chromatographic resolution and unconventional local practices, such as wrapping columns in aluminum foil. Such factors may not be apparent from the written analytical procedure but can affect comparability between sites.

Instrument lifecycle and vendor support must also be considered. A QC method may remain in use for many years, so organizations need a plan for maintaining or replacing the instrument and software platform without disrupting the validated method. Software must support appropriate audit trails and other requirements for use in a regulated environment.

Participants also identified practical infrastructure considerations, including instrument footprint, electrical requirements, nitrogen supply, and ease of installation. These considerations may favor simpler platforms even when higher-resolution systems offer greater analytical capability.

4. How should new peak detection criteria be set, justified, and acted on when a peak appears?

New peak detection was recognized as one of the most powerful but challenging aspects of MAM. Participants discussed uncertainty around the fundamental question of what should qualify as a new peak and when a newly detected feature should trigger an investigation.

A key challenge is distinguishing meaningful product changes from normal analytical variability, sample-preparation artifacts, and known peaks previously observed during development. If a peak was characterized during development and found not to be problematic, it may not be appropriate to treat its later observation as an entirely new event.

Participants emphasized the need to understand where natural fluctuations occur and to establish a representative baseline before setting new peak detection criteria. Criteria should focus on changes plausibly related to the product rather than analytical noise or predictable method variability.

The choice of material used to establish and challenge new peak detection was also discussed. Peptide standards alone may not represent the full behavior of a product. Stressed monoclonal antibodies and forced-degradation samples may provide more realistic test materials, although care is needed to avoid stress conditions that are so extreme that they no longer represent plausible product changes.

One example involved a new peak observed using a conventional reversed-phase release method. Subsequent MS investigation showed that the peak resulted from a vendor change. Participants noted that using MS from the beginning might have allowed the origin of the peak to be identified more quickly.

New peak detection may be particularly valuable as a purity or surveillance tool because it can reveal unexpected changes before product release. At the same time, an inadequately defined new peak detection workflow can create unnecessary investigations and make MAM difficult to operate in a commercial setting.

Participants emphasized that unexpected peaks should be evaluated in the context of sample-preparation controls, instrument performance, historical product profiles, and prior development knowledge before being classified as new product-related impurities.

The discussion indicated that new peak detection has the potential to be more specific and informative than conventional profile-based methods. However, successful implementation depends on well-justified thresholds, a representative reference dataset, consistent sample preparation, and a predefined procedure for evaluating and acting on detected peaks.

5. What hinders global regulatory acceptance of MAM as a release method, and what would it take to change that?

Participants described examples of MAM being used for release testing of multiple products across many countries. Overall, MAM appears to be increasingly accepted, but familiarity with the technology and specific expectations can vary across regulatory jurisdictions.

Some countries may request additional information, local testing, or criteria that are not routinely used elsewhere. Regulatory acceptance may therefore require adaptation of supporting documentation and continued engagement before approval.

Participants discussed examples in which regulators raised questions during implementation but ultimately accepted the method. Smaller markets may adopt newer analytical approaches later, although the discussion indicated that acceptance is gradually increasing.

The ability to transfer MAM between laboratories is an important part of global implementation. Participants reported that MAM methods can be transferred successfully between sites, particularly when the receiving laboratory is already familiar with the underlying methodology. In some cases, methods were transferred without substantial difficulty.

Challenges remain when laboratories lack experience with MS or when additional support is needed to operate the instrument and interpret the results. Co-validation at the receiving site should involve experienced personnel, and the software must provide the necessary audit trails and regulated workflow support.

Instrument complexity and cost can also limit implementation. High-resolution instruments provide greater mass range and analytical flexibility but may be too expensive to deploy in sufficient numbers across every QC laboratory. Instrument footprint, electrical requirements, gas supplies, maintenance, and ease of installation are also relevant. Simpler instruments may be easier to transfer and operate, although limitations in mass range and

unit resolution may require modified digestion strategies or restrict the attributes that can be monitored.

The discussion suggested that broader acceptance will depend on selecting fit-for-purpose platforms, demonstrating robust interlaboratory performance, establishing clear validation and transfer strategies, and providing regulators with sufficient familiarity and confidence in the methodology. Continued successful use of MAM in commercial programs should further support adoption across regions.

Key Takeaways

- MAM is not limited to a particular therapeutic modality. Its strongest value comes from consolidating multiple assays, providing site-specific information, and reducing testing time.
- MAM can support activities throughout development, but QC implementation requires focused, robust, and actionable reporting. A practical strategy may be to first target conventional assays with significant limitations rather than attempt to replace an entire control strategy.
- Long-term robustness depends on consistent sample preparation, analyst training, appropriate controls, automation where beneficial, defined system-suitability and assay-acceptance criteria, and management of instrument and software lifecycles.
- New peak detection is both a major advantage and a significant implementation challenge. Successful use requires representative baseline data, justified thresholds, control of analytical variability, and a clear process for evaluating unexpected signals.
- Global regulatory acceptance is increasing, but broader adoption will depend on robust interlaboratory performance, successful method transfer, fit-for-purpose instrumentation, and practical compatibility with routine QC environments.