Roundtable Session 1 – Table 3 – Multi-Attribute Method (MAM) in Development vs. MAM in QC

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Abstract:

The Multi-Attribute Method (MAM) has transitioned from its origins in biopharmaceutical development to becoming a valuable tool in Quality Control (QC) across the industry. However, despite its growing adoption, challenges persist when applying MAM downstream.

In MAM, mass spectrometry (MS) techniques monitor product and critical quality attributes (PQAs and CQAs). Targeted quantification focuses on known features, while a non-targeted approach called New Peak Detection (NPD) identifies unexpected signals. Both development and QC implementations rely on robust liquid chromatography (LC) and MS instruments, consistent data processing and reporting.

While flexibility is crucial during development to establish PQAs and CQAs, QC favors robust, user-friendly methodologies. As MAM move downstream, automation becomes increasingly important.

Discussion Questions:

1. Why haven't we seen MAM simply adopted as the de facto QC-standard for biotherapeutics?
2. How important is the curation of PQAs and CQAs to establishing a QC protocol?
3. Where is the most beneficial role for automation in MAM in QC?
4. What is the best opportunity for improvement to robustness and user-friendliness in MAM?
5. Is there a naturally beneficial point at which to involve QA colleagues in transferring MAM from development to QC?
6. How much do processes in QC rely on human controls, rather than automated approaches? What is preventing these being replaced with software-based controls?
7. How do you manager the varied experience levels in lab staff across a MAM process that spans development & QC?
8. Which elements of the MAM in development are most amenable (if at all) to risk assessed processes in QC?

Notes:

In this roundtable, we had attendees ranging from pharma, vendors, and academia. Some attendees were implementing MAM in their QC labs while many wanted to learn more about MAM and how to implement it.

Initially, the first discussion point circled around current challenges. How do we implement mass spec in QC? What validations do we use, and do we have systems for GMP? One point of discussion was on computer system validation such as using Empower. Many mentioned that we have many vendors that have software available; some bugs were found while using them but the interaction with the vendors were positive, after finding the right person to help. Bugs were immediately addressed by vendors and fixed.

There were some concerns about how to bring these softwares to compliance. Especially since the softwares need control system and flexibility to give different access to colleagues with different skills. Many are waiting on guidance.

Another point of discussion was around chromatography separation and how to leverage LC. There is a need to design a strategy around LC method, using multiple standards to validate your method that meets your needs and user controls. Regarding LC method, it is important to understand your needs. There are major challenges, you need to think about LC and mobile phase solvents. Such as: long term usage of the column (use of the column does not have a linear degradation), quality control of the column, storage conditions. A point was made about what is best to use, commercial buffer or making your own buffer. The consensus was it is safer to make your own buffer in case there is supply issues; limit using commercial. A solution to the LC challenges is writing a very detailed SOP (including specifically stating how to condition the column, as that can be extremely important in a QC setting).

A popular topic of discussion was around new peak detection. Many agreed that using MAM was doable especially once you build a database with the PQAs and CQAs, and training colleagues in MS1 data is within reason. But new peak detection can be difficult to employ in QC. There were some strategies that were suggested to implement. First is using DIA since you can get less variable results compared to DDA. Next, is to run replicates to make sure that the peak is real, and that is not a sample preparation artifact. Additionally, all samples must be processed simultaneously together with controls. It is important that scientists have a sense of their method's variation; that variation depends on the method design. It is crucial to understand the variation, in terms of standard deviation and specification needs to be build on that.

Some common themes discussed were about how to handle if your method is failing in one attribute, does the whole method get invalidated. Colleagues that are currently implementing MAM, stated that each attribute need to be handled separately. Another theme was about reproducibility of results. How do you optimize reproducibility? Many mentioned automating

sample prep and they found it to be crucial to using them. Some were mentioning Andrew Alliance or Agilent Assaymap Bravo.

Lastly, we discussed some control strategies.

1. Make sure you have a good system suitability. Need to understand day-to-day variation (depends on system).
2. Use automation to digest sample.
3. Qualify instruments using standards.
4. Choose a system suitability to use as a control for sample prep, and instrument performance.
5. Use a system readiness testing such as Pierce Peptide Mix. Check retention time is reproducible.