European Federation of Pharmaceutical Industries and Associations

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

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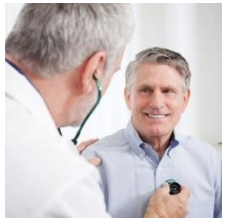
On behalf of EFPIA






CASSS CMC Strategy Forum EU
Rotterdam, The Netherlands
21 October 2024

OUTLINE

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

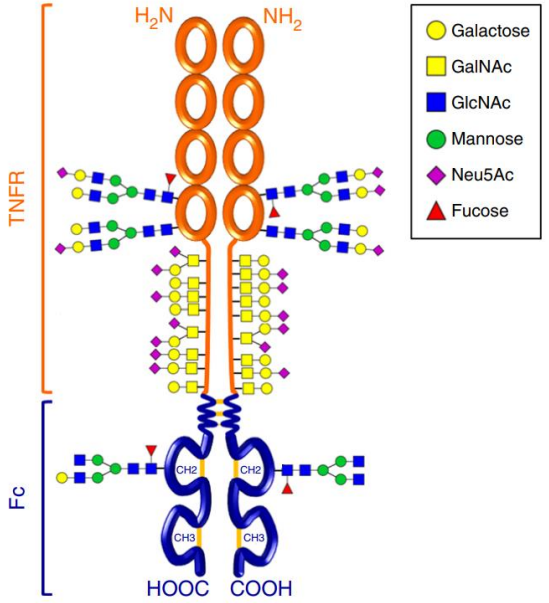
- Why MAM as a QC tool?
- The EFPIA MQEG ‘MAM as a QC tool’ working group initiative & deliverables
- Introducing MAM in QC – quality compliance & regulatory pathways and related aspects
- Conclusions & challenges

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

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 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.

Etanercept (Enbrel®)

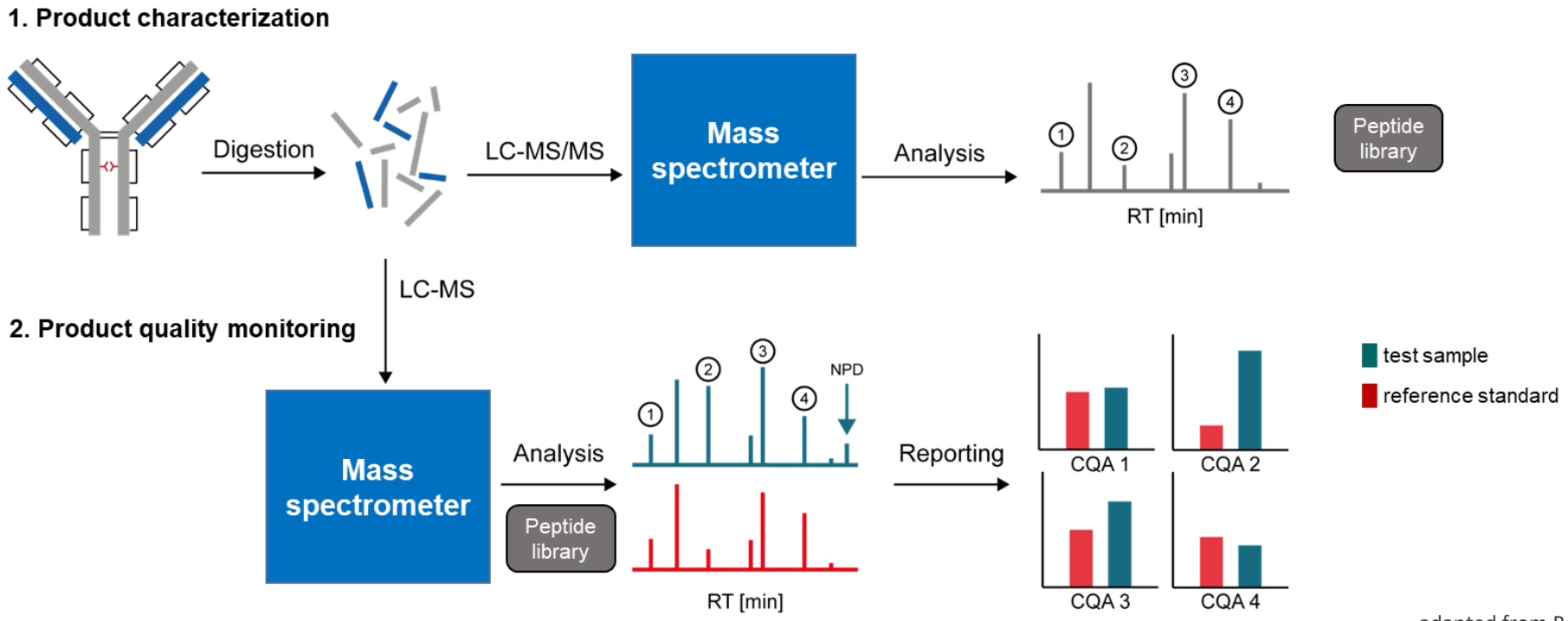


- approx. 128 kDa
- 934 amino acids (two chains) partially modified
- 6 N-glycosylation sites with 11 structures
- 26 O-glycosylation sites with 3 different structures

$>10^{27}$ possible combinations = product related variants

see also Wohlschlager *et al.*, 2018

Prototypical MAM by LC-MS peptide mapping workflow



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.

CQA = Critical Quality Attribute; NPD = New Peak Detection

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
    - limited experience with filing of MAM as a QC tool
    - regulatory unfamiliarity with MAM as QC tool

QbD = Quality by Design; EFPIA = European Federation of Pharmaceutical Industries and Associations ; MQEG = Manufacturing and Quality Expert Group

Publications

- This initiative has resulted so far in 3 publications

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Position Paper

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.

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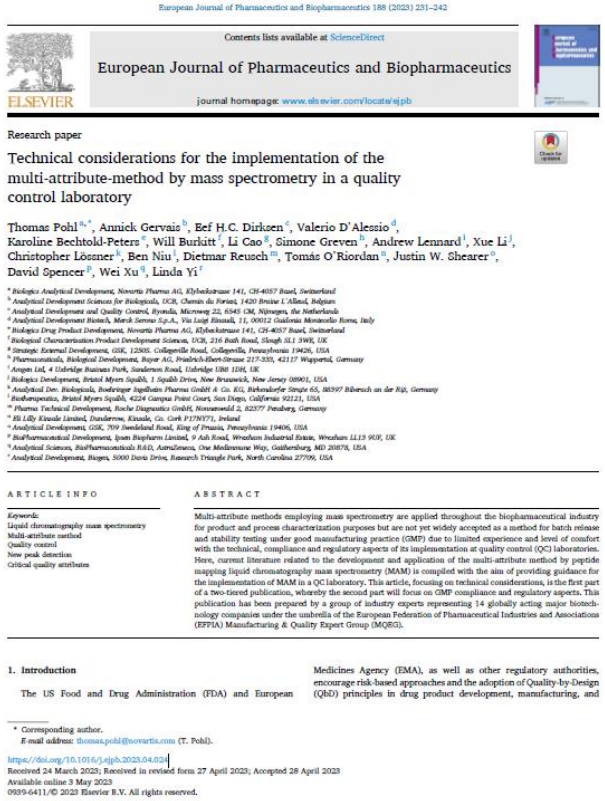
https://www.efpia.eu/media/676706/efpia-regulatory-position-paper_mam-as-qc-tool_final.pdf



European Journal of Pharmaceutics and Biopharmaceutics 188 (2023) 231–242

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Technical considerations for the implementation of the multi-attribute-method by mass spectrometry in a quality control laboratory

Thomas Pohl, Annick Gervais, Eef H.C. Dirksen, Valerio D'Alessio, Karoline Bechtold-Peters, Will Burkitt, Li Cao, Simone Greven, Andrew Lennard, Xue Li, Christopher Lössner, Ben Niu, Dietmar Reusch, Tomás O'Riordan, Justin W. Shearer, David Spencer, Wei Xu, Linda Yi

ARTICLE INFO

Keywords:
Liquid chromatography mass spectrometry
Multi-attribute method
Quality control
New peak detection
Critical quality attributes

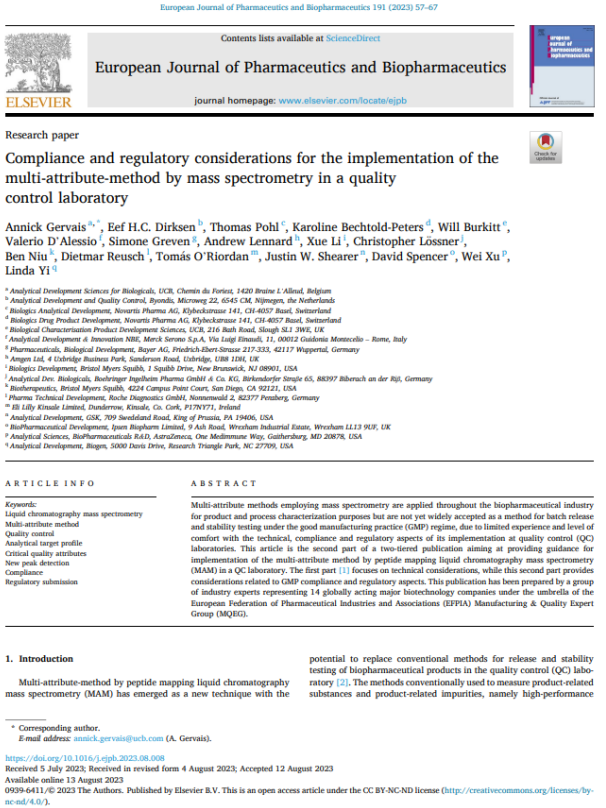
ABSTRACT

Multi-attribute methods employing mass spectrometry are applied throughout the biopharmaceutical industry for product and process characterization purposes but are not yet widely accepted as a method for batch release and stability testing under good manufacturing practice (GMP) due to limited experience and level of comfort with the technical, compliance and regulatory aspects of its implementation at quality control (QC) laboratories. Here, current literature related to the development and application of the multi-attribute method by peptide mapping liquid chromatography mass spectrometry (MAM) is compiled with the aim of providing guidance for the implementation of MAM in a QC laboratory. This article, focusing on technical considerations, is the first part of a two-tiered publication, whereby the second part will focus on GMP compliance and regulatory aspects. This publication has been prepared by a group of industry experts representing 14 globally acting major biotechnology companies under the umbrella of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Manufacturing & Quality Expert Group (MQEG).

1. Introduction

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA), as well as other regulatory authorities, encourage risk-based approaches and the adoption of Quality-by-Design (QbD) principles in drug product development, manufacturing, and

Pohl *et al.*(2023)
https://doi.org/10.1016/j.ejpb.2023.04.024



European Journal of Pharmaceutics and Biopharmaceutics 191 (2023) 57–67

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Compliance and regulatory considerations for the implementation of the multi-attribute-method by mass spectrometry in a quality control laboratory

Annick Gervais, Eef H.C. Dirksen, Thomas Pohl, Karoline Bechtold-Peters, Will Burkitt, Valerio D'Alessio, Simone Greven, Andrew Lennard, Xue Li, Christopher Lössner, Ben Niu, Dietmar Reusch, Tomás O'Riordan, Justin W. Shearer, David Spencer, Wei Xu, Linda Yi

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Multi-attribute method
Quality control
Analytical target profile
Critical quality attributes
New peak detection
Compliance
Regulatory submission

ABSTRACT

Multi-attribute methods employing mass spectrometry are applied throughout the biopharmaceutical industry for product and process characterization purposes but are not yet widely accepted as a method for batch release and stability testing under the good manufacturing practice (GMP) regime, due to limited experience and level of comfort with the technical, compliance and regulatory aspects of its implementation at quality control (QC) laboratories. This article is the second part of a two-tiered publication aiming at providing guidance for implementation of the multi-attribute method by peptide mapping liquid chromatography mass spectrometry (MAM) in a QC laboratory. The first part [1] focuses on technical considerations, while this second part provides considerations related to GMP compliance and regulatory aspects. This publication has been prepared by a group of industry experts representing 14 globally acting major biotechnology companies under the umbrella of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Manufacturing & Quality Expert Group (MQEG).

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) laboratory [2]. The methods conventionally used to measure product-related substances and product-related impurities, namely high-performance

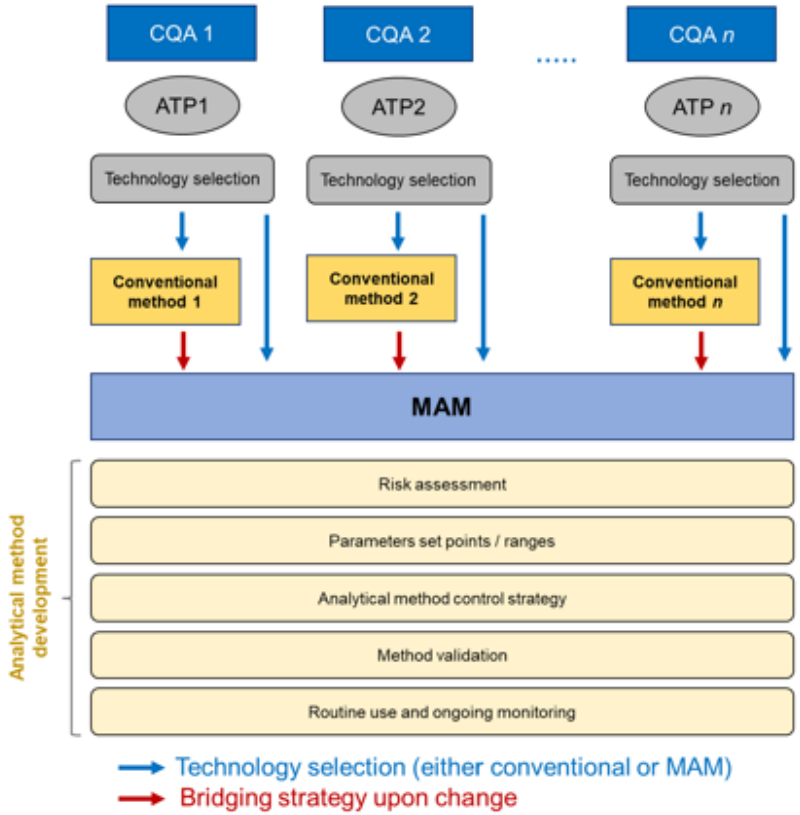
Gervais *et al.*(2023)
https://doi.org/10.1016/j.ejpb.2023.08.008

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_y in constant domain of mAb-A

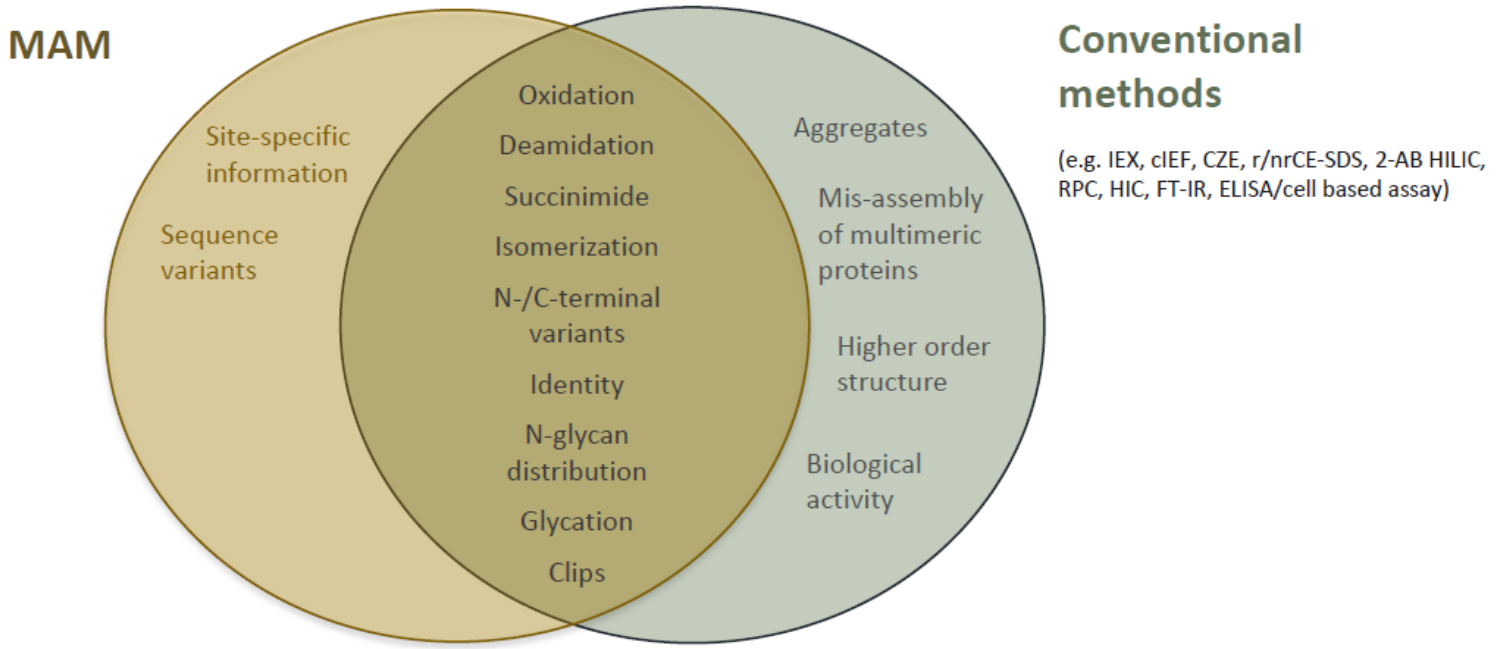


Gervais *et al.,* EJPB (2023)

N = Asparagine; M = Methionine ; CDR = Complementary–Determining Region, CQA = Critical Quality Attribute

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.



Pohl *et al.*, EJPB (2023)

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 Scenarios

Phase-appropriate validation

- 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

Specification setting

- 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

Scenarios 1 & 2 only

Bridging

- 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.

SST = System Suitability Test; CQA = Critical Quality Attribute; PQA = Product Quality Attribute; PQS = Pharmaceutical Quality System; ATP = Analytical Target Profile

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**.

CQA = Critical Quality Attribute, FIH = First in Human

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?

ACKNOWLEDGMENT

Currently: 20 representatives from 15 pharmaceutical companies

Name	Company
Andrew LENNARD	Amgen
Zhang ZHONGQI	Amgen
Hao ZHANG	Amgen
Wei XU	Astra Zeneca
Simone GREVEN	BAYER
Linda YI	BIOGEN
Ben NIU	BMS
Rekha Tulsan	BMS
Christopher LÖSSNER	Boehringer Ingelheim
Eef DIRKSEN	Byondis

Name	Company
Tomas O'RIORDAN	Eli Lilly
Justin SHEARER	GSK
David SPENCER	IPSEN
Valerio D'ALESSIO	MERCK
Thomas POHL **(Lead)**	Novartis
Karoline BECHTOLD-PETERS	Novartis
Dietmar REUSCH	Roche
Gwenael NYS	Sanofi
Annick GERVAIS **(Co-lead)**	UCB
Will BURKITT	UCB

Thank you