

Table 2: Multi-Attribute Method (MAM) in Development vs. MAM in QC

Facilitator: Aude Tartiere, *Genedata, Inc., San Francisco, CA USA*

Scribe: Ying Zhang, *Pfizer, Inc., Andover, MA USA*

Scope:

The Multi-Attribute Method (MAM) has evolved from a process established originally in biopharmaceutical development to a methodology that has been adopted in Quality Control (QC) and is increasingly being implemented across the biopharmaceutical industry. Despite MAM's growing footprint, there remain challenges – analytical, technological, and procedural – for moving MAM into more GMP regulated environment.

MAM implementations in development and QC areas rely heavily on the performance and robustness of the liquid chromatography (LC) and MS instruments, as well as consistent and reproducible data processing and reporting. In development, method flexibility is often needed to efficiently determine and characterize product and critical quality attributes (PQAs and CQAs). However, in a GMP environment, a robust, user-friendly, and unchanging methodology, hardware and software packages are typically required. Furthermore, as MAM implementation moves further into QC, it potentially requires greater capability on automation across the entire process.

Discussion Notes:

1. How can we implement MAM in QC faster? What are the hurdles?
 - Only a small number of companies have put validated MAM assay in QC, hence limited experiences from industry in general
 - Instrumentation and software are no longer the main resistance of moving MAM into QC
 - Cost, capital budget, hiring, potential high failure rate are the main reasons, as well as significant FTEs needed upfront for developing methods/progressing the science
 - Some of the CQAs or PQAs (for process consistency) could be measured by MAM. However, other CQAs or PQAs (example, glycation) could not be monitored reproducibly and reliably by MAM
 - Replacing conventional assays using MAM need to be applied to production lots and the ROI is low to management teams
 - Possible to perform MAM in CMO
2. None of the attendees have experience in validating MAM in their own organizations. Very few publications indicate success in validating peptide MAM
3. Is NPD absolutely needed for MAM?
 - Extensive heightened characterization is typically carried out during process development, little benefit can be achieved by NPD using MAM
 - NPD stays as a discovery practice
 - However, if MAM is used as a purity assay, then NPD is needed

4. Why is implementation of NPD in QC difficult?

- Software is not readily available
- False positives require expertise and time/resources to examine. If NPD is implemented in QC, false positives could delay batch release
- Main source for false positives observed: sample prep related, metal adduct, spurious peaks
- NPD round robin study publication just demonstrated that NPD is not easy to perform

5. MAM evolutions and success

- Half of the MAM consortium talks relate to sample preparation optimization/development, and it is highly recommended to include automated sample preparation procedures in a GMP environment
- Sample prep-> software (monitoring)-> software NPD
- One of the attendees has successfully included MS1-only high throughput MAM method in the analytics lab. It is a simple method to run and integrating the MS1 peaks is almost the same practice as integrating peaks in chromatograms, which is routine work for non-MS experts
- Some CQAs that linked to MOA could not be detected by conventional assay and MAM could be significantly helpful

6. How to minimize the cost of MAM in QC?

- MAM is cost efficient only when it could replace other assays and save FTE/resources
- Need replicated instrumentation at every release site
- Unfortunately, at this point, MAM has been mainly utilized as a testing strategy for product development. Using MAM to replace the majority of conventional assays has only been theoretical and paper practices

7. Existing knowledge

- Multiple companies have publications and even less companies included MAM data in their regulatory filings
- Early stage mAb programs could leverage existing knowledge of IgGs except CDRs

8. Next steps

- When tech transfer to a different site, could a different instrument (from the same vendor or a different vendor) be utilized? Currently no. Need to have the same instrument from the same vendor in all sites. ZZ's 2020 mAb paper demonstrated a great statistical approach to potentially allow comparison of data between different instrumentation. However, QC lab could not implement this approach. Hence, lifecycle of the instruments is one of the concerns
- Tech transfer requires high level automation capability and straightforward workflow