Table 31: Multi-attribute Methods (MAM) Implementation Status in Biotherapeutics

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Scope:

Multi-attribute methods, traditionally referring to LC-MS peptide mapping, simultaneously monitor multiple critical quality attributes (CQAs) in a single method run with high specificity and resolution. The method has been well-established in non-GMP environment to characterize biotherapeutics during early discovery and development. Recently, many pharmaceutical companies have been working to bring MAM as a QC tool for potential lot release and stability studies during manufacturing according to GMP. The method also has the potential to replace multiple conventional HPLC or CE-based QC methods. However, the path is not easy. Multiple challenges exist due to the complexity of the method (data collection and data analysis) and lack of regulatory experiences.

MAM may also be applicable to new approaches, for example, monitoring DNA impurities (e.g., hcDNA, plasmid DNA) in viral vector drug product. MAM enables the ability to monitor several attributes with a single method, increasing efficiency, dramatically decreasing cost, minimizing drug product volume required for testing, and collapsing the QC footprint into a single technology.

This roundtable focuses on the technical and strategic considerations when implementing MAM as an addition or replacement to conventional QC methods for biotherapeutics.

Discussion Topics:

1. Method development for targeted attribute analysis and new peak detection;
    a. What are the biggest challenges during method development?
    b. What product formats are using MAM? E.g., mABs, ADCs or new modalities?
    c. What phases of products are employing MAMs? Any plan for commercial implementation?
2. Validation strategy for different phases of products;
    a. How to leverage platform information for phase-appropriate validation?
3. Regulatory considerations to file MAM as an addition or replacement method for conventional methods;
    a. How to bridge MAM with conventional methods;
    b. How to set up appropriate specifications for targeted analysis and new peak detection;
4. New MAM applications in the gene therapy field, e.g., MAM for monitoring DNA impurities in LVV drug products.

Discussion Notes:

1) Biggest challenges with MAM as a QC method and experience of roundtable participants in using MAM?
    a) Used in development for peptide mapping for many years and starting to move into release and stability studies in QC.
    b) Associated challenges moving into commercial space.

i) Performance
ii) Expectations for detection and capabilities of methodologies
iii) Justification to use of MAM over conventional methods
iv) Setting acceptance criteria
v) Moving into the QC space
vi) Appropriate software

c) Correlation with traditional methods
   i) Doesn't necessarily correlate with methods it is replacing, so a good scientific rationale is needed.
d) If using MAM for purity something might be missed; also a concern of regulators
e) Something unexpected may appear.
   i) How can new peak detection be controlled?
f) Validation for these types of methods can be difficult.
g) Barrier is having right software, robustness, data integrity, and ease of use.
h) For clinical work data integrity can be challenging; Need something where you "just push a button" – some attendees have had success.
i) Key challenges with methods for new peak detection being sensitive enough to detect what you want but cannot detect false positives. Need to find the balance.

2) How are attendees using MAM?
   a) Use as an additional method in the clinical setting.
   b) Most still only using MAM for identity because this is simpler to implement for QC but using for purity is an interest.

3) Validation strategy for different stages of product
   a) Many use it as an additional method; some companies have already implemented it to replace other methods starting from Ph1.
   b) For Ph1 often do not have acceptance criteria for release and specifications are set for Ph2 based on knowledge gained in Ph1

4) How to set up appropriate specifications for targeted analysis and new peak detection MAM
   a) Can validate with proof-of-concept studies and then new companies demonstrate new peak detection and not comfortable with validation and production.
   b) New peak detection can be most challenging aspect of adopting MAM in QC

5) What are hurdles to adopting MAM in QC?
   a) It requires high skill level.
   b) Comment from QC laboratory leader in roundtable is that they only implement MAM in QC if they feel they get enough value from it.
   c) Identity methods that use MAM are long, take high engagement and may not add high additional value compared to existing peptide mapping assay for identity testing.
   d) Sample prep, software, data integrity can provide challenges in QC.
   e) Clinical versus commercial QC differences – more likely to be adopted with clinical QC due to much higher requirement from commercial QC.
   f) Purity however may be a better application in terms of value in QC.

6) Has anyone replaced traditional methods successfully with MAM method?
    a) Yes, in clinic setting (Janssen R &D paper) for release and stability testing of a bispecific antibody.
        i) In this case sample prep and data interpretation was less complex
    b) Amgen uses MAM and replaced 3 assays for 5 attributes (published data)
    c) Examples of released products using MAM, but still few.
    d) Can use released product to do cross validation of MAM.
    e) Phase 2 ETT guidance – keep both methods in parallel until method is released, but problem is that often there are not many lots to bridge methods.
        i) At least 3 lots to replace with bridging.
    f) Can you drop specs and go with MAM – yes that is the idea, but companies are hesitant to do this work.

7) How about starting with new programs? Starting FIH with only MAM. This is a possibility if it is fit-for-purpose.
    a) Can be hard to switch if you don't start with it.
    b) Chose characterization experiences established during early development to begin with.
    c) MAM could offer speed and specificity that you don't get with traditional methods.
    d) Only use for ID, but what about a tiered approach - with new formulations there is advantages to starting with MAM.
    e) Data analysis is challenging.

8) Use often for stability and formulation.
    a) Good presentation on what is validatable for measurement of oxidation and deamination.
        i) 5% modification was easy to validate.
        ii) <0.5% could not be reliable to validate the attribute.

9) NIST efforts – no good standards for MAM and difficult to set limits.

10) Can you make a case that changes at one site could be surrogate for changes at another site?
    a) May be good enough platform methods already – how much value does MAM bring.
    b) Establish surrogate attribute and then use surrogate to measure target attribute if MOA is the same - need to show direct correlation to surrogate.
    c) Can also bundle changes measured, but really need to show clear relationship between targets and surrogates.
    d) Setting up the specification on surrogates could be challenging.

11) How do you demonstrate that you aren't missing anything?
    a) Need to demonstrate adequate coverage with orthogonal method. Use spiked-in sample to establish confidence level.

12) Discussed using CDMO's for MAM, but not considered cost-effective.

13) How do people use automation in MAM

a) Automated sample prep – not widely implemented but some keys to use.
    i) Use for enzymatic digestion, but software, and picking the right automation solution is key.
    ii) Potential to remove human variability in QC.
b) Takes time to implement because people run things in parallel for years.

14) New peak detection at early stage do not have relevant stress panels, so need sensitivity, but after process validation, could be perfect model system for new peak detection.
    i) Can share new peaks with relevant stress models to identify new peaks in reference standard more easily.
    ii) New peak compared with reference std.
        (a) NIST mab - degradation pathways are known, increased confidence.