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Considerations for the Application of Multi-Attribute-Method (MAM) by Mass Spectrometry for QC Release and Stability Testing of Biopharmaceuticals

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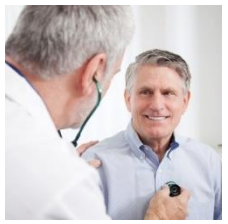


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OUTLINE

Considerations for the Application of Multi-Attribute-Method (MAM) by Mass Spectrometry for QC Release and Stability Testing of Biopharmaceuticals

- *EFPIA topic team "MAM as QC tool"*
- *MAM by LC-MS peptide mapping as QC tool*
- *Benefits and challenges*
- *Regulatory pathways*
- *Supporting elements*

Why this initiative?

- *Multi-attribute-method (MAM) by mass spectrometry is well established across the industry in non-GMP environments for product and process characterization purposes*
- *The majority of pharmaceutical companies and many instrument providers are currently working on the extension of MAM to QC labs*
- *The use of MAM for lot release and stability testing according to GMP is not well established across the industry due to:*
  - ongoing evolution and alignment of best practices
  - complexity of method (sample preparation, instrumentation, data analysis)
  - limited experience with filing of MAM as a QC tool
  - regulatory unfamiliarity with MAM as QC tool

Mission and vision

- *Team of 25 representatives from 17 pharmaceutical companies*
- *Founded in March 2021 under the umbrella of EFPIA MQEG [1] to promote*

Global acceptance
of MAM addressing multiple product quality attributes in a single method for QC release and stability, replacing conventional QC methods (e.g. purity / identity)

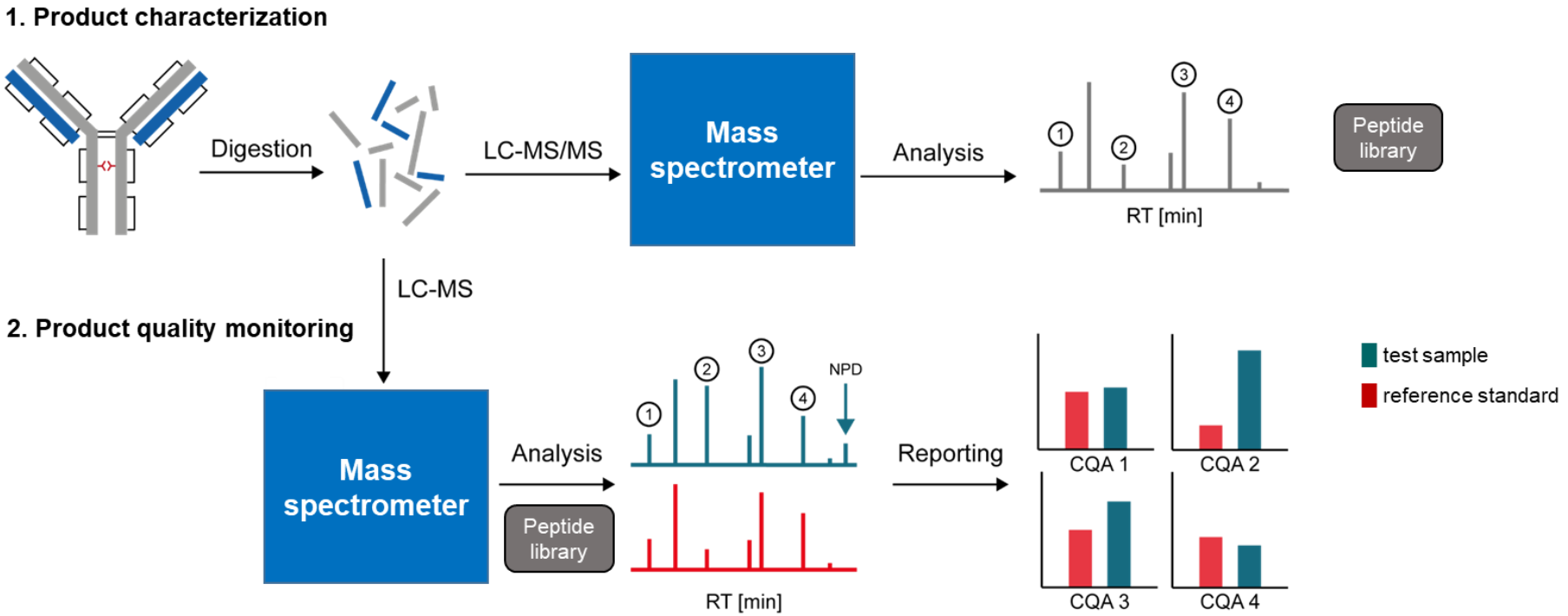
→ Share and align on best practices across the industry

→ Promote & encourage regulatory filing of MAM for lot release and stability testing under GMP

→ Reduce regulatory unfamiliarity and obtain acceptance by health authorities

EFPIA = European Federation of Pharmaceutical Industries and Associations, MQEG = Manufacturing and Quality Expert Group

Prototypical MAM by LC-MS peptide mapping workflow



- *Targeted monitoring of critical quality attributes + 'New Peak Detection' (NPD) are required to establish MAM by LC-MS peptide mapping as purity assay in a QC environment.*

adapted from Rogers *et al.*, 2018

TECHNICAL CONTEXT

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

Quality Attribute	Conventional method	Replacement method
Charge variants	IEX, cIEF, CZE	MAM by LC-MS peptide mapping
Fragments	rCE-SDS	
Glycans	2-AB HILIC, HPAEC PAD	
Oxidation	RPC, HIC, peptide mapping LC-UV	
Identity	ELISA, peptide mapping LC-UV	

- *The technology is well-advanced with instruments and software solutions being developed from several vendors allowing routine use in a GMP environment.*
- *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.*

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

EXPECTED BENEFITS & CURRENT CHALLENGES

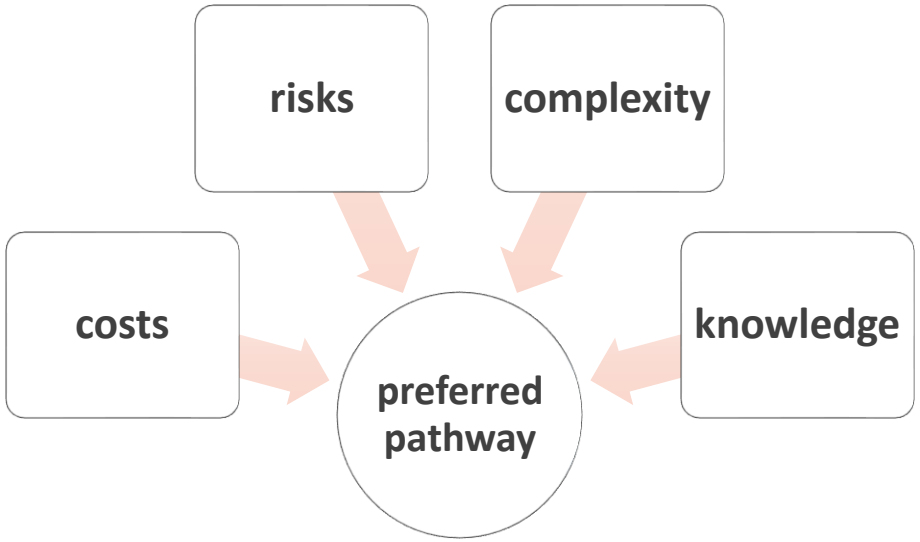
Improved quality control testing and shortened development timelines through enhanced product and process understanding

- *Provides quantitative information on individual site-specific CQAs therefore enabling more specific control of the safety and efficacy of the drug*
- *Increase speed by leveraging MAM as platform method with a potential for automation*
- *De-risks accelerated development by retrospective assessment of newly identified (p)CQAs using previous data sets*

MAM is so far not widely accepted for lot release and stability testing under GMP due to regulatory unfamiliarity & potential business risks

- *Limited experience with filing MAM as QC method, replacing conventional methods*
- *Diverse and unclear regulatory landscape as potential business risks*
- *Increased effort and risk by parallel testing using MAM & conventional methods*
- *Limited experience to validate New Peak Detection (NPD) and set appropriate specifications*

REGULATORY PATHWAYS & SUPPORTING ELEMENTS



Introduction of MAM

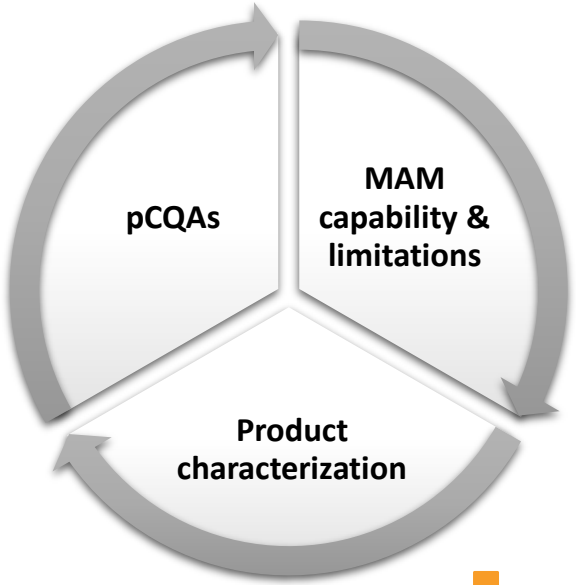
	Risk assessment	Method bridging	Method validation	Specification setting	NPD
Prior to FIH studies – instead of conventional methods	yes	no	yes	yes	yes
After FIH / prior to registration – in addition to conventional methods	no	no	yes	yes	no
During development / as LCM activity – replace conventional methods	yes	yes	yes	yes	yes

see also Rogstad *et al.*, 2019

Risk assessment

- *"Evaluate the capacity and performance of MAM in the context of the CQAs of the candidate product and its overall control strategy"* [1]*, which requires thorough understanding of the*
  1. capabilities & limitations of MAM by LC-MS peptide mapping
  2. pCQAs of the product obtained by structure elucidation and forced degradation studies

- *typical limitations of MAMs by LC-MS peptide mapping include*
  1. clipping site (degradation) = clipping site (sample preparation)
  2. peptide fragments are too small to be retained on the LC column
  3. bottom-up approach: modification on peptide *vs* intact level
  4. potential risk of sample preparation-induced artefacts



[1] Rogstad *et al.*, 2019

Method bridging

- *bridging data package as for any other conventional method, i.e. analysis of*
  - clinical batches → link to clinical experience / safety and efficacy
  - stability samples incl. forcibly-degraded samples → coverage of all relevant pCQAs
  - IPC samples → absence of matrix interferences (if relevant)

- *reportable results for MAM and conventional methods will be different*
  - not meaningful to compare absolute values, only trends and rate of evolution of the CQA during stability (long term, accelerated conditions) should be compared

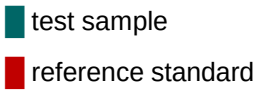
- *leverage the performance characteristics as defined in the Analytical Target Profile (ATP)*

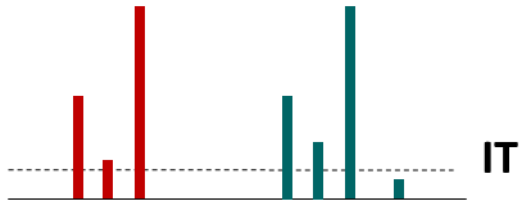
SUPPORTING ELEMENTS

Method validation

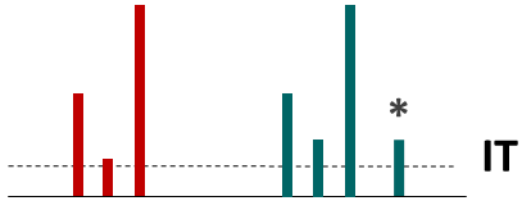
- *targeted monitoring according to ICH Q2(R1) - quantitative testing for impurities*
  - accuracy, precision (repeatability, intermediate precision), specificity, quantitation limit, linearity and range
- *NPD parameters (if applicable)*
  - fold-change & intensity threshold, mass & retention time windows
- *leverage MAM platform in line with ICH Q14, i.e. consider to apply*
  - platform robustness data to streamline product specific validation
  - prior knowledge e.g. same peptide / same modification
  - risk-based approaches e.g. similar peptides / same modification
  - performance requirements as defined in the ATP

New peak detection

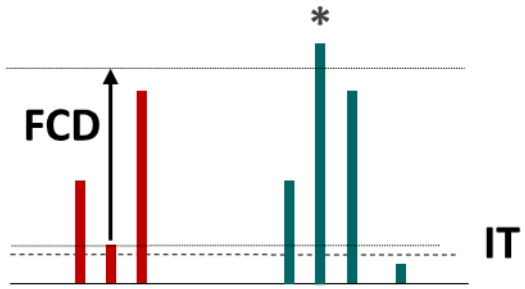




no new peak



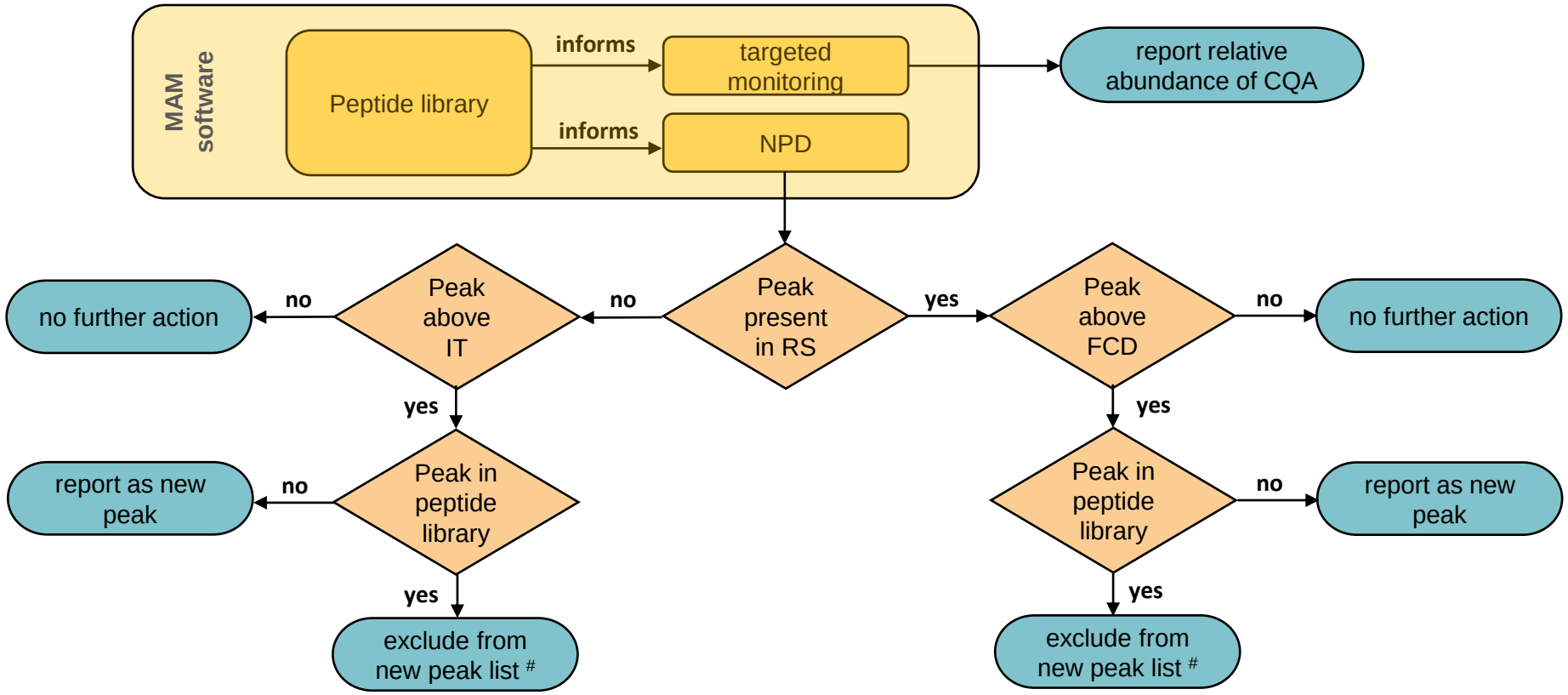
✓ new peak (*) detected



✓ changed peak (*) detected

IT: intensity threshold, minimum signal threshold
FCD: fold-change detection threshold

New peak detection



⇒ *requires targeted monitoring and NPD to be part of one integrated workflow !*

RS: product specific reference standard
IT: intensity threshold, minimum signal threshold
FCD: fold-change detection threshold
selected peaks / product variants may be trended to support internal process consistency monitoring

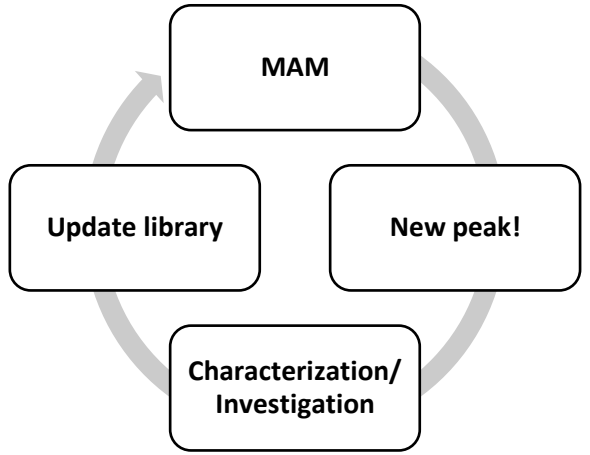
Specification setting

- *for the targeted monitoring according to ICH Q6B as for conventional methods*
  - specification limits only for CQAs
  - limits informed by clinical experience, criticality assessment of quality attributes and performance characteristics of the MAM

- *for NPD in a stage-appropriate manner as library and NPD parameters are expected to evolve*

  <u>clinical development</u>
  - lower warning limit → characterize / update library
  - higher action limit → OOS investigation

  <u>commercial</u>
  - detection of unknown peak above validated NPD thresholds → OOS investigation



SUMMARY AND CONCLUSIONS

- *Replacement of conventional methods with MAM by LC-MS enables improved CQA-centric quality control testing in line with QbD principles*
- *Depending on the regulatory pathway for the introduction of MAM in a QC lab, different elements such as risk assessment, method bridging and NPD will be required*
- *The development and validation of a robust NPD workflow is considered a pre-requisite for the use of MAM by LC-MS as a purity assay and the successful replacement of conventional methods*
- *Method validation and specification setting for the target monitoring should follow established regulatory guidelines, such as ICH Q2 / ICH Q6B and will benefit from upcoming ICH Q14*
- *Introduction of MAM by LC-MS as a QC method prior to FIH studies is expected to reduce complexity but requires frontloading in terms of early product characterization studies*

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Current members of the EFPIA topic team «MAM as a QC tool»

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Thank you