



Use of Multi-Attribute-Method by Mass Spectrometry as a QC release and stability tool for Biopharmaceuticals – the EFPIA perspective

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OUTLINE

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

* Why MAM as a QC tool?

* The EFPIA MQEG 'MAM as a QC tool' working group initiative & deliverables

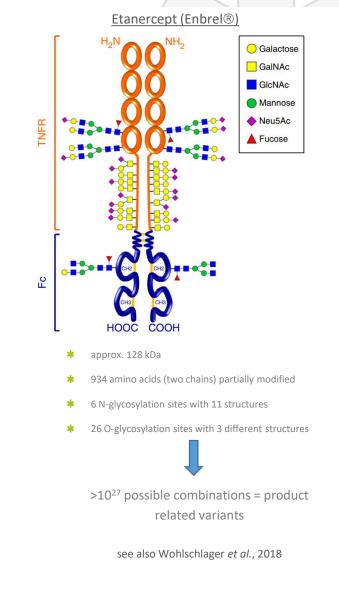
Introducing MAM in QC – quality compliance & regulatory pathways and related aspects

Conclusions & challenges



WHY MAM AS A QC TOOL? Benefits of MAM

- Using multiple conventional methods for release and stability testing is time- and instrument-consuming.
- The conventional HPLC /CE based methods address categories of productrelated 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.





TECHNICAL ASPECTS Prototypical MAM by LC-MS peptide mapping workflow

1. Product characterization

(4)Peptide Mass (1) LC-MS/MS Digestion (2)Analysis library spectrometer RT [min] LC-MS 2. Product quality monitoring test sample NPD reference standard (4) 1 Reporting Analysis CQA 1 CQA 2 Mass spectrometer Peptide library RT [min] CQA 3 CQA4 adapted from Rogers et al., 2018

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

THE EFPIA MQEG 'MAM AS A QC TOOL' WORKING GROUP

Founded by 24 representatives from 16 pharmaceutical companies

- * The working group was founded in March 2021 under the EFPIA MQEG umbrella
- * 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 multiple conventional QC methods**.

- Why this initiative?
 - *** MAM enables QbD** (ICH Q8) by providing **increased product and process understanding**
 - MAM is frequently applied for the analytical characterization of biopharmaceuticals (non GMP environment) but not for QC testing purposes yet. This may be due to:
 - ***** ongoing evolution and alignment of best practices
 - * complexity of method (sample preparation, instrumentation, data analysis)
 - * capital investment & associated trainings of QC personnel
 - Iimited experience with filing of MAM as a QC tool
 - regulatory unfamiliarity with MAM as QC tool



THE EFPIA MQEG 'MAM AS A QC TOOL' WORKING GROUP **Publications**

* This initiative has resulted so far in 3 publications



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 lopment. Moreover, the aforementioned analytical methods address categories of product de product-related variants (e.g., oxidized variants, charge variants) but do not always allow easy separation of individual product quality attributes (POA) 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



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https://www.efpia.eu/media/676706/efpia-regulatoryposition-paper mam-as-qc-tool final.pdf

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Research paper					
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1. Introduction

Medicines Agency (EMA), as well as other regulatory authorities, The US Food and Drug Administration (FDA) and European (QbD) principles in drug product development, manufacturing, and

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Pohl et al. (2023)

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ELSEVIEF Research paper Compliance and regulatory considerations for the implementation of the multi-attribute-method by mass spectrometry in a quality control laboratory Valerio D'Alessio^f, Simone Greven⁸, Andrew Lennard^h, Xue Liⁱ, Christopher Lössner^j, Linda Yi q 4 Andystein Donleynem Görsen (afr Medigish), USL Chenter Jaho Jovine, 1200 Parisel (Johand, Majjan, Andystein) and Charlog Carella, Johan Markov, 2014 (Schwarz, 2014), Schwarz, 2014 (⁸ Pharmaceuticals, Biological Development, Bayer AG, Friedrich-Ebert-Strusse 217-333, 42117 Wuppertal, Germany Amgen Lul, 4 Uzbridge Business Park, Sanderson Road, Uzbridge, UBB 1DH, UK Biologics Development, Britoal Myers Supth J. Synub Drive, New Brunsevick, NJ 08901, USA Analytical Dev. Biologicals, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, 88397 Biberach an der Röß, Germany Biotherapeutics, Bristol Myers Squibb, 4224 Campus Point Court, San Diego, CA 92121, USA Pharma Technical Development, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Peraberg, Germany th Eli Lilly Kinsale Limited, Dunderrow, Kinsale, Co. Cork, P17NY71, Ireland Analytical Development, GSK, 709 Swedeland Road, King of Prussia, PA 19406, USA BioPharmaceutical Development, Ipsen Biopharm Limited, 9 Ash Road, Wrexham Industrial Estate, Wrexham LL13 9UF, UK Analytical Sciences, BioPharmaceuticals R&D, AstraZmeca, One Medimmune Way, Gaithersburg, MD 20878, USA Analytical Development, Biogen, 5000 Davis Drive, Research Triangle Park, NC 27709, USA

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1. Introduction Multi-attribute-method by peptide mapping liquid chromatography mass spectrometry (MAM) has emerged as a new technique with the

potential to replace conventional methods for release and stability testing of biopharmaceutical products in the quality control (QC) labo ratory [2]. The methods conventionally used to measure product-related substances and product-related impurities, namely high-performance

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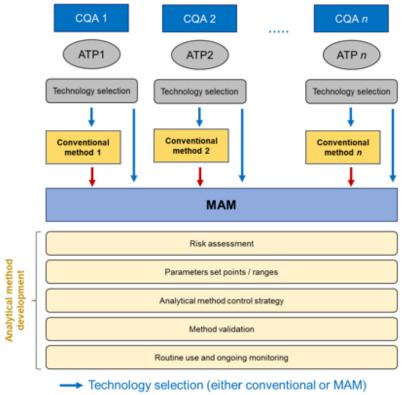
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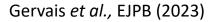
Annick Gervais^a,^a, Eef H.C. Dirksen^b, Thomas Pohl^c, Karoline Bechtold-Peters^d, Will Burkitt^e, Ben Niu^k, Dietmar Reusch¹, Tomás O'Riordan^m, Justin W. Shearerⁿ, David Spencer^o, Wei Xu^p

THE EFPIA MQEG 'MAM AS A QC TOOL' WORKING GROUP Regulatory engagement

- Interaction with EMA BWP participation in Interested Parties meeting in May 2022
- Interactions with EDQM
 - * One webinar & one seminar in EDQM, Strasbourg
 - Selected elements related to the principles and applications of MAM may be considered as part of the revision of Ph. Eur. General chapter 2.2.43 Mass Spectrometry.
- Contribution to ICH Q14 training material illustration of the enhanced approach for the measurement of 3 CQAs using a single MAM analytical procedure:
 - Deamidation of N_x in CDR of mAb-A
 - Oxidation of M_z in CDR of mAb-A
 - * Relative abundance of Man-5 on N_v in constant domain of mAb-A



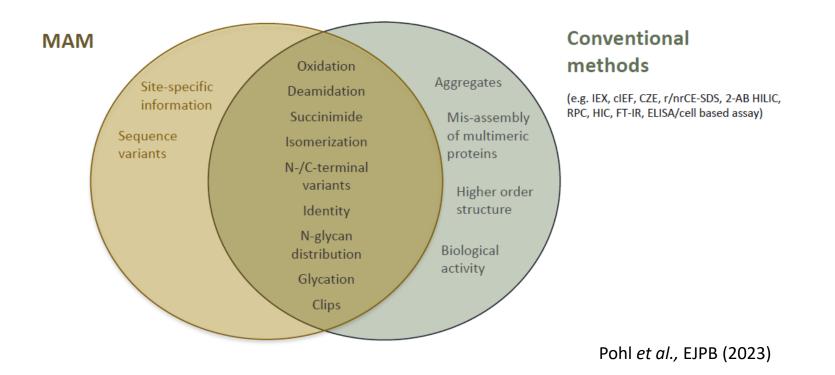
Bridging strategy upon change





INTRODUCING MAM IN QC – QUALITY & REGULATORY PATHWAYS AND RELATED ASPECTS Can MAM replace all conventional methods?

No, it is NOT the intention to replace all QC assays with MAM because of the nature of the peptide mapping methodology.





INTRODUCING MAM IN QC – QUALITY & REGULATORY PATHWAYS AND RELATED ASPECTS

Validation, Specification Setting & Bridging – same approach as for conventional methods

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

All Sce	Scenarios 1 & 2 only	
Phase-appropriate validation	Specification setting	Bridging
 According to ICH Q2 Prior knowledge from similar molecules (platform method) – ICH Q14 Certain quality attributes can be used as surrogates On-going monitoring during routine use: trending of SST results (method performance over time) – ICH Q14 	 ICH Q6B Based on method performance characteristics (ATP), process capability, stability profile, clinical experience For CQA only Monitoring of other PQA via company PQS (not via specifications) Retrospective assessment of data possible for newly identified CQA 	 Demonstration of at least equivalent or better performance for the intended purpose By design, MAM has improved specificity (individual site specific CQA) Relevant samples incl. clinical batches, stability/stressed samples Extent of data package depends on scope and phase of development. Risk-based approach. Adherence to ATP Data generated by the 2 methods may not be equivalent. Acceptable if differences are understood. Similar stability trends and rate of changes of the CQA.



CONCLUSIONS

MAM is a mature technology ready for implementation as a QC tool

- * MAM is recognized as a valuable developing technology and there is no regulatory impediment to introduce 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 ICH Q14 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.



PERSPECTIVES & REMAINING CHALLENGES

In practice, MAM implementation remains challenging ...

- * 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.
- *** Testing for importation** is still considered a hurdle as MAM instrumentation remains costly and technically complex.
- MAM in replacement of conventional methods Generally, bridging is considered a major burden for industry to adopt an innovative technology
 - * Can we leverage existing knowledge and avoid continued bridging with conventional methods?
 - * What would ease the implementation of MAM from a regulatory standpoint?
 - * Could Regulators envision no parallel testing at some point considering experience with technology and established guidance e.g., compendial chapters?
- What is the regulators view on:
 - The maturity of the technology today?
 - * The extent MAM is taken up and presented in regulatory filings?



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Currently: 20 representatives from 15 pharmaceutical companies

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