European Federation of Pharmaceutical Industries and Associations

Regulatory considerations for the application of Multi Attribute Methods by Mass Spectrometry for QC release and stability testing of Biopharmaceuticals

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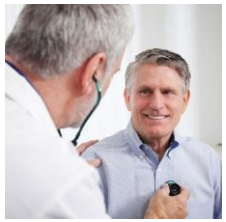
on behalf of EFPIA






CASSS CMC Strategy Forum Europe

Brugge, October 18, 2022

OUTLINE

- Background on the EFPIA MAM as QC tool initiative
- Technical aspects
- Regulatory pathways and elements – what is the industry preferred approach?
- Challenges related to New Peak Detection
- Conclusion

BACKGROUND

EFPIA MAM as QC tool working group

- Team of 25 representatives from 17 pharmaceutical companies founded under EFPIA MQEG in March 2021.
- The primary objective of this working group is:

> To promote **global acceptance** of MAM addressing **multiple product quality attributes** in a **single method for QC** release and stability, **replacing conventional QC methods**.

- So far this has resulted in:
  - A presentation at CASSS CMC strategy forum EU in 2021.
  - A presentation at EMA BWP Interested Parties meeting in May 2022
  - A **regulatory position paper** (available on the EFPIA website): "Use of Multi Attribute Method by mass spectrometry as a QC release and stability tool for biopharmaceuticals – Regulatory Considerations".

https://www.efpia.eu/media/676706/efpia-regulatory-position-paper_mam-as-qc-tool_final.pdf

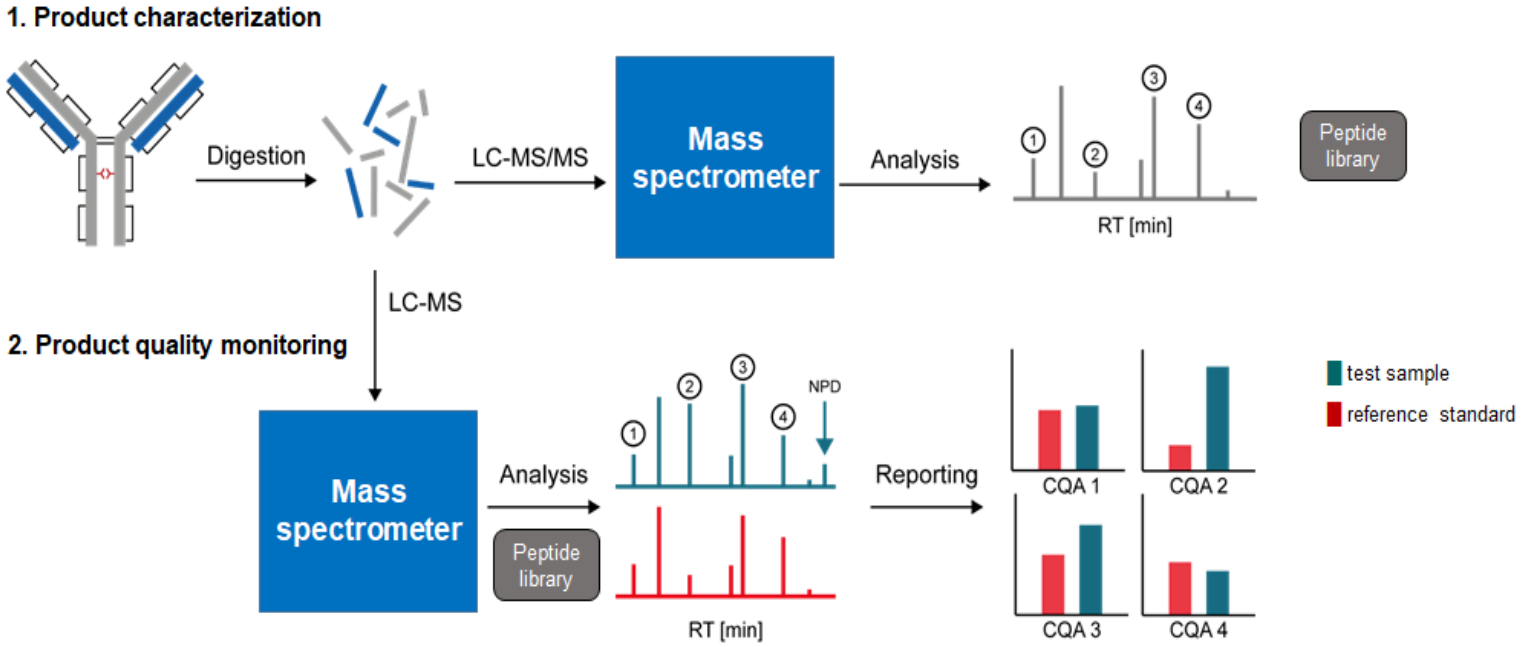
BACKGROUND

Why MAM as QC tool?

- Using **multiple conventional methods for release and stability** testing is **time- and instrument-consuming**.
- The **conventional** HPLC /CE based **methods** address categories of product-related variants and **do not always allow easy separation of individual product quality attributes** that have relevance to safety and efficacy (CQAs).
- **MAM by mass spectrometry** have the capability to **quantify multiple product quality attributes** with **high specificity** within a **single method** and in a **highly automated** fashion.
- The technology is well-advanced with instruments and software solutions being available from several vendors allowing routine use in a GMP environment.
- In-scope:
  - MAM by LC-MS peptide mapping
  - Therapeutic proteins

CQA = critical quality attribute

Prototypical MAM by LC-MS peptide mapping workflow



adapted from Rogers *et al*., AAPS J. (2018), **20**, 7.

- The LC-MS peptide mapping workflow can be used in two ways:
  - Targeted approach - only a set of specific CQAs is evaluated by targeting specific m/z values corresponding to the modified and to the non-modified peptides (multi-attribute monitoring[1]). NPD is out of scope.
  - Non-targeted approach - multiple quality attributes are evaluated as well as any new peaks. NPD is in scope.

[1] Evans *et al*., Anal.Chem (2021), 93, 9166

LC-MS = Liquid Chromatography-Mass Spectrometry; CQA = Critical Quality Attribute NPD = New Peak Detection

TECHNICAL ASPECTS

Which conventional methods can be replaced by MAM?

- MAM by LC-MS peptide mapping has the proven[1] capability to replace multiple conventional HPLC / CE based QC methods.

Quality Attribute	Conventional method
Charge variants	IEX, cIEF, CZE
Fragments	rCE-SDS*
Glycans	2-AB HILIC, HPAEC PAD
Identity	peptide mapping LC-UV, ELISA (in combination with IEX or cIEF)
Oxidation	RPC, HIC

*SEC or nrCE-SDS could also be used for clip monitoring

Methods used to monitor process-related impurities (e.g. Host Cell Proteins) are not in the scope of the position paper

- It is NOT the intention to replace all QC assays with MAM

Quality Attribute that CANNOT be monitored by MAM
High Molecular Weight species (dimers, oligomers, aggregates)
Incompletely assembled antibody species
Higher Order Structure
Biological activity
Microbiological properties

[1] see e.g. Rogers *et al.*, 2015; Song *et al.*, 2021; Guan *et al.*, 2022

REGULATORY PATHWAYS & ELEMENTS

Is introduction of MAM different from other methods?

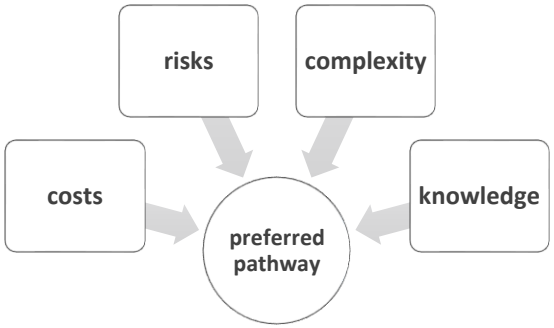
- No, it is not.
- There are, in principle no identified regulatory hurdles to file MAM for QC release & stability testing.
- **Regional regulatory differences** could be a **challenge** (maintenance of two sets of methods globally).
- Implementation of MAM is supported by established and draft guidelines (e.g, ICH Q2, ICH Q6B, ICH Q14) and will facilitate advanced control strategies in line with ICH Q8.
- As for any other methods, regulatory agencies expect:
  - A comprehensive understanding of the analytical procedure
  - Adherence to predefined criteria for performance characteristics according to ICHQ14 (specificity/selectivity, accuracy and precision over the reportable range)
  - And in case of change from conventional method to MAM:
    - A thorough understanding of how the performance characteristics of the different methods compare for any CQA
    - A thorough understanding of how the data obtained in earlier phases of development connect with the new data.

CQA = critical quality attribute

How to introduce MAM as a QC tool?

- Possible scenarios:
  - **Scenario 1:** introduction of MAM during product development replacing conventional methods
  - **Scenario 2:** introduction of MAM as a LCM activity in the commercial phase replacing conventional methods.
  - **Scenario 3:** introduction of MAM prior to FIH studies instead of conventional methods – **INDUSTRY PREFERRED**

- Required elements depends on the scenario chosen



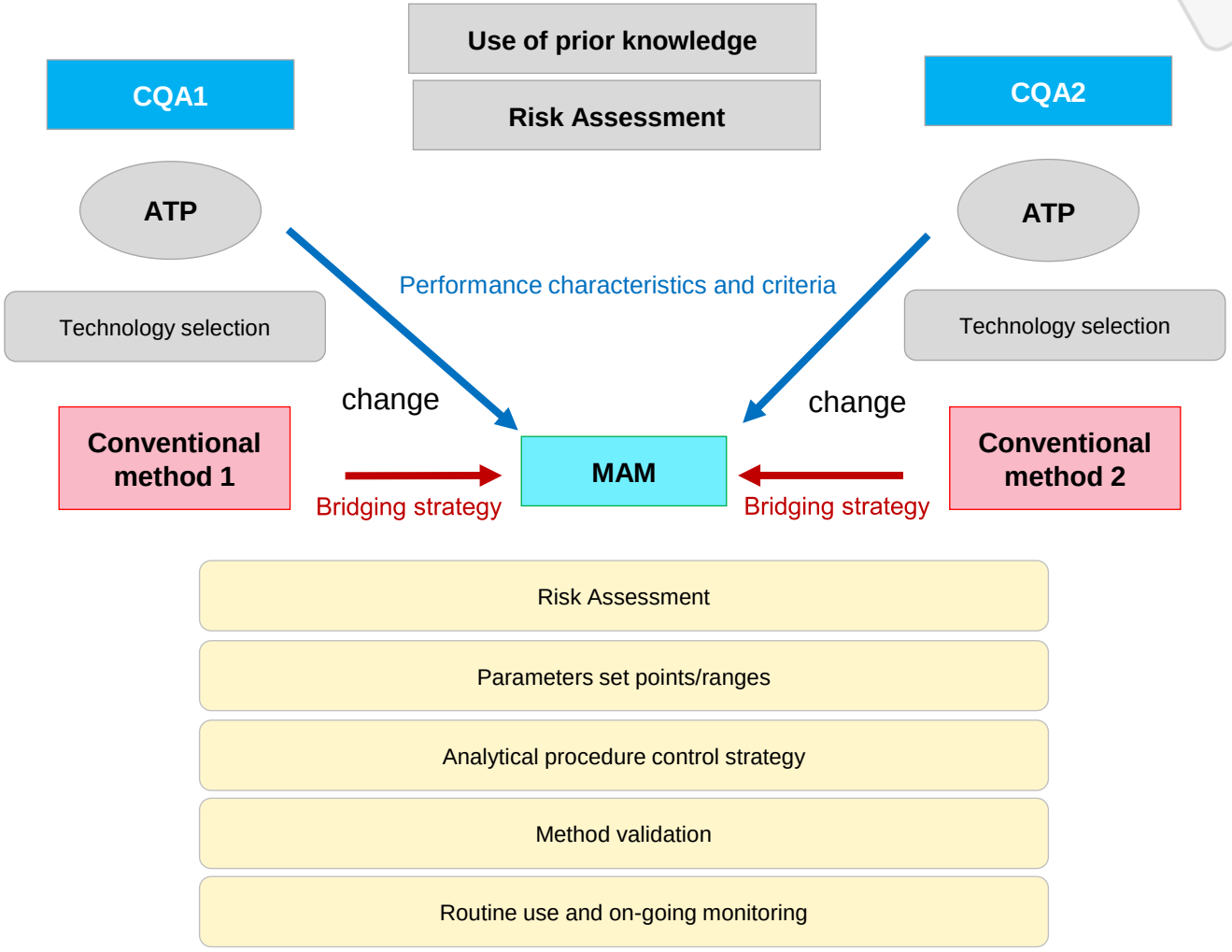
Introduction of MAM

	Risk assessment	Method bridging	Method validation	Specification setting	NPD*
Scenario 1 – During development – replace conventional methods, where relevant	yes	yes	yes	yes	yes
Scenario 2 – Lifecycle management – replace conventional methods, where relevant	yes	yes	yes	yes	yes
Scenario 3 – Prior to FIH studies – instead of conventional methods, where relevant	yes	no	yes	yes	yes

*NPD : only relevant for non-targeted approach

NPD = New Peak Detection

MAM would benefit from use of ICHQ14 enhanced approach principles



Bridging with conventional methods – scenarios 1 & 2

- Introduction of MAM during product development or during LCM will require bridging exercise to demonstrate that **MAM is at least equivalent or superior to the conventional method** for the intended purpose (measurement of CQA).
- MAM and the conventional method may not generate equivalent data, which is acceptable but requires thorough understanding of the root cause.
- MAM has, **by design**, advantages over conventional methods: **improved specificity** via measurement at a defined location of the protein (individual site-specific CQAs).
- Extent of the data package for method comparison will depend on the scope of the method and the phase of development. It should be supported by a **risk assessment**.
- Relevant samples need to be considered in the method comparison package including clinical/commercial batches to support specification setting.
- Stability data should demonstrate **similar trends and rate of change** of the CQA**.**

CQA = critical quality attribute

Method qualification/validation – scenarios 1, 2 & 3

- Phase-appropriate validation of MAM follows the same principles as any physico-chemical method for the defined CQAs.
- **Certain quality attributes** may be used **as surrogates** depending on their behavior (e.g., ionization efficiency) or their relevance for a degradation pathway (e.g., Fc-methionine oxidation).
- Grouping of certain attributes is possible e.g., sum of all Fc-methionine oxidized species.
- **Prior knowledge** from similar molecules (e.g., subclass of mAb) can be used (ICHQ14).

CQA = critical quality attribute

Specification setting – scenarios 1, 2 & 3

- Setting specification for MAM is not different from any other method.
- Despite MAM measures multiple quality attributes, specification is only for CQAs.
- For early phase, specification could be based on early indicator peptides representative of a certain product QA class.
- For late stage, one key benefit of MAM : **data** previously acquired can be **retrospectively reassessed** for newly identified CQAs

CQA = critical quality attribute, QA = quality attribute

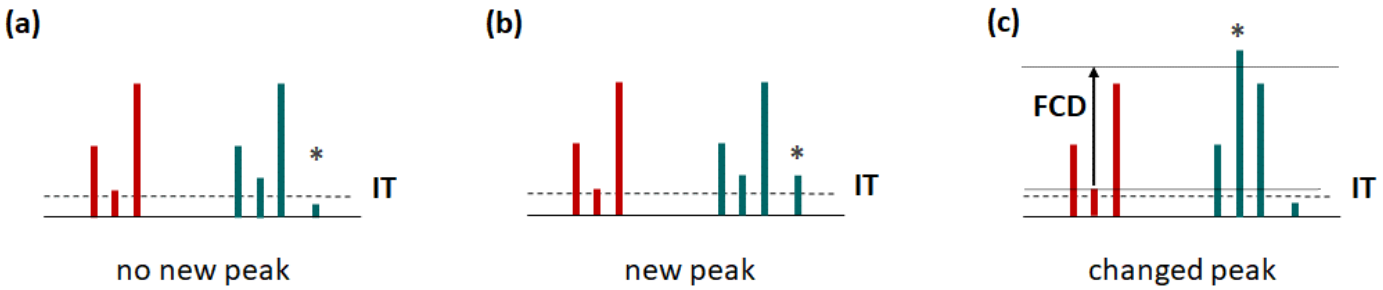
Industry preferred scenario – introduction of MAM prior to FIH instead of conventional methods (scenario 3)

- Method development
  - Facilitated by **prior knowledge** (e.g., platform method) and inherent selectivity of LC-MS
  - Construction of **MAM peptide library** from early development.
  - Perform **risk assessment** to justify use of MAM for the monitoring of all relevant CQAs within overall control strategy
  - Establish & refine NPD parameters during product development
- Method validation
  - Generic/platform validation & robustness data supporting early development stages
  - **Full validation of targeted CQA monitoring** according to ICHQ2 prior to MAA
  - **Validation of NPD parameters prior to MAA**
- Specification setting for CQA
  - As for any other methods i.e., based on clinical & preclinical experience, on method performance characteristics (ATP), on process capability and on stability profile
- No bridging required

CQA = critical quality attribute; NPD = New Peak Detection; MAA = Market Authorisation Application

NEW PEAK DETECTION

Challenges for application in QC environment



Scope = for non-targeted approaches

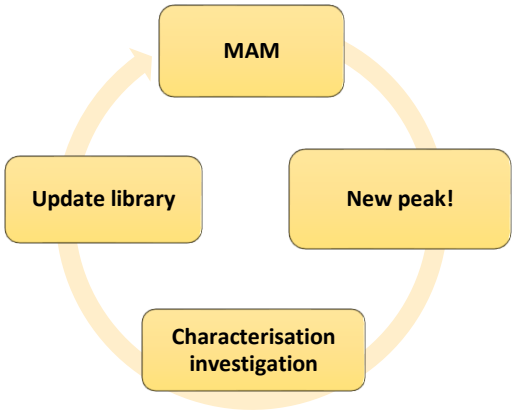
- It is key to **define smartly** the **NPD parameters**, Intensity Threshold (IT) and Fold-Change Detection Threshold (FCD) **to minimize false positives and false negatives**. Mass & retention time tolerance windows are other key parameters to consider.
- There is **limited experience** within industry on validation of NPD parameters.
- **NPD parameters validation** will be **made once the peptide library is considered comprehensive** (at time of PPQ batches).
- Specifications for NPD would be **phase-appropriate** to mitigate the risk of inappropriate batch disposition and risk to delay batch supply to patients.

NPD = New Peak Detection; PPQ = Process Performance Qualification

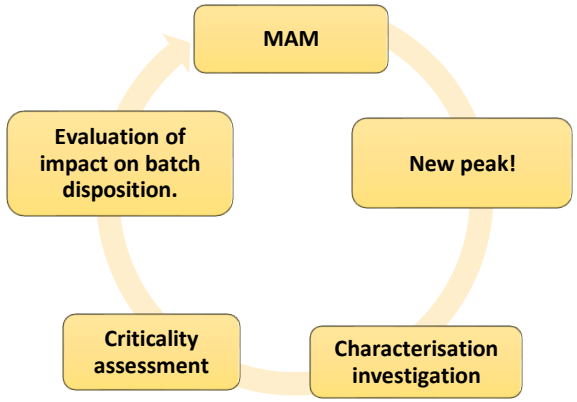
NEW PEAK DETECTION

Challenges for application in QC environment

- During development – the **peptide library** is **being built** and **enriched** with new peaks detected especially during accelerated/stressed stability studies & forced degraded studies



- After PPQ & during LCM – the **peptide library** is expected to be **fully comprehensive**.
  NPD parameter validation is available (at the time of PPQ).



NPD = New Peak Detection; PPQ = Process Performance Qualification; LCM = Life Cycle Management

CONCLUSION

MAM is a mature technology ready for implementation

- **MAM is recognized as a valuable developing technology and there is no regulatory impediment** to introducing it in QC (GMP).
- It is not expected to replace all conventional methods by MAM (e.g. bioassays).
- MAM introduction (development, validation, specification setting, bridging) is **not different from any other method** and **would benefit from** use of **ICHQ14 concepts.**
- **MAM** brings several **advantages compared to conventional** analytical methods,
  - unique ability to assess individual site-specific CQAs.
  - derisking of accelerated development by retrospective assessment of newly identified CQAs.
- Introduction of MAM in a regulatory filing for QC applications may require significant initial resource by the Applicant but it offers advantages on the longer run.
- The **preferred Industry approach** is to introduce **MAM prior to FIH instead of conventional methods**.
- Absence of regulatory harmonization is a challenge and could potentially lead to maintenance of two sets of methods globally as well as issues with in-country testing.

CQA = Critical Quality Attribute; FIH = First in Human

EFPIA REGULATORY POSITION PAPER

https://www.efpia.eu/media/676706/efpia-regulatory-position-paper_mam-as-qc-tool_final.pdf

Use of Multi Attribute Method by mass spectrometry as a QC release and stability tool for biopharmaceuticals – Regulatory Considerations

Author: EFPIA **Date:** 05/10/2022

Version: final

1 Introduction and background

Biopharmaceuticals require extensive quality control (QC) testing for batch release and during stability monitoring using multiple high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) based purity/impurity assays. Considering the time needed to a) develop, validate, and transfer this set of analytical methods and b) to execute them on all release and stability samples, this QC testing approach employing multiple analytical method is not supportive of accelerated product development. Moreover, the aforementioned analytical methods address categories of product-related variants (e.g., oxidized variants, charge variants) but do not always allow easy separation of individual product quality attributes (PQA) that have relevance to safety and efficacy, as these methods lack the specificity that allows location of potential chemical changes on the polypeptide backbone. Therefore, many applied purity/impurity test criteria are based on the method rather than on the specific molecular quality attribute.

Acknowledgement
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Thank you!