Table 25: The Multi-Attribute Method: Best Practices for Continued Success

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SCOPE:

Multi-attribute method (MAM) has captured the attention of many analytical, process and product development laboratories across the biopharmaceutical industry since its introduction in 2015. MAM employs LC/MS–peptide mapping and automated data analysis to simultaneously monitor an array of product quality attributes (PQAs) in therapeutic proteins, bringing forward real possibility of replacing several conventional electrophoretic and chromatographic assays with MAM for increased testing efficiency and knowledge. Appropriate implementation requires rigorous evaluation of performance metrics to demonstrate suitability for an intended purpose. This roundtable aims to identify the advantages, challenges, and current deployment of MAM, as well as best practices for more consistent implementation of MAM across the industry.

QUESTIONS FOR DISCUSSION:

1. What is the status of implementation of MAM within your company?
2. What are good examples of system suitability solutions and performance criteria for MAM? Is an industry-wide system suitability approach advantageous?
3. Should we restrict MAM to peptide mapping only or should it be extended to subunit/intact level analysis for a better understanding of therapeutics drugs?
4. Which CQAs should be included to monitor in MAM? What is the relative abundance threshold for monitoring CQAs? What is acceptable MAM performance and what if CVs for MAM are higher than conventional release/ID/stability assays?
5. What is the recipe for success in terms of replacing conventional release assays with MAM routinely in QC? What is the regulatory opinion and expectations for the use of MAM in product development and for batch release/ID/stability?
6. 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?
7. For “new peak detection” in MAM, what are acceptable thresholds and fold changes that constitute a new species?

DISCUSSION NOTES:

1. What is the status of implementation of MAM within your company?

Very few companies have implemented MAM in their QC. Most of the companies are either exploring or on the lookout for MAM application.

2. What are good examples of system suitability solutions and performance criteria for MAM? Is an industry-wide system suitability approach advantageous?

System suitability is critical to monitor daily performance of LC-MS system.

Reference standard could be a good solution to the change of mass spec as a result of discontinuation of mass spec from vendor or adding new mass spec to MAM implementation. An industry-wide system suitability approach is advantageous when comparing results from different companies using different type of instrument etc.

USP is preparing big bulk of pre-digested mAb that can potentially be served as industry-wide system suitability. This product will come in with a CoA form that specify level of PTMs that are measured by USP. Including product-specific assay control in each experiment might be beneficial, as it enables assessment of impact of day-to-day variability in sample preparation, LC separation on attribute quantitation.

3. Which CQAs should be included to monitor in MAM? What is the relative abundance threshold for monitoring CQAs? What is acceptable MAM performance and what if CVs for MAM are higher than conventional release/ID/stability assays?

CQA to be monitored in MAM should be a case-by-case scenario. One company observed high variability in abundant N-glycan% using same aliquot of sample but analyzed on two different instruments (same model) whereas other PTMs are comparable. Suggestion from the table was 1) to check the sodium adduct level as that may affect quantitation results; 2) optimize in-source parameters

What is the recipe for success in terms of replacing conventional release assays with MAM routinely in QC? What is the regulatory opinion and expectations for the use of MAM in product development and for batch release/ID/stability?

Sample automation is recommended to reduce sample variability; throughput for MAM in QC environment can be different from development environment. Vendor should emphasize on automation for both sample prep and data analysis.

4. Should we restrict MAM to peptide mapping only or should it be extended to subunit/intact level analysis for a better understanding of therapeutics drugs?

N/A

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?

Few submissions have incorporated MAM data up to date, the best practice will continue to evolve.

6. For “new peak detection” in MAM, what are acceptable thresholds and fold changes that constitute a new species?

Threshold for new peak detection needs to be consistent (ideally across the industry). Vendor needs to improve their software to exclude the list of known attributes from stability, and some vendors have already built this feature in the report.

Off topic 1: What levels of attribute we should monitor?

It is a case-by-case scenario and needs to be based on risk assessment. Risk assessment could rely on performing forced degradation to gain product and process understanding.

Off topic 2: Can we use MAM as an impurity method, with unknown impurity at trace level and resolve the issue through new peak detection in QC?

The unknown impurity needs to be identified, guideline needs to be in place, providing step by step instruction. Needs to build a decision tree to avoid going down the rabbit hole.

Off topic 3: How many companies have considered to apply new peak detection in QC?

3 companies use new peak detection, whereas 2 companies have MAM in QC

Off topic 4: good practice for method qualification/validation such as accuracy assessment?

MAM method qualification/validation needs to follow ICH guideline in general.

For example, to demonstrate accuracy of MAM method for N-glycan quantitation, samples at high or low level of glycan subtype of interest are selected or prepared, and spiking study is performed by mixing the two samples at different ratios to assess method recovery or accuracy. Some of the method qualification/validation work may not need to be repeated every single time, prior knowledge can apply as long as the attribute(s) of interest falls in the established range.