Quality Considerations for the Multi-Attribute Method (MAM)

Sarah Rogstad

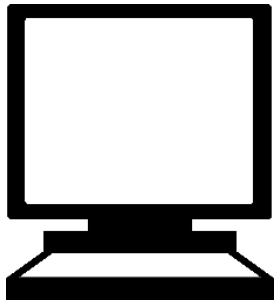
FDA/CDER/OPQ/OTR

Overview

- Pharmaceutical Quality
- Emerging Technology Program
- MS in BLAs
- Multi-attribute method (MAM)
- MAM research at FDA
- Summary and future of MAM research

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Emerging Technology Program

Mission

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

ETT Guidance and MAPP

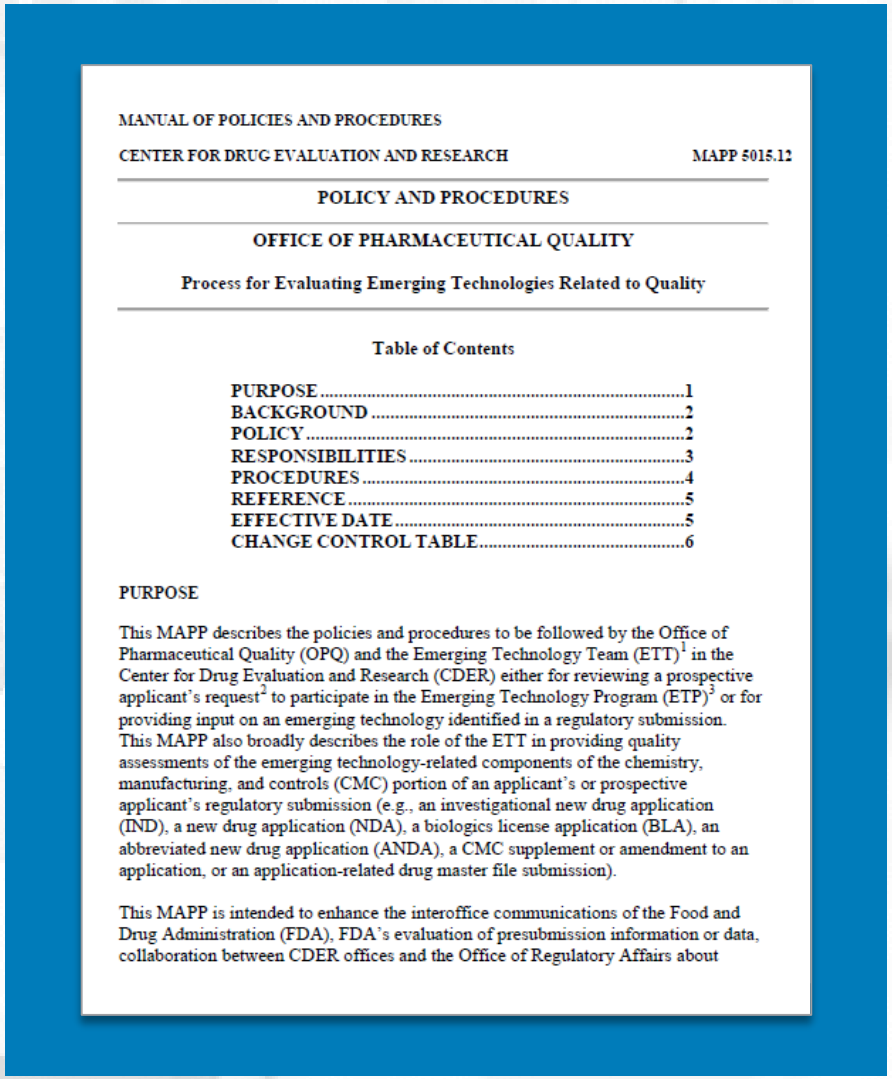
Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2017
Pharmaceutical Quality/CMC

2483881 FNL



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5015.12

POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Process for Evaluating Emerging Technologies Related to Quality

Table of Contents

PURPOSE

This MAPP describes the policies and procedures to be followed by the Office of Pharmaceutical Quality (OPQ) and the Emerging Technology Team (ETT)[1] in the Center for Drug Evaluation and Research (CDER) either for reviewing a prospective applicant's request[2] to participate in the Emerging Technology Program (ETP)[3] or for providing input on an emerging technology identified in a regulatory submission. This MAPP also broadly describes the role of the ETT in providing quality assessments of the emerging technology-related components of the chemistry, manufacturing, and controls (CMC) portion of an applicant's or prospective applicant's regulatory submission (e.g., an investigational new drug application (IND), a new drug application (NDA), a biologics license application (BLA), an abbreviated new drug application (ANDA), a CMC supplement or amendment to an application, or an application-related drug master file submission).

This MAPP is intended to enhance the interoffice communications of the Food and Drug Administration (FDA), FDA's evaluation of presubmission information or data, collaboration between CDER offices and the Office of Regulatory Affairs about

Use of MS in BLAs

- Identification
- Characterization
- Comparability (process change by same manufacturer)
- Comparative Analytical Assessment (biosimilar vs reference product)
- Surveillance for Adulteration
- Process Improvement
- PK/PD measurement

Rathore, D. et al., Expert Review of Proteomics, DOI: 10.1080/14789450.2018.1469982

MS in BLAs: Characterization

J. Am. Soc. Mass Spectrom. (2016)
DOI: 10.1007/s13361-016-1531-9

FOCUS: 28th SANIBEL CONFERENCE, CHARACTERIZATION OF PROTEIN THERAPEUTICS BY MS: RESEARCH ARTICLE

A Retrospective Evaluation of the Use of Mass Spectrometry in FDA Biologics License Applications

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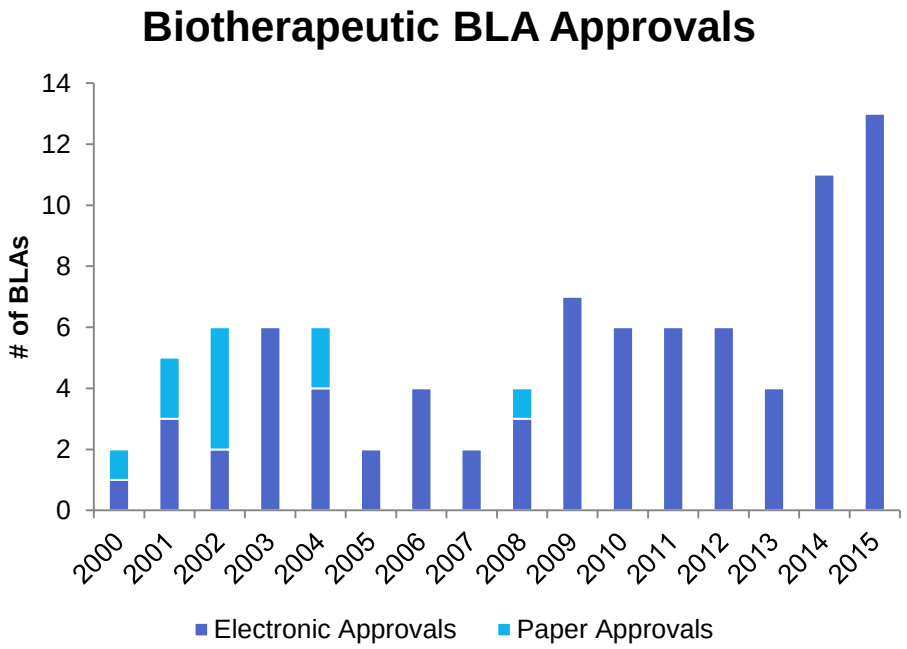
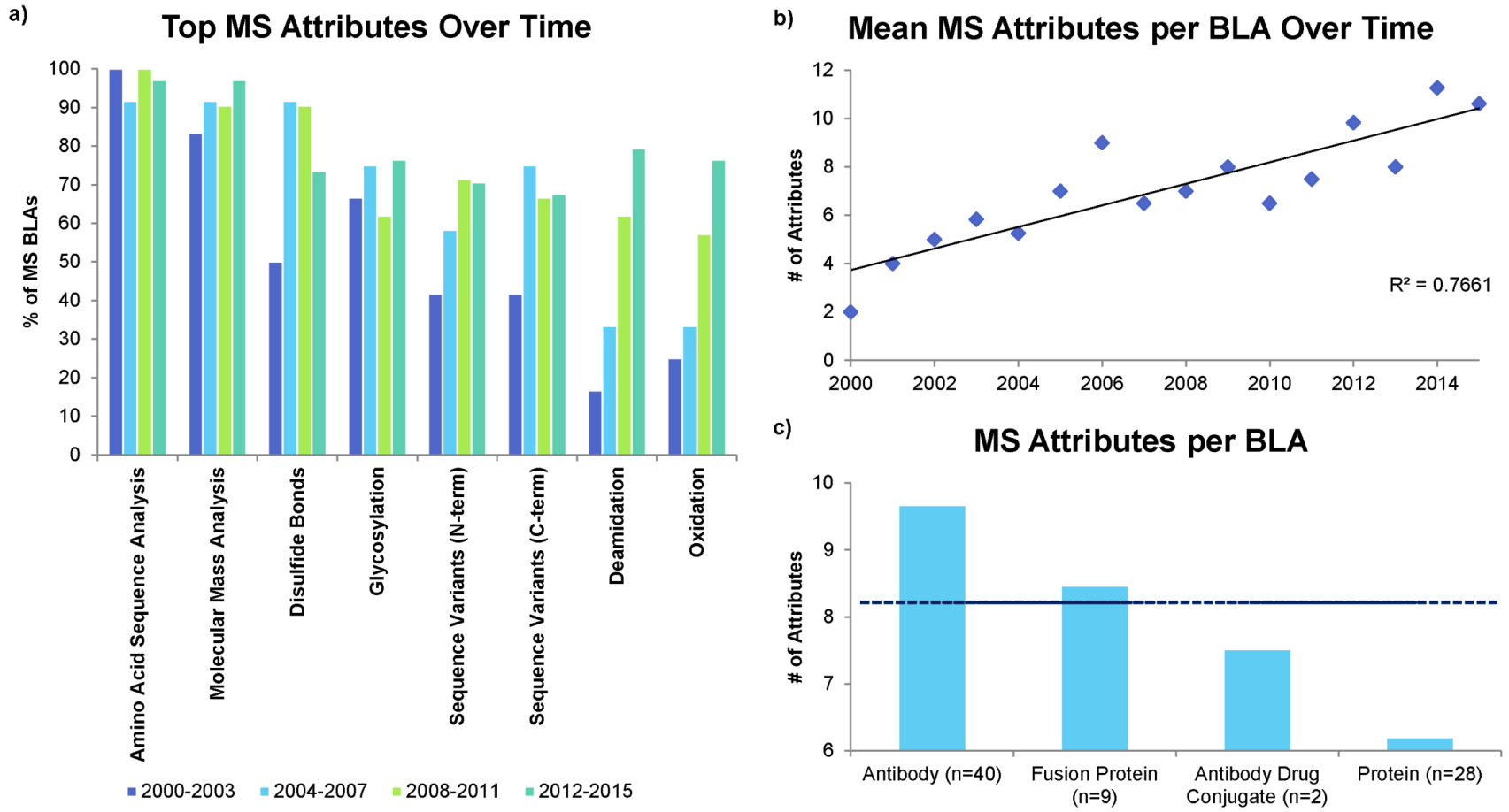


79 of 80* BLAs approved between 2000 - 2015 used MS in DS characterization

***electronically submitted**

MS Usage in Protein Therapeutic BLAs



Rogstad, S. et al., JASMS. 2016.

Use of MS in QC Testing

- MS is less commonly used in QC testing of therapeutic proteins due to complexity of therapeutic proteins and MS-method related considerations

MS Usage (As of 2017)	Protein BLAs	Peptide NDAs
Characterization	100%	100%
Control	0	65%

- Advances in technology (e.g. high resolution and high mass accuracy instruments) have led to increased use

Rogstad, S. et al., JASMS. 2016 and unpublished data

Regulatory Considerations for QC

- General regulatory expectations and considerations for MS are not different from other methods
- The principal expectation is to demonstrate that the method is fit for intended purpose
  - 21 CFR 211.165(e) and 211.194(a)(2)
- MS method specific challenges should also be addressed.
- Amount of information on method procedure and suitability typically varies with phase of development

Slide borrowed from Frances Namuswe (CDER/OPQ/OBP)

MAM and ETT

- Recent improvements in instrumentation have led to a push toward MS for control of therapeutic proteins
- ETT is reviewing use of MAM for control purposes
  - After several rounds of review, agreed to sunset strategy for conventional methods for one applicant
- Applications inspired in-house assessment of MAM methodology focusing on reproducibility, robustness, and applicability (vs conventional methods)

General Benefits of MAM

- Testing multiple attributes at once

  → Fewer instruments and assays
- More detailed information at the molecular level
  - Analysis of site-specific modifications can allow for tighter control
- Can differentiate between species that may overlap using chromatographic approaches
- New peak detection allows for control of unexpected new modifications

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

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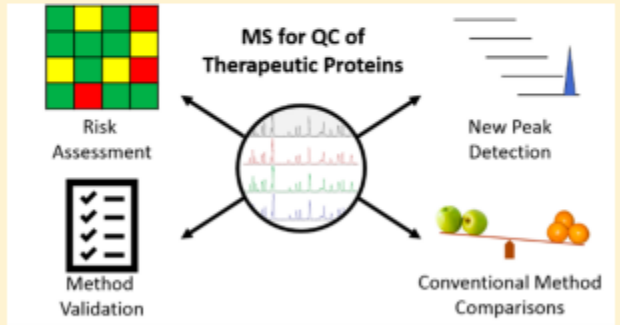
[‡]Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER, U.S. Food and Drug Administration, Silver Spring, Maryland 20993, United States

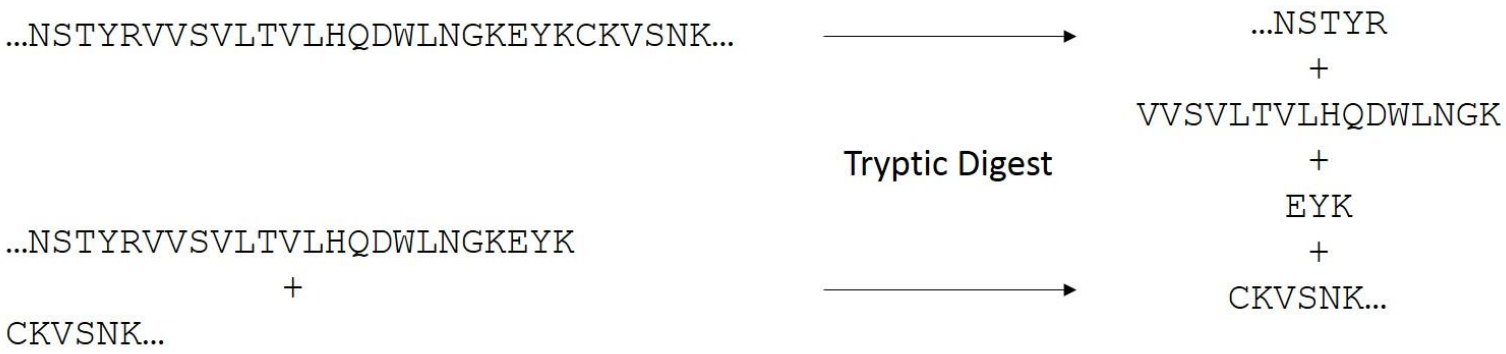
ABSTRACT: Recent advances in high resolution mass spectrometry (MS) instrumentation and semi-automated software have led to a push toward the use of MS-based methods for quality control (QC) testing of therapeutic proteins in a cGMP environment. The approach that is most commonly being proposed for this 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.



Risk Assessment

- Should weigh benefits and risks for implementation
- Product and CQA specific

- Potential risk example:
  - Loss of clipped species information



Rogstad, S. et al., Analytical Chemistry, 2019.

Method Validation

- As an analytical method, MAM needs to be validated
- Can base on ICH Guidelines and FDA Guidances
- More challenging aspects include:
  - Precision
  - LOD/LOQ
  - System suitability

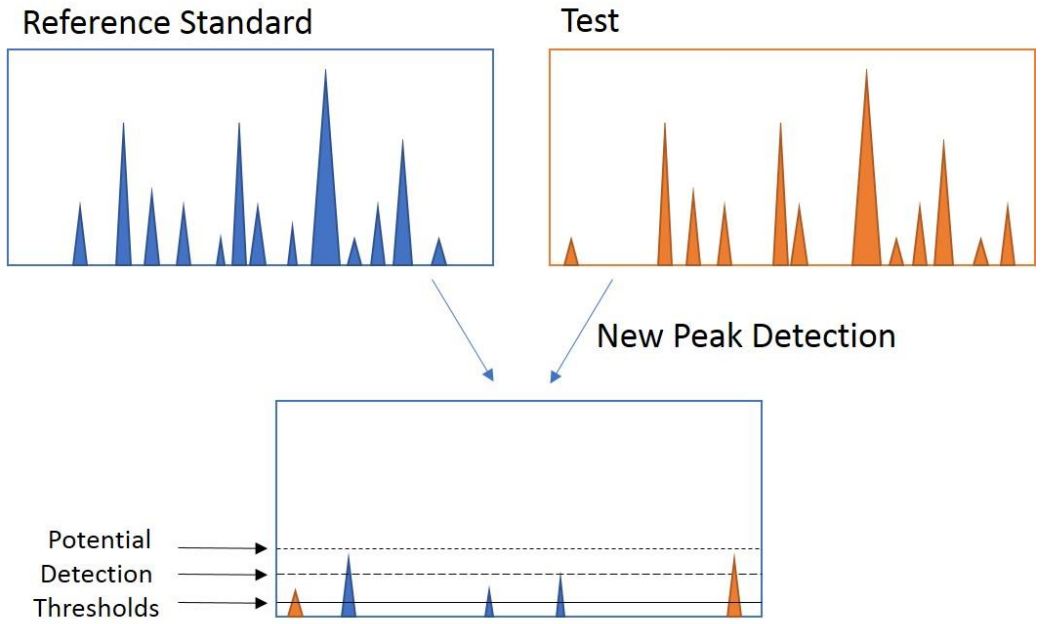
Relevant Guidance Documents:

- ICH Q2 (R1) – Validation of Analytical Procedures
- ICH Q6B – Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- FDA Guidance on Validation of Chromatographic Methods
- FDA Guidance on Analytical Procedures and Methods Validation for Drugs and Biologics

Rogstad, S. et al., Analytical Chemistry, 2019.

New Peak Detection

- Allows for detection of changes not directly monitored
- As a stability-indicating method, should detect unknown impurities
- Success highly dependent on software parameters:
  - Retention time window
  - Mass accuracy window
  - Peak detection threshold



Rogstad, S. et al., Analytical Chemistry, 2019.

Conventional Method Comparisons

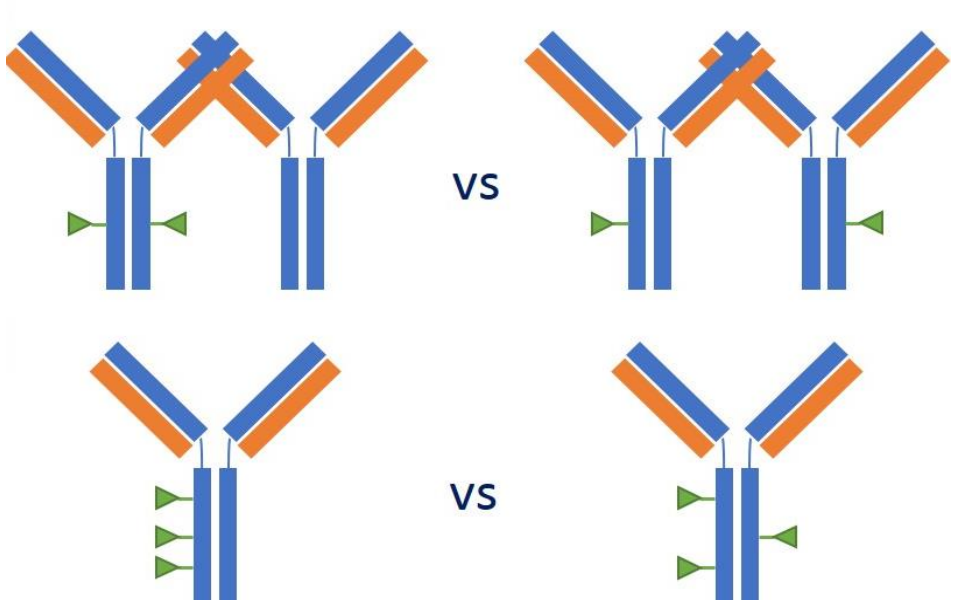
- Comparisons should be informed by risk assessment
- Help to better understand advantages and disadvantages
- Perform during method and product development
- Measurements may not correlate

Attribute by Conventional Method	Target by MAM
Released N-glycans by HILIC glycan profiling	Glycopeptides
Charged variants by CEX	Specific post-translational modifications, N- and C- terminal variants, sialylated species
Clipped species and other size impurities/variants by rCE-SDS	Specific clipped species

Rogstad, S. et al., Analytical Chemistry, 2019.

Additional Considerations

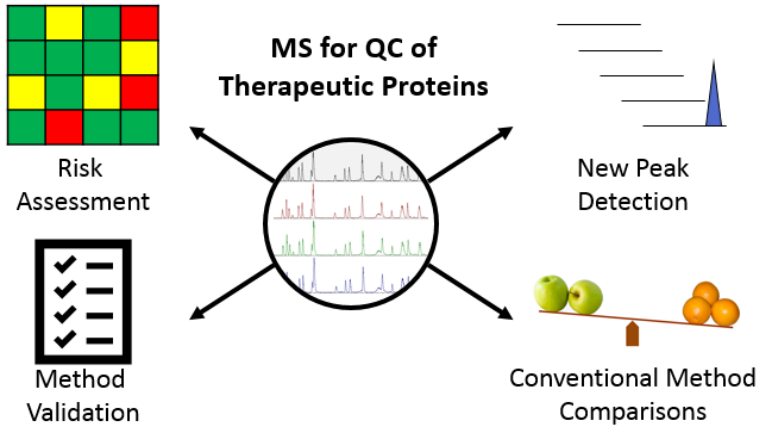
- May lose information at the protein level
  - Can't tell distribution of modifications based on bottom up approaches
- Would a difference in distribution of a modification affect safety or efficacy?
  - Case by case based on risk assessment
- Fit for purpose
  - Demonstrate that new QC method is monitoring all relevant CQAs
  - Which PQAs are CQAs and need to be monitored is product specific



Rogstad, S. et al., Analytical Chemistry, 2019.

FDA Research Overview

- Established in-house MAM capabilities to explore and better evaluate usage of the approach
- Used rituximab (approved and unapproved) as a model protein



Method Validation

- System Suitability
- Precision
- LOD/LOQ

New Peak Detection

- User Comparisons
- Forced Degradation

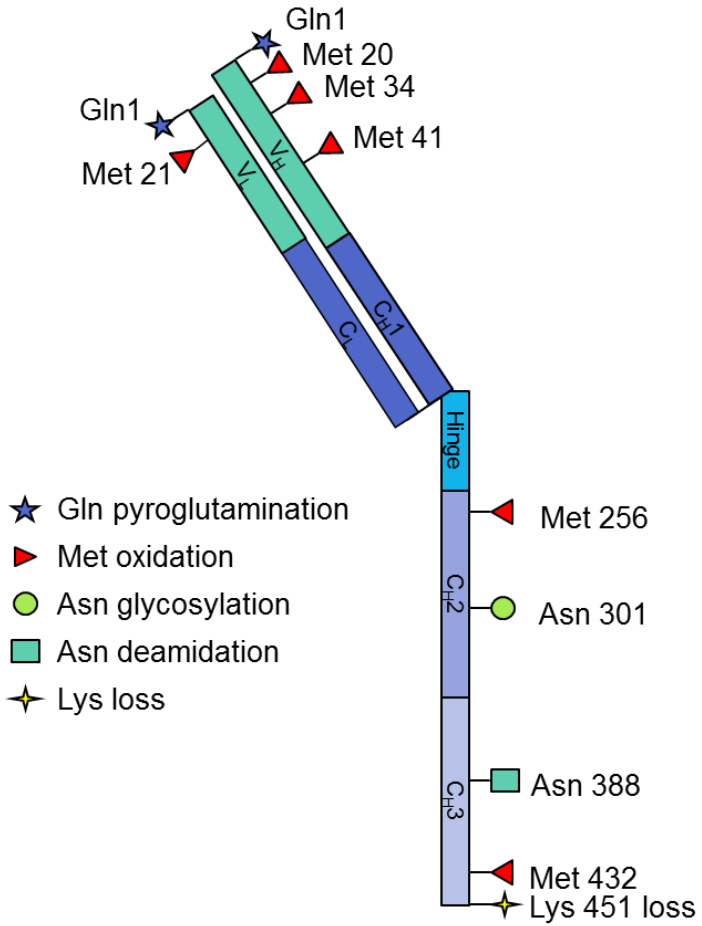
Conventional Method Comparisons

- Forced Degradation
- Glycan Profiling

Method Overview

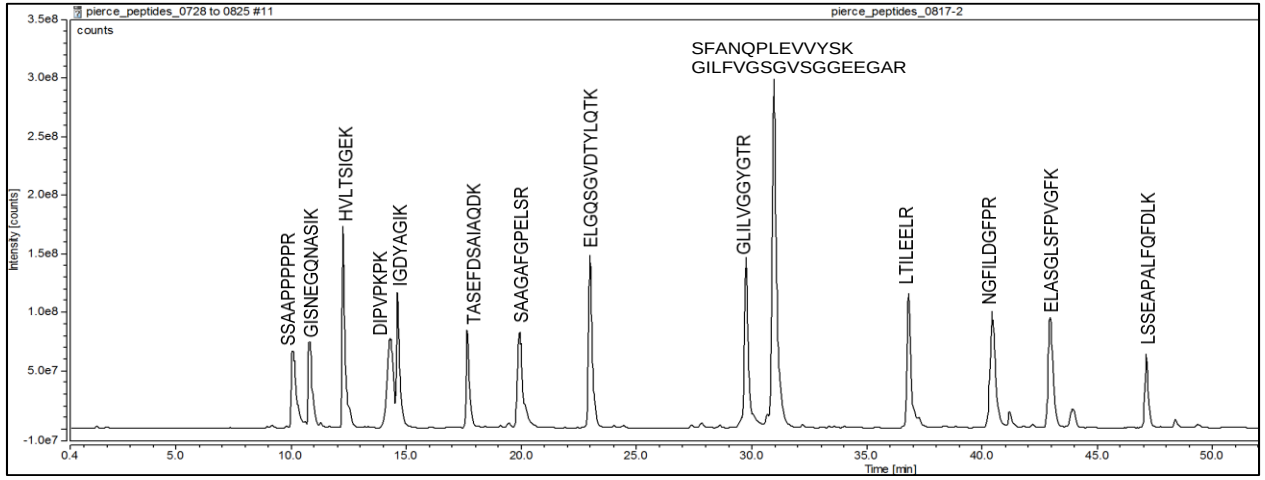
- Monitored the relative abundance levels of 21 product quality attributes (PQAs) across 11 sites

- Method was capable of distinguishing between approved and unapproved products for 10 of those PQAs



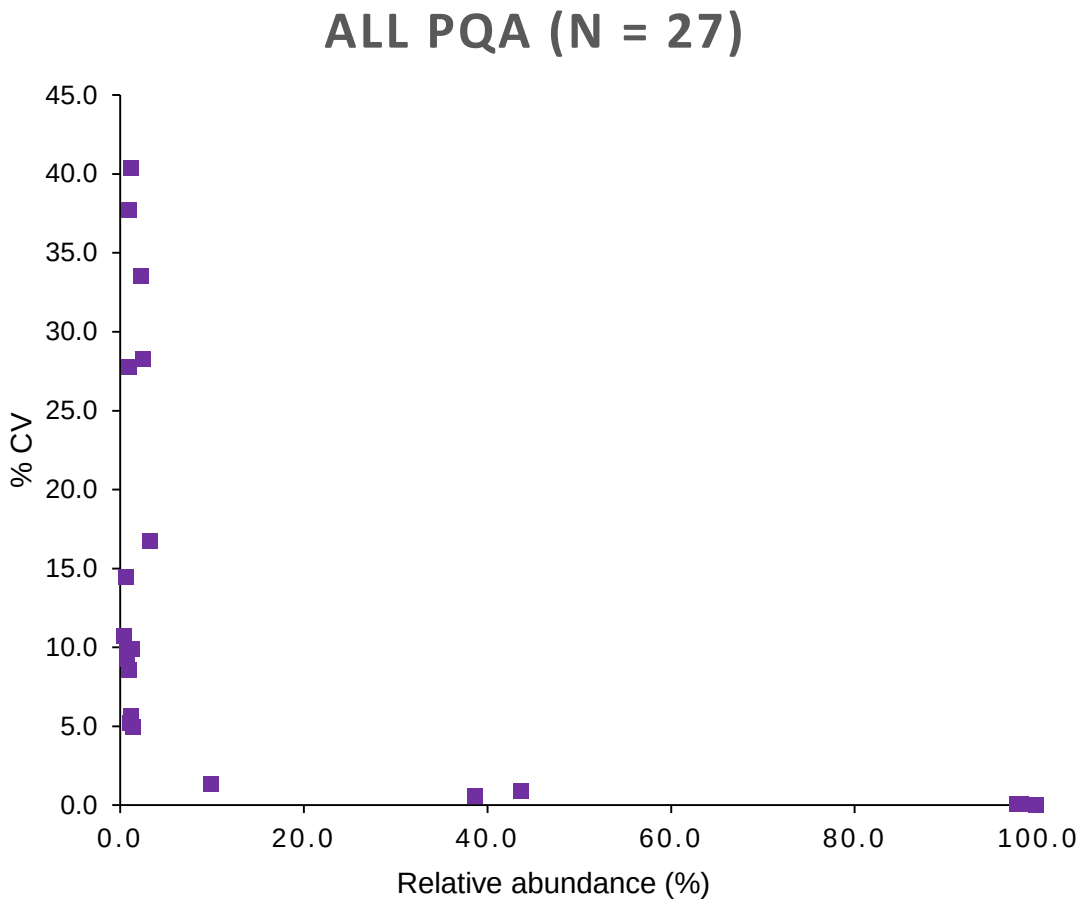
Method Validation: System Suitability

- Pierce Peptide Mix – 15 peptides
  - Use 12 for SST
- Set RT and Rel. Abundance limits based on historical data
- Additional Limits for RT and Rel. Abundance %CV
- Also assess mass accuracy, resolution, and signal:noise

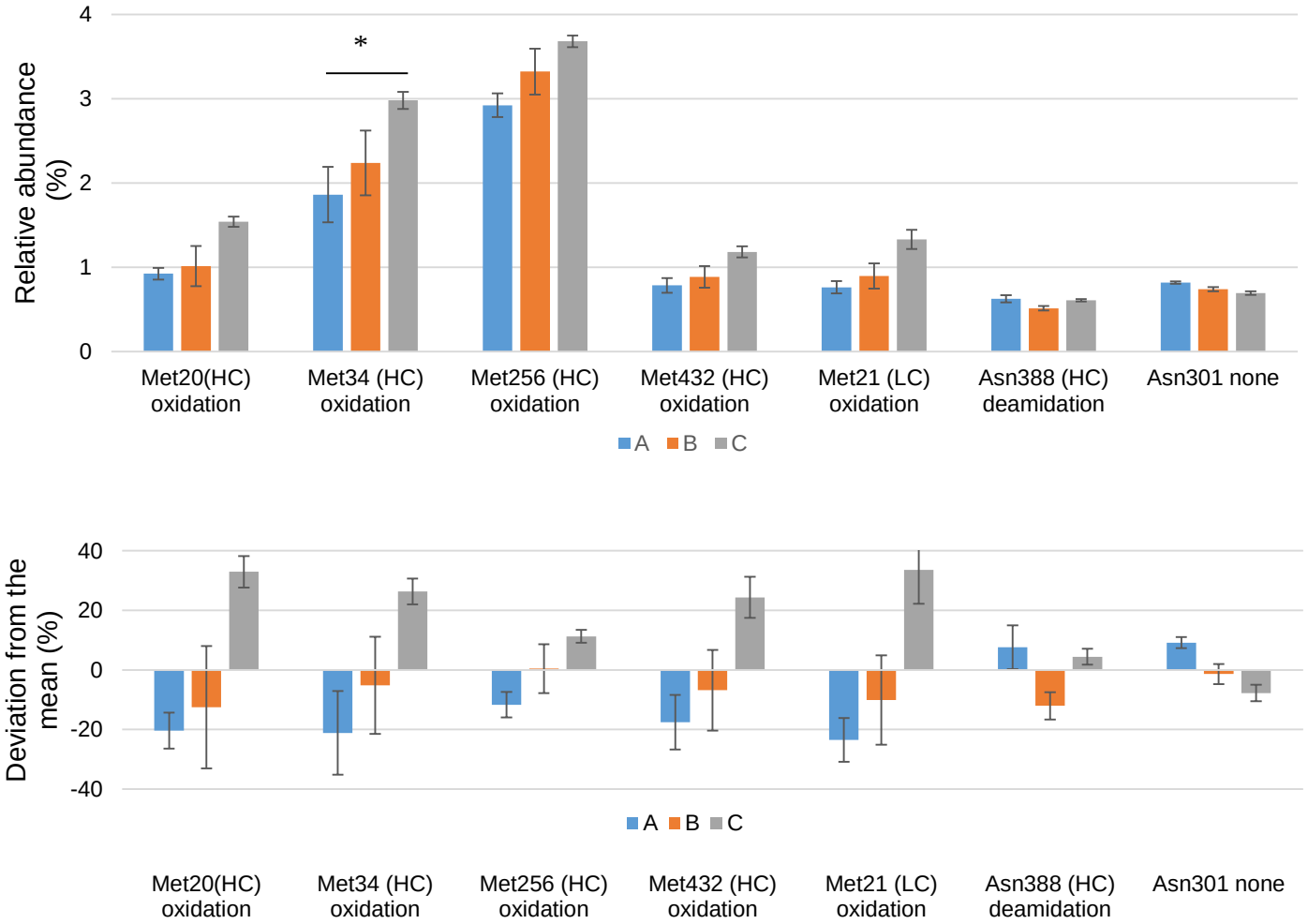


Method Validation: Reproducibility and Precision

- 3 users x 3 digests x 3 injections
- Results generally reproducible
- Highest variability for low abundance oxidation sites
- User experience correlated with variability

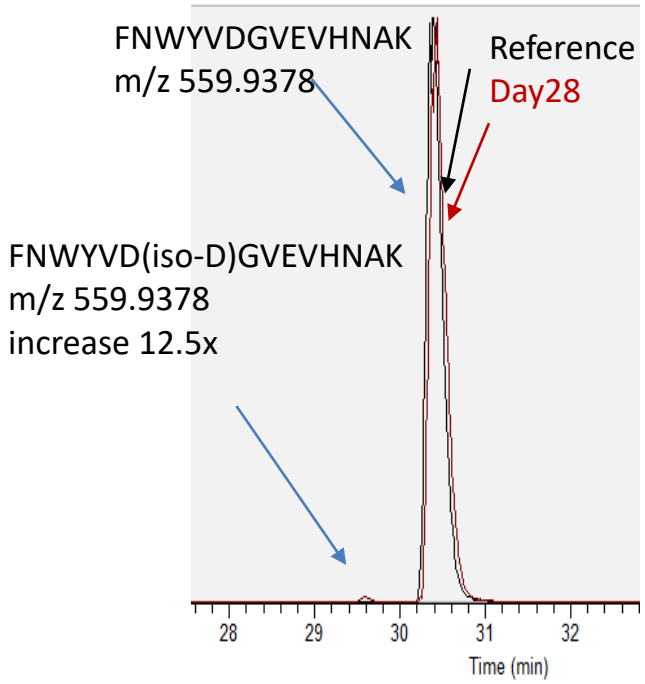


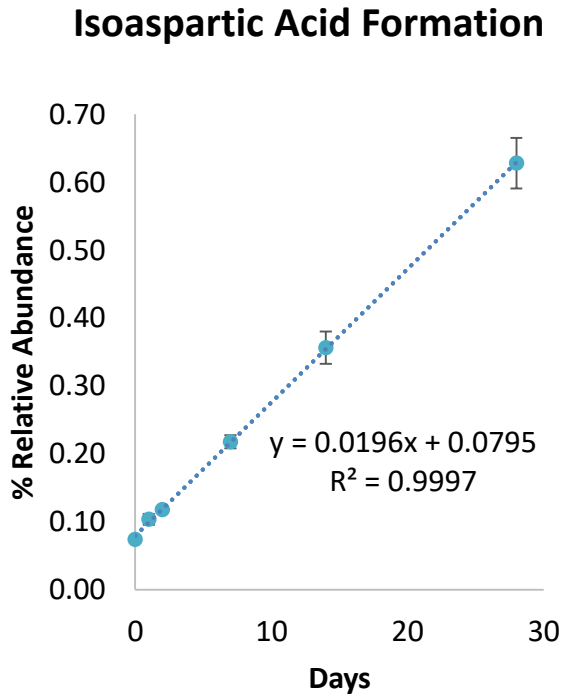
Method Validation: User Variation



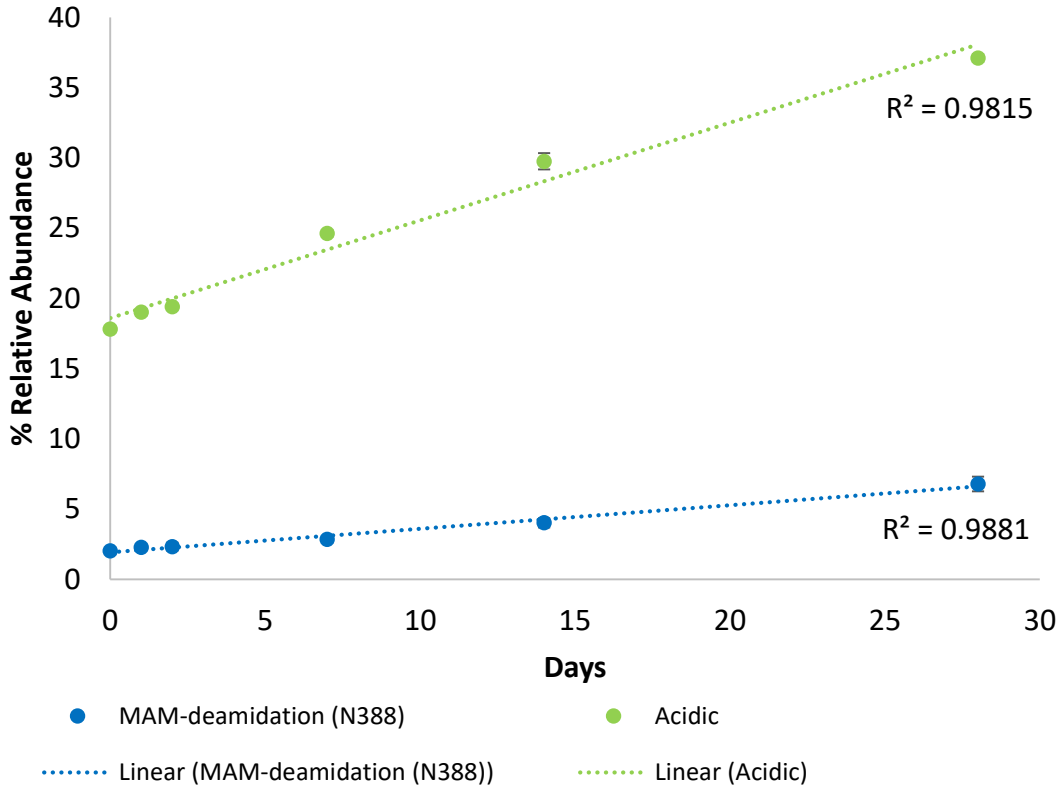
New Peak Detection: Forced Degradation

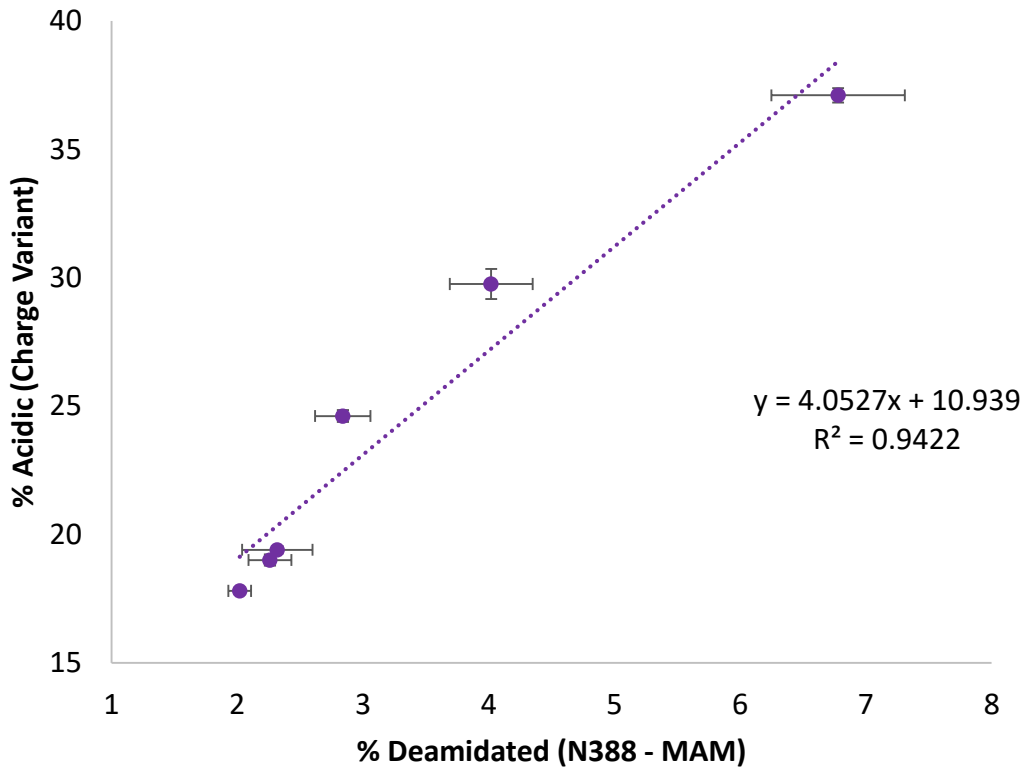
- Forced degradation – 28 days at 40 °C/75% RH
- Linear increases in oxidation and deamidation over time-course
- One new peak was detected
  - Aspartic Acid → Isoaspartic Acid
- > 12.5-fold increase over 28 days

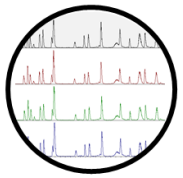




Method Comparisons: Forced Degradation

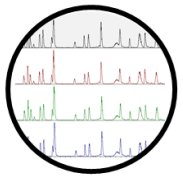






Summary

- Risk Assessment: should be considered when developing MAM
- Method Validation: established SST approach, assessed precision, reproducibility, LOD/LOQ, and more
- New Peak Detection: established NPD suggested parameters and used to test forced degradation samples
- Method Comparisons: compared forced degradation trends and glycan profile



Ongoing and Future Research

- Currently running and analyzing data from year-long stability and accelerated stability studies with MAM and conventional methods
- Conducting software comparison
- Site-to-site MAM comparison coming soon

Acknowledgements

OTR

- Mercy Oyugi
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- Xiaoshi Wang
- Haoheng Yan
- Phil Angart
- Bazarra Damdinsuren
- David Powers
- Kurt Brorson

ETT