Quality Considerations for the Multi-Attribute Method (MAM) for Therapeutic Proteins

Sarah Rogstad, PhD
Division Director
FDA/CDER/OPQ/OPQR/DPQR VI

GRx + Biosims: MAM and Non-Clinical Immunogenicity Studies

October 22, 2024

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Emerging Technology Program (ETP)

Mission

Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing through close collaboration with industry and other relevant stakeholders

Emerging Technology Program (ETP) Objectives

To serve as a centralized location for external inquiries on novel technologies

To provide a forum for firms to engage in early dialogue with FDA to support innovation

To ensure consistency, continuity, and predictability in review and inspection

To engage international regulatory agencies to share learnings and approaches

To identify and evaluate potential roadblocks relating to existing guidance, policy, or practice

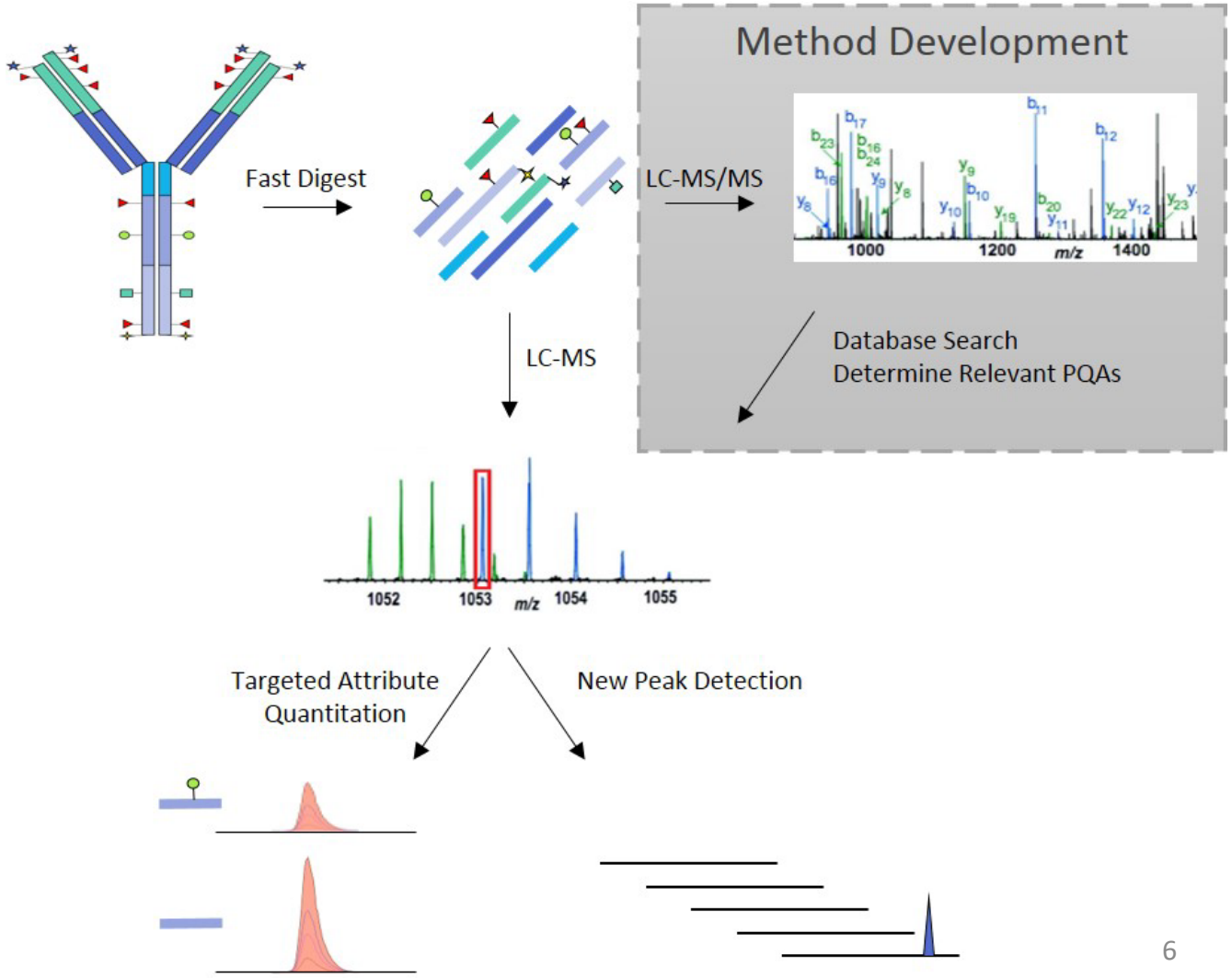
To facilitate knowledge transfer to relevant CDER and ORA review and inspection programs

To help establish scientific standards and policy, as needed

Contact us: CDER-ETT@fda.hhs.gov

Multi-Attribute Method (MAM)

- LC-MS based peptide mapping method for assessment of therapeutic proteins
  - Proposed for use in control testing
- USP published <1060> in USP-Pharmacopeial Forum (PF) for public comments in Sep 2023. <1060> will be official on Aug 01, 2025



Rogstad et. al. Anal Chem. 2019

MAM and ETP

- Recent improvements in instrumentation have led to a push toward MS for control of therapeutic proteins

- ETP is reviewing use of MAM for control purposes
  - Multiple applicants at different stages of product development and implementation

- Initial applications inspired in-house assessment of MAM methodology focusing on reproducibility, robustness, and applicability (vs conventional methods)

MAM Implementation

Four major points to consider:

- Risk assessment
- Method validation
- Capabilities and specificities of new peak detection feature
- Comparison to conventional methods

analytical chemistry

Perspective

Cite This: *Anal. Chem.* 2019, 91, 14170−14177

pubs.acs.org/ac

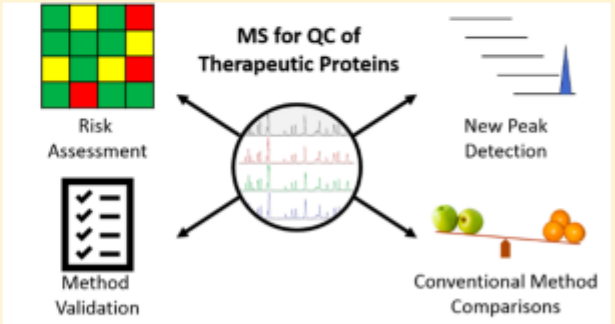
Multi-Attribute Method for Quality Control of Therapeutic Proteins

Sarah Rogstad,*[†] Haoheng Yan,[‡] Xiaoshi Wang,[‡] David Powers,[‡] Kurt Brorson,[‡,§] Bazarragchaa Damdinsuren,[‡] and Sau Lee[†]

[†]Office of Testing and Research, Office of Pharmaceutical Quality, CDER, U.S. Food and Drug Administration, Silver Spring, Maryland 20993, United States

[‡]Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER, U.S. Food and Drug Administration, Silver Spring, Maryland 20993, United States

ABSTRACT: Recent advances in high resolution mass spectrometry (MS) instrumentation and semi-automated software have led to a push toward the use of MS-based methods for quality control (QC) testing of therapeutic proteins in a cGMP environment. The approach that is most commonly being proposed for this purpose is known as the multi-attribute method (MAM). MAM is a promising approach that provides some distinct benefits compared to conventional methods currently used for QC testing of protein therapeutics, such as CEX, HILIC, and CE-SDS. Because MS-based methods have not been regularly used in this context in the past, new scientific and regulatory questions should be addressed prior to the final stages of implementation. We have categorized these questions into four major aspects for MAM implementation in a cGMP environment for both new and existing products: risk assessment, method validation, capabilities and specificities of the New Peak Detection (NPD) feature, and comparisons to conventional methods. This perspective outlines considerations for each of these main points and suggests approaches to help address potential issues.



Regulatory Expectations and Considerations for MAM in QC

- General regulatory expectations and considerations for MAM are not different from other methods
- Core expectation is to demonstrate the method is fit for intended purpose
  - 21 CFR 211.165(e) and 211.194(a)(2)
  - ICH Q2(R2) and ICH Q14
  - Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (2015)
- Setting clinically relevant and meaningful specifications
  - ICH Q6B
  - FDA MAPP 5017.2: Establishing Impurity Specifications Acceptance Criteria Based on Clinical Relevance
- Amount of information on method and suitability typically varies with phase of development and intended purpose
- Lifecycle management
- MAM method specific challenges should be addressed

Slide provided by Frances Namuswe

Phase Appropriate Method Development

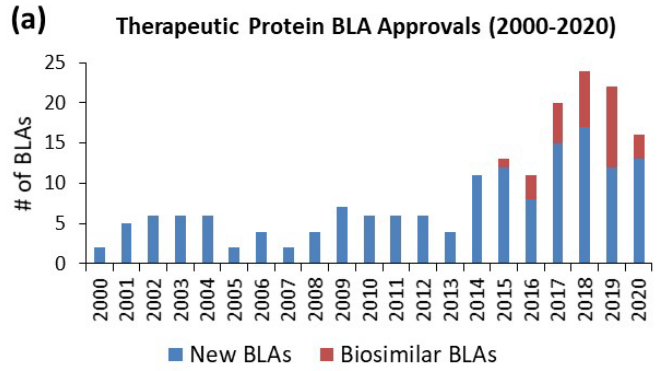
R&D	IND enabling	Phase 1 & 2 (Safety)	Phase 3 (Efficacy)	Post Marketing
• Limited characterization • Assay development		• In depth characterization • Continued assay development/improvement • Phase-appropriate release and stability specifications	• Continued characterization • CQAs assignment • QC assay validation • Refining specification/ setting commercial specification	• Life cycle management

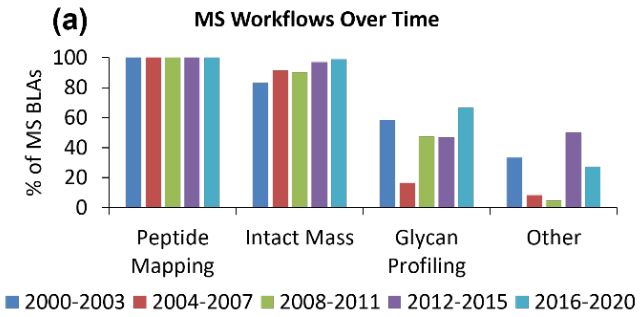
- Phase appropriate approach builds on knowledge gained from product development
- Selection of CQAs to be monitored by MAM relies on extensive characterization and understanding of the product from clinical studies and manufacturing experience

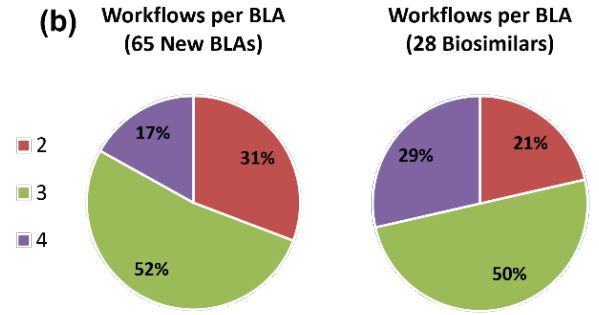
Slide provided by Frances Namuswe

MS for Biosimilarity

- Assessed use of MS in BLAs from 2000-2020
- MS used consistently in characterization and biosimilarity sections
- Increase in number of MS-based workflows used per BLA in biosimilar vs new BLAs
- Increase in more complex MS techniques (e.g., HDX-MS, PEG analaysis) in biosimilar vs new BLAs



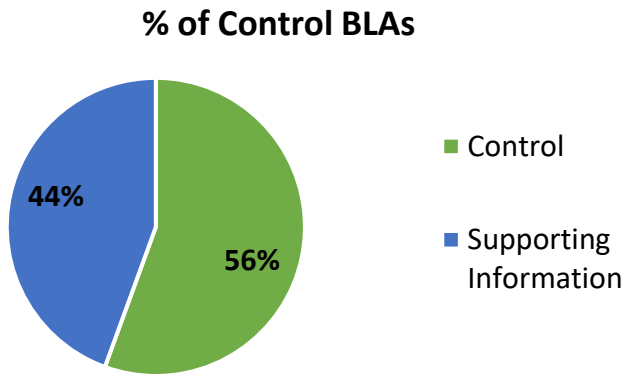


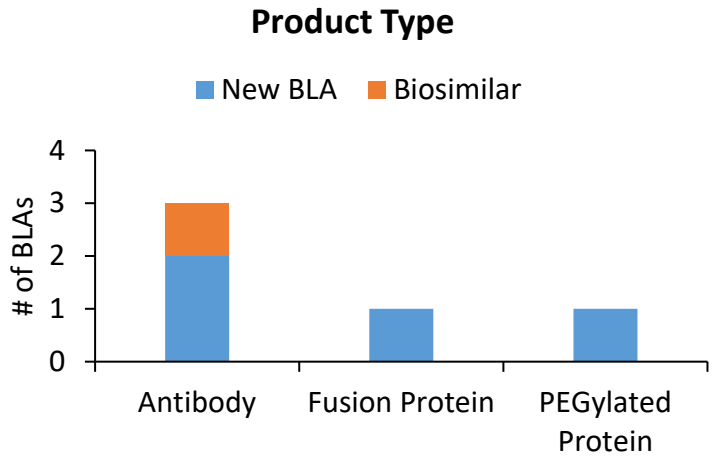


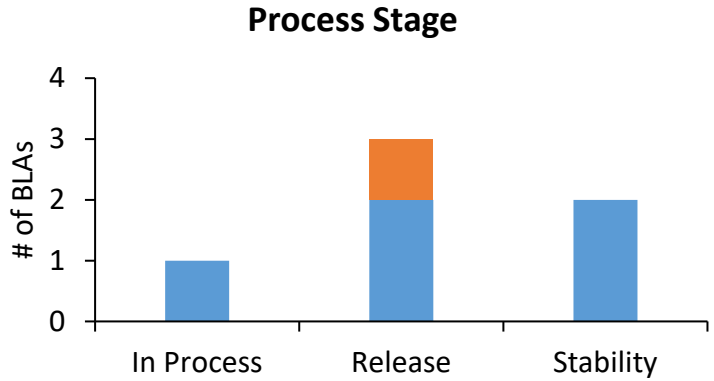
Rogstad et. al. JASMS. 2016
Mans et. al. JASMS. 2023

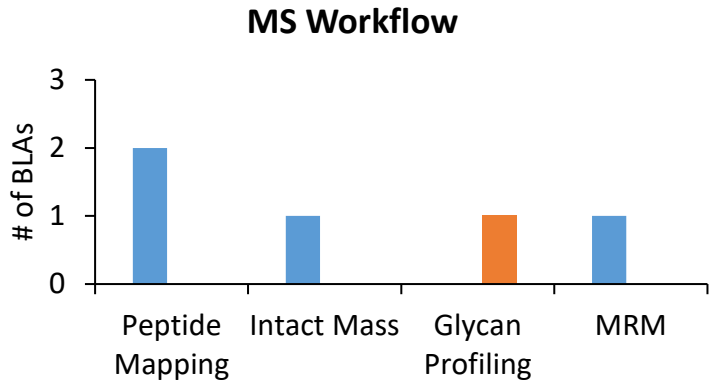
MS for Quality Control

- No MS for QC of therapeutic proteins before 2015
  - Older BLAs may have MS for QC in post-approval supplements
- From 2016-2020, 9 BLAs referenced MS in Control of Drug Substance section
  - Including 2 biosimilars
- MS used for identity, modification quantitation (oxidation, deamidation, and glycosylation), HCP quantitation, and polydispersity
- Variety of approaches used across multiple stages









Rogstad et. al. JASMS. 2016
Mans et. al. JASMS. 2023