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

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Scope:

While the multi-attribute method (MAM), most commonly an LC-MS peptide mapping method for the simultaneous quantitation of product quality attributes, is a powerful analytical technique, organizations have drastically different approaches for implementing the technology. On the extremes, several organizations have implemented the technology for product development in a characterization setting, while other organizations are developing the method as a validated method in QC. While both approaches add value, we aim to discuss rationales for implementation strategies, current limitations in the technology, and key objectives needed to advance the technology – whether for development or release. In addition to the discussion topics presented below, we encourage attendees to bring forward their own topics of interest focused on MAM.

Questions for Discussion:

1. What is the primary strategy for implementing MAM in an organization? What are roadmaps for determining if MAM should be in development vs. QC? Consideration points:
   -What components are included in MAM?
   -What sort of samples are being tested by MAM?
   -How many and what attributes are being monitored?
   -Is MAM being done in addition to / instead of alternate tests?
   What would trigger the change from a development strategy to a QC strategy?
2. What are the largest challenges to implementing MAM in development and how do those compare to implementing MAM in QC? Consideration points:
   -Available colleagues and resources/cost?
   -Ease of implementation (system/software)?
   -System performance / false positives?
   -Access to data?
   -Method transfer and method quality assessments across groups/sites?
3. What is the strategy for determining which attributes to monitor? Does this vary in development vs. QC? Consideration points:
   -Relative abundance of attributes?
   -Availability of other methods?
   -CQA vs PQA?
   -Criticality of new peak detection?

4. Where should the community focus to improve MAM? Once addressed, how should MAM be implemented in the future?

Discussion Notes:

1. What is the primary strategy for implementing MAM in an organization? What are the roadmaps for determining if MAM should fit in a developmental space vs. in the QC labs?

   Consideration points:

   - What components are included in MAM?
   - What sort of samples are being tested by MAM?
   - How many and what attributes are being monitored?
   - Is MAM being done in addition to / instead of alternate tests?
   - What would trigger the change from a development strategy to a QC strategy?

   QC and GMP - roadblocks?

   - software is important

   -collaboration with MS vendors and MS helps , starts in development and move into manufacturing , back when Amgen started not as many tools and no standard at FDA but not is easier but still take time to develop SOPs

   - Currently more software offerings

   - MAM is complementary to standard released assays ,

   - Release stability testing MS in QC requires load of work with agencies such as FDA initially

   - Raw data , would that be considered as part of the submission? FDA has MS and software capabilities however for submissions it might be easier to submit reports rather than raw data.

2. What are the largest challenges in implementing MAM in the development space? How do those challenges compare to the issues faced in the QC labs?

   Consideration points:

   - Available colleagues and resources/cost?
   - Ease of implementation (system/software)?
   - System performance / false positives?
   - Access to data?
   - Method transfer and method quality assessments across groups/sites?

- Software

-User experience

-Expense (in-country testing - different budget)

-Difficult to change minds internally

-MS is complicated - if that fails in QC ? also happen with other technologies in QC

-Having system suitability is fundamental

-Education across departments/units, alternative to keepQC in development but different department

3. What is the strategy for determining what attributes are being monitored? How does this vary based on MAM in development vs. QC?

<u>Consideration points:</u>

- Relative abundance of attributes?
- Availability of other methods?
- CQA vs PQA?
- Criticality of new peak detection?

-What would be the trigger to move MS to QC?

- CQA that is well controlled

-QC (specific) vs Characterization (all of the above) workflows

-QC very focused, no extra data as more things can go wrong

-Timeline differences, validation will increase per CQA

- MAM can help with troubleshooting during stability studies

- MAM concept that can be applied to a wide variety of modalities

- what about the threshold? low or only abundance

-1%

-below 0.5%

-TBD in general start with a list and reduce over the time , part of a group of experts decision

-Where do we stand with NPD?

-traditionally UV, do we need to move away from that ?

-other assays like CD could also show new peaks

-MS advantage over UV is to have a mass and intensity

-Software is reliable but takes time to have it well defined

-Fix a set of parameters - well defined SOW

-In QC with user training , automation, robust methods minimizes the stigma of 'its complicated'

-MS sensitivity might not require as high sensitivity in QC

-Software

-upgrades are not possible in QC due to SOP

4. What are the areas where the community should focus most on for MAM? Assuming we can address these items – where should MAM be applied in the future?

-Instrument robustness

-Columns , LC related imprecision