Regulatory Considerations for Multi-Attribute Method Implementation

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Disclaimer

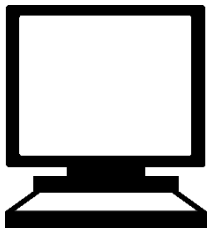
This speech reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Pharmaceutical quality and emerging technology program/team
- MS usage in biologics license applications
- Multi-Attributes Method proposed as a QC method
- General considerations for QC methods vs characterization methods
- Points-to-considers for implementation of MAM as a QC method

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.


FDA
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

US FDA Center for Drug Evaluation and Research

Updated August 2019

Mission

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

Team

A small cross-functional Emerging Technology Team (ETT) with representation from all relevant FDA quality review and inspection programs (CDER/OPQ, CDER/OC, & ORA)

ETT Guidance and MAPP

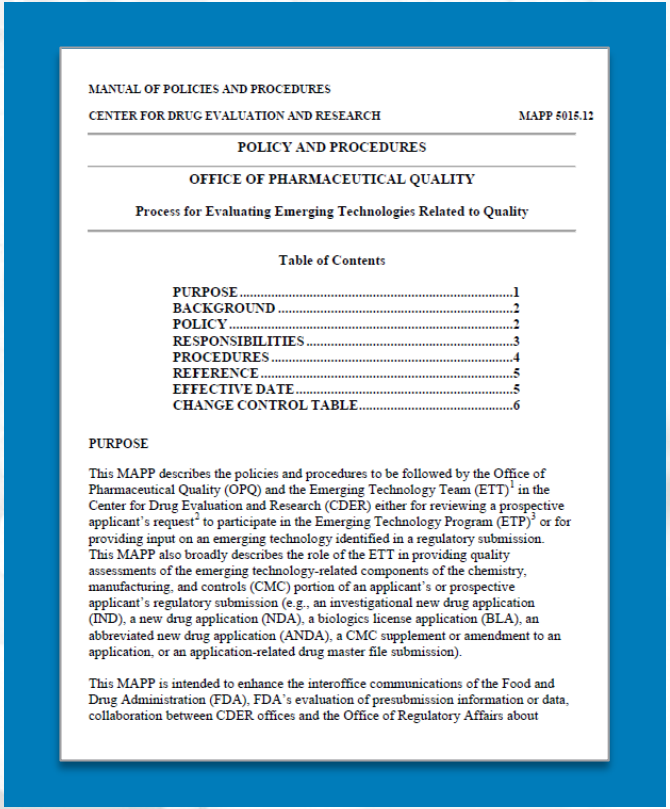
Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization

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

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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).

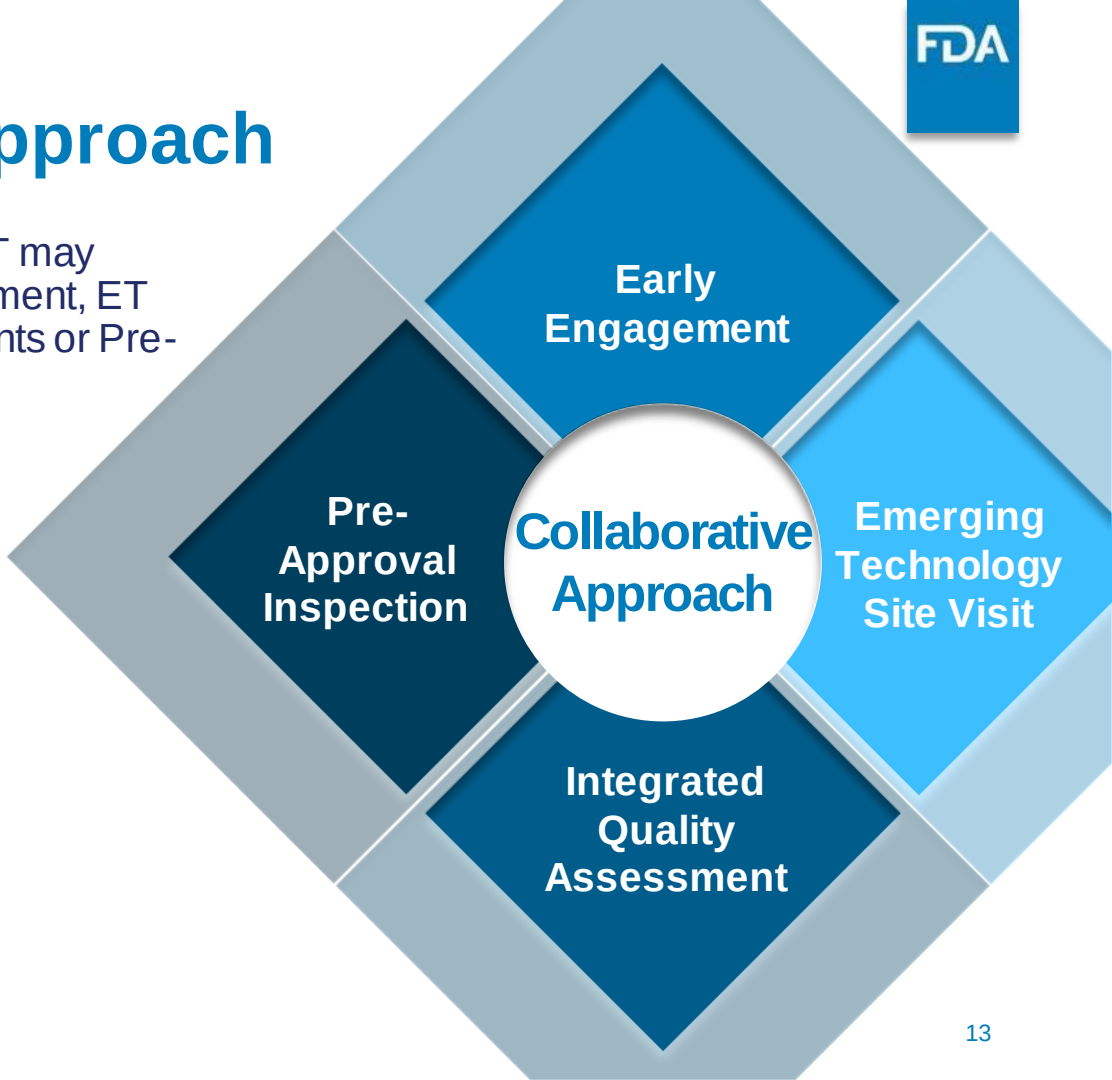
This MAPP is intended to enhance the interoffice communications of the Food and Drug Administration (FDA), FDA's evaluation of presubmission information or data, collaboration between CDER offices and the Office of Regulatory Affairs about

ETT Collaborative Approach

Over the course of an ETP project, ETT may employ a combination of early engagement, ET site visits, integrated quality assessments or Pre-Approval Inspections

The same ETT representative(s) will be involved in the entire process

The composition of a review team will likely remain the same throughout the entire process



ETT Collaborative Approach: Early Engagement

01

Start during early technology development even without a drug candidate identified

02

Follow procedures described in the ET guidance to request participation in the ET program

03

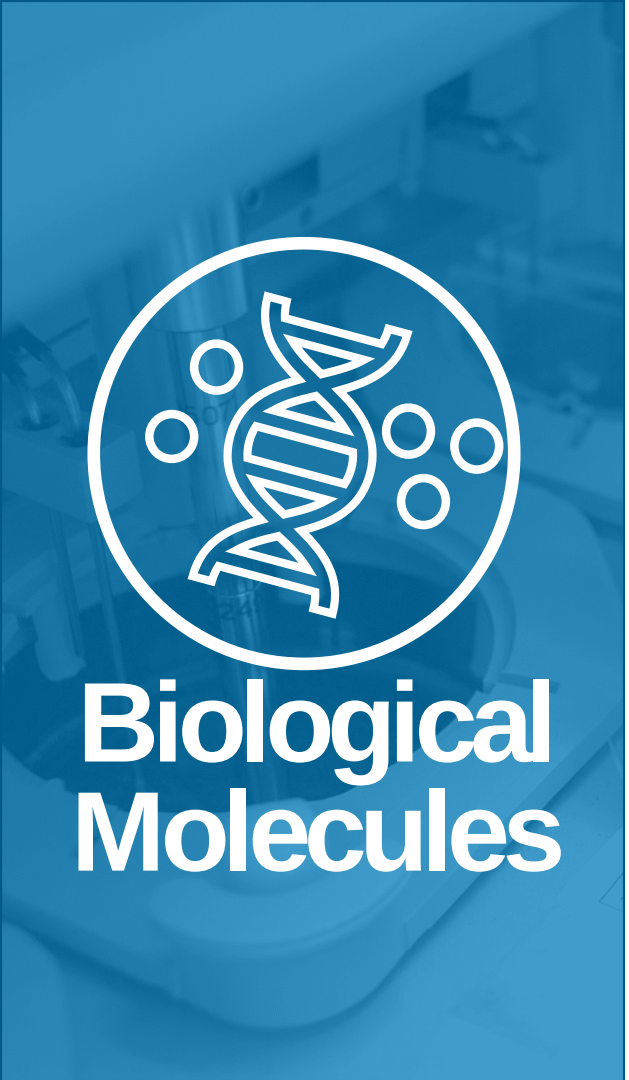
Develop five-page proposal

- Describe the technology and explain why it is novel or unique
- Describe how it improves products
- Summarize development plan and implementation roadblocks
- Develop submission timeline

The sponsor must justify how the proposed emerging technology meet two criteria:

(1) Pharmaceutical Novelty
(2) Product Quality Advancement

Email proposals to: CDER-ETT@fda.hhs.gov

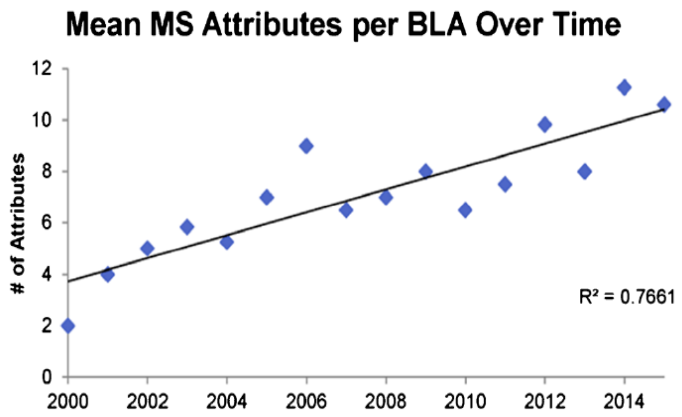


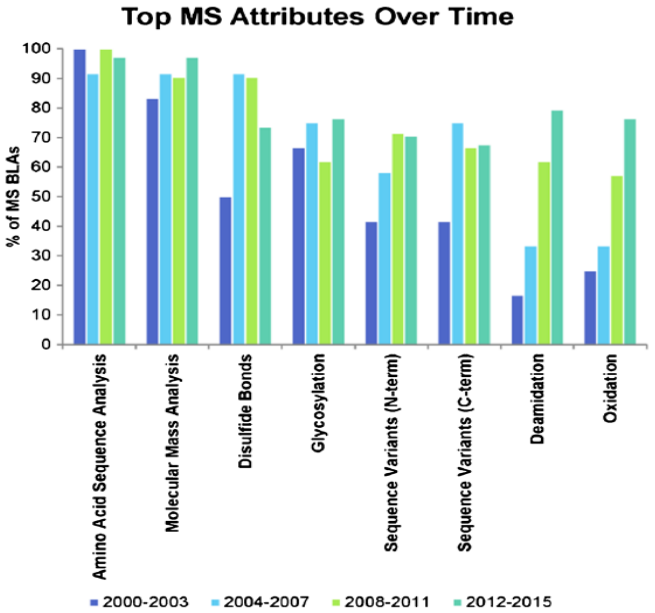
FDA Experience: Emerging Technologies

- Controlled ice nucleation for lyophilization processes
- Comprehensive product testing using a single multi-attribute assay (multi-attribute method)
- Continuous manufacturing for a downstream process
- End-to-end integrated bioprocess
- Pharmacy on demand (small manufacturing platform for continuous bioprocesses)

Mass spectrometry method usage in BLA

- 79 out of 80 electronic BLAs approved from 2000-2015 used mass spectrometry (MS) methods for DS characterization.



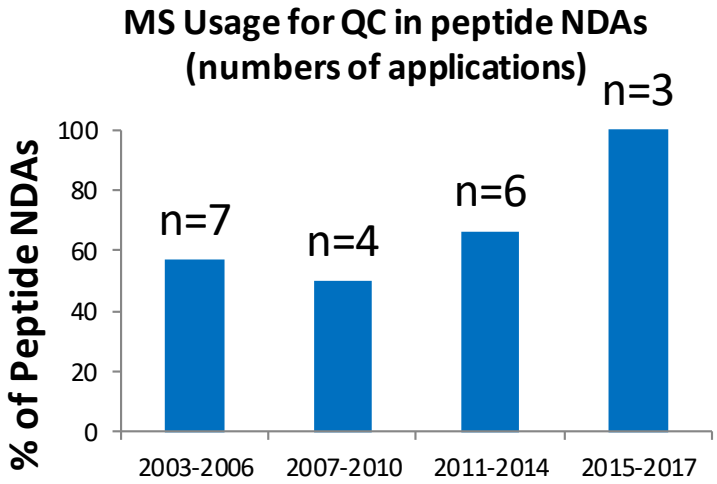


Sarah Rogstad, et.al. JASMS, 2016.

Usage of MS in QC testing

- MS is less commonly used in QC testing of protein molecules mainly due to the complexity of the protein molecules and technology limitations.

MS usage (as of 2017)	Protein BLAs	Peptide NDAs
Characterization	100%	100%
QC control	0%	65%

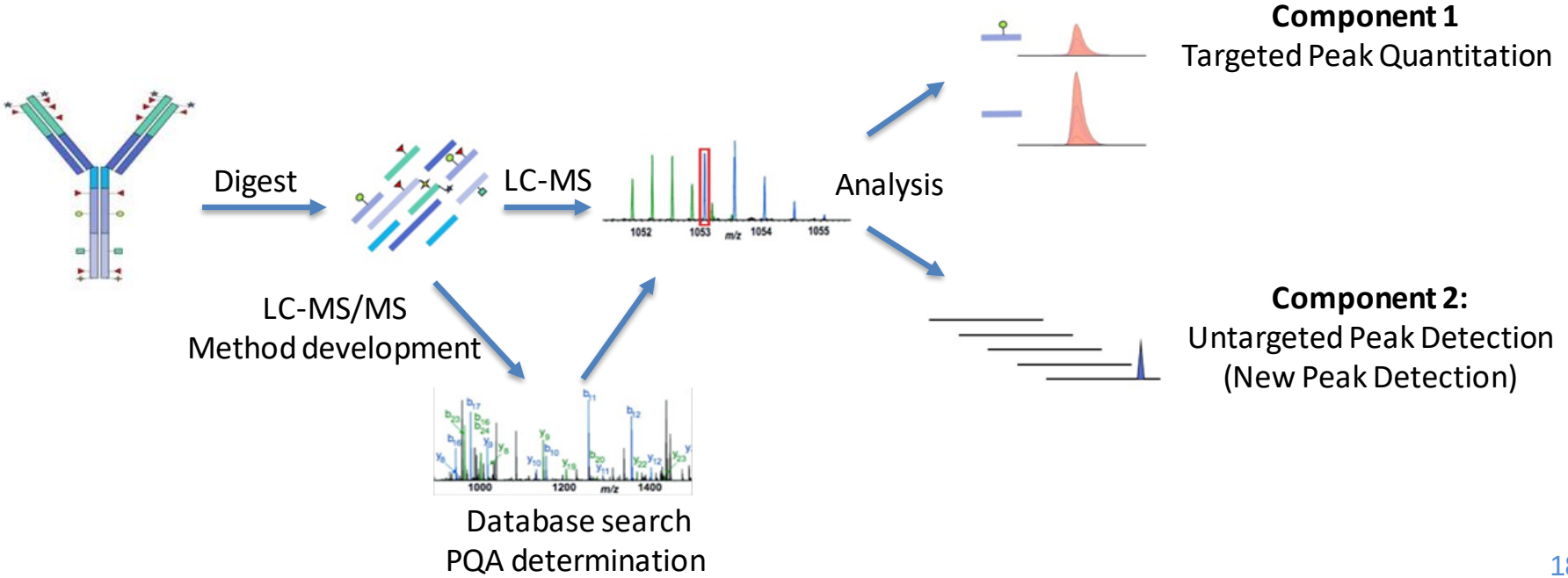


- With the improvement of MS technology (e.g., high resolution and high accuracy instruments), MS method has been proposed to control protein products recently.

FDA internal data mining, unpublished data

Introduction of MAM as a QC method

- Multi-Attribute Method (MAM) workflow: reduced peptide mapping LC-MS based method
- MAM has two important components.



MAM to replace conventional QC methods

- MAM has been proposed to replace multiple conventional methods in the control strategy.

Attributes	Conventional methods
Identification	Peptide map-UV
	ELISA
Purity and impurities	Charge variants by IEX/CEX
	Oxidation impurities by RP-HPLC
	Fragments variants by rCE-SDS
Glycan profiling	HILIC

General benefits of MAM

- MAM provides detailed information at the molecular level.
- MAM provides extensive structural information by quantifying multiple attributes in one single run.
- New peak detection allows unbiased screening of unexpected changes in product quality.
- MAM can differentiate between species that may overlap using conventional chromatographic methods.

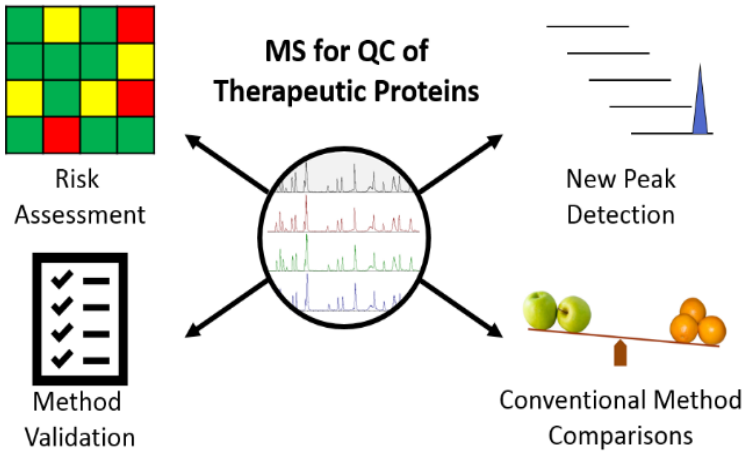
Regulatory considerations for QC methods

- General regulatory considerations for QC methods, and different expectations compared with characterization methods.

Regulatory considerations	QC methods		Characterization methods
	Release	Stability	
"Getting to know the molecule, its structure, and function"	No		Yes
Validated method	Yes		No
Specifications with acceptance criteria	Yes		No

- There are also some MAM specific regulatory challenges as a QC method.

Points-to-consider for MAM as a QC method

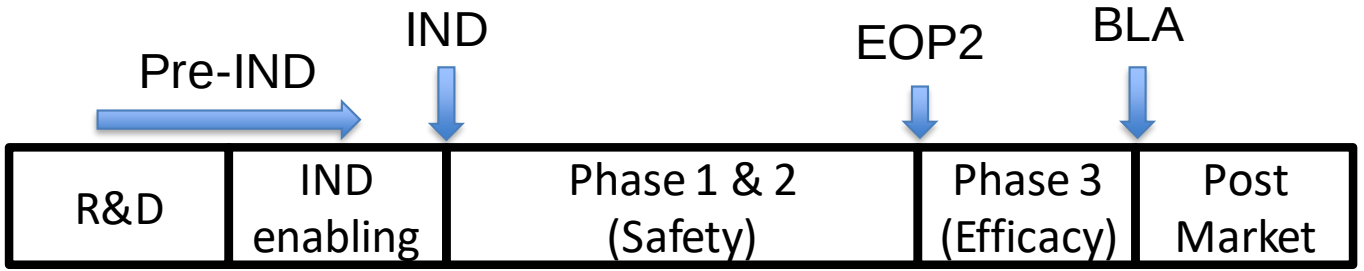


1. Product and CQA specific risk assessment relevant to the method
2. Approach for method validation
3. Capabilities and specificities of new peak detection feature
4. Bridging MAM with conventional methods (comparison)

Sarah Rogstad, et.al. Analytical Chemistry, 2019

Product and CQA specific risk assessment

- The risk assessment is a phase appropriate approach with the knowledge gained from product development.
- The selection of CQAs to be monitored by MAM relies on extensive characterization and understanding the specific product, therefore, **product specific data** is needed to support the risk assessment.
- Assess relevance/criticality of the information lost and gained compared with conventional methods to the quality, safety and efficacy of the product.

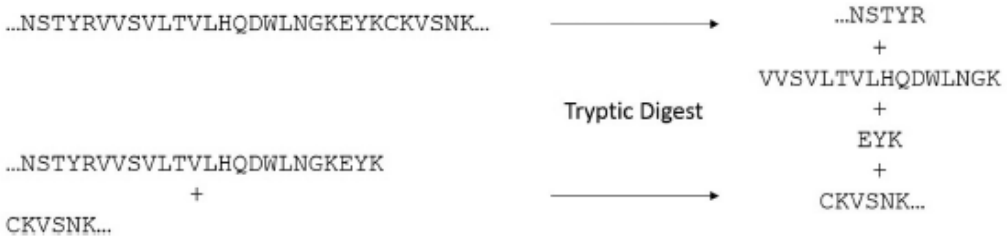


Potential example 1: risk and benefit assessment for MAM to replace rCE-SDS method to control low molecular weight species

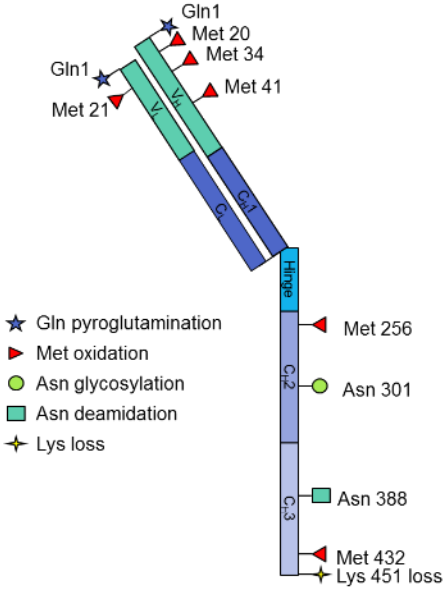
Low molecular weight species (LMWS) of Mab product may impact the biological function. LMWS is conventionally controlled by rCE-SDS. Can MAM replace rCE-SDS method to control LMWS?

- Benefit: MAM adds extra molecular level specificity.
- Potential risk: MAM would lose the information on the LMWS if the cleavage site is after lysine or arginine (masked by trypsin digestion).

Should weight benefits and risks for MAM implementation.



Potential example 2, risk and benefit assessment for MAM to replace RP-HPLC to control Met oxidation



Met oxidation on CDR region or Fc region of Mab product may impact the biological function. Met oxidation is conventionally controlled by RP-HPLC. Can MAM replace RP-HPLC method to control Met oxidation?

- Benefit: MAM adds extra molecular level specificity.
- Potential risk: MAM is not able to differentiate single oxidation or double oxidations on the same molecule.

Should weight benefits and risks for MAM implementation.

Approach for method validation

- 21 CFR 211.165 requires MAM as a QC method to be validated at the time of licensure.
- The goal of analytical assay validation is to demonstrate that the procedure is suitable for its intended use.
- There are some special considerations for MAM validation.

- Analytical procedure should describe in detail the steps necessary to perform the test.
  - Principle/Scope
  - Apparatus/Equipment
  - **Operating parameters**
  - Reagents/standards
  - **Sample preparation**
  - Standards control solution preparation
  - **Procedure**
  - **System suitability**
  - **Calculations**
  - **Data reporting**

- Validation based on ICH guidelines (ICH Q2) and FDA guidances.

Typical validation characteristics:

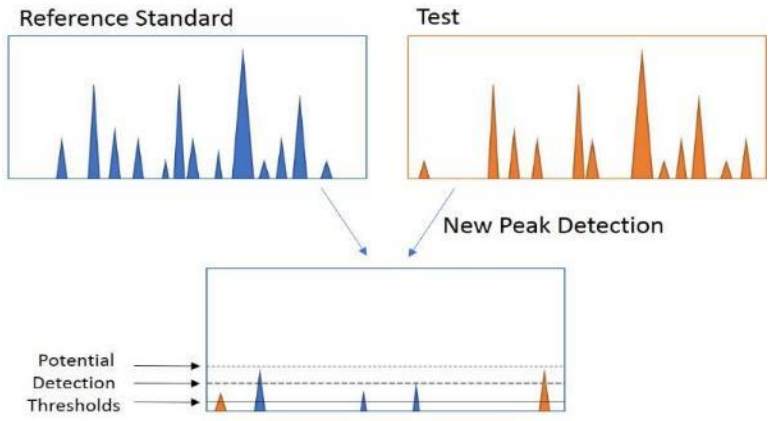
  - Specificity
  - Accuracy
  - **Precision**
    - Repeatability
    - Intermediate precision
  - **LOD and LOQ**
  - Linearity
  - Range
  - **Robustness**

Potential example 3: System suitability

- System suitability is important components for MAM to ensure LC and MS performance.
- System suitability samples selection (e.g., pierce peptide mixtures, digested known proteins, product reference standard).
- Concurrently digested standards would allow for assessment of digestion process as well.
- Establish proper acceptance criteria based on experience
  - Signal intensity
  - Retention time
  - Mass accuracy
  - Relative abundance % (e.g., an oxidation species)
  - Quantitation precision (%CV)

Capabilities and specificities of NPD

- NPD allows for the detection of unexpected changes.
- Data is needed for the justification of the selection of NPD parameters. (e.g., peak intensity threshold).
- Validation of NPD parameters should be performed on product specific samples. (e.g., product sample spiked with pierce peptide retention time calibration mixture).

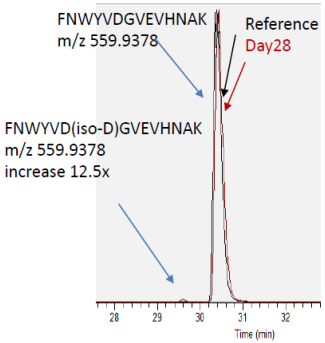


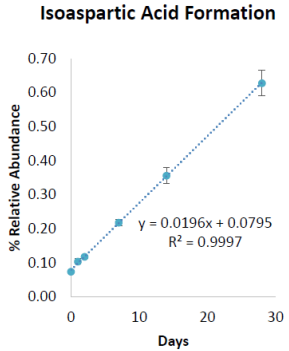
Potential example 4: NPD in stability testing

MAM is a stability indicating method.

- Targeting analysis of MAM should monitor the changes of the stability indicating PQAs.
- NPD during stability testing is able to detect unexpected changes.

If a new peak and a trending of the new peak was identified from stability samples over time, the identity of the new peak should be characterized and its potential impact on product quality should be assessed. If it is CQA, this peak should be included in targeted analysis.





Poster #61 presentation by Mercy Oyugi
Long-term stability testing of rituximab using the MAM

FDA internal research unpublished data

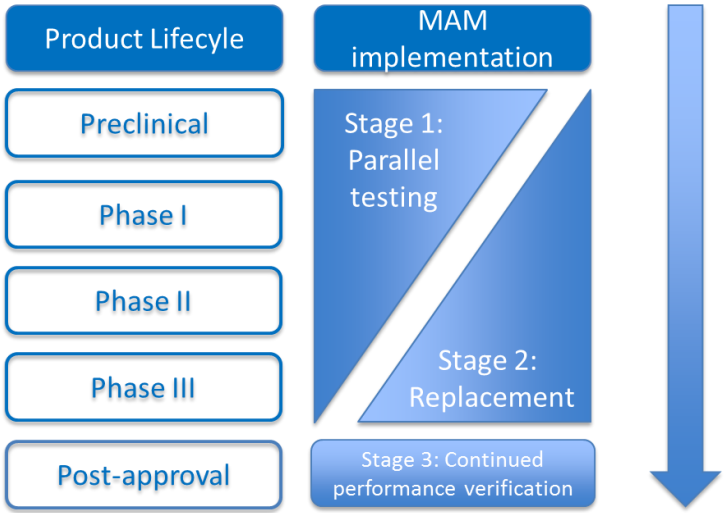
Bridging MAM with conventional methods

Comprehensive and product specific comparison between MAM and to be replaced conventional methods is needed. Data might include:

- Extensive characterization of product to identify CQAs. (e.g., identities and bioactivities of individual peaks of CEX)
- Stressed studies (e.g., thermo, low pH, high pH, photo, oxidation and freeze-thaw).
- Establish a correlation/trend for CQAs.

MAM implementation, sunset strategy

- A parallel testing phase is recommended for MAM and conventional methods before more production specific comparison data are available.
- The drive for MAM replacement is by product knowledge and method comparison data, not by phase of development.



- Meeting with the Agency for your implementation plan →ETT program: CDER-ETT@fda.hhs.gov

Conclusions

- Points-to-considers when implementation MAM as a QC method.
  - Risk Assessment
  - Method validation
  - New peak detection
  - Method comparison

- Timing of conventional method phase out depends on availability of product specific knowledge and method comparison data.

Acknowledgements

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- Yan Wang

Thank you!


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