Regulatory Considerations for Multi-Attribute Method Implementation

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Disclaimer

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

MANUAL OF POLICIES AND PROCEDURES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL QUALITY
Process for Evaluating Emerging Technologies Related to Quality

Table of Contents

- PURPOSE .................................................. 1
- BACKGROUND .......................................... 2
- POLICY .................................................. 2
- RESPONSIBILITIES .................................... 3
- PROCEDURES .......................................... 4
- REFERENCE ............................................. 5
- EFFECTIVE DATE ...................................... 5
- CHANGE CONTROL TABLE ........................... 6

PURPOSE

This MAPP describes the policies and procedures to be followed by the Office of Pharmaceutical Quality (OPQ) and the Emerging Technology Team (ETT) in the Center for Drug Evaluation and Research (CDER) either for reviewing a prospective applicant’s request to participate in the Emerging Technology Program (ETP) or for providing input on an emerging technology identified as 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), a 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 pre-submission 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.
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.

<table>
<thead>
<tr>
<th>MS usage (as of 2017)</th>
<th>Protein BLAs</th>
<th>Peptide NDAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characterization</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>QC control</td>
<td>0%</td>
<td>65%</td>
</tr>
</tbody>
</table>

- 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.

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Conventional methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Peptide map-UV</td>
</tr>
<tr>
<td></td>
<td>ELISA</td>
</tr>
<tr>
<td>Purity and impurities</td>
<td>Charge variants by IEX/CEX</td>
</tr>
<tr>
<td></td>
<td>Oxidation impurities by RP-HPLC</td>
</tr>
<tr>
<td></td>
<td>Fragments variants by rCE-SDS</td>
</tr>
<tr>
<td>Glycan profiling</td>
<td>HILIC</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Regulatory considerations</th>
<th>QC methods</th>
<th>Characterization methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Getting to know the molecule, its structure, and function”</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Validated method</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Specifications with acceptance criteria</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- 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.

### Timeline

<table>
<thead>
<tr>
<th>Pre-IND</th>
<th>IND enabling</th>
<th>Phase 1 &amp; 2 (Safety)</th>
<th>Phase 3 (Efficacy)</th>
<th>Post Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&amp;D</td>
<td>IND</td>
<td>EOP2</td>
<td>BLA</td>
<td></td>
</tr>
</tbody>
</table>

- **Pre-IND**:
  - Limited characterization

- **IND enabling**:
  - In depth characterization
  - Assay development
  - Tentative release and stability specifications

- **Phase 1 & 2 (Safety)**:
  - Continue characterization
  - CQAs assignment
  - QC assay validation
  - Specification setting
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.
  o Principle/Scope
  o Apparatus/Equipment
  o Operating parameters
  o Reagents/standards
  o Sample preparation
  o Standards control solution preparation
  o Procedure
  o System suitability
  o Calculations
  o Data reporting

➢ Validation based on ICH guidelines (ICH Q2) and FDA guidances.
  Typical validation characteristics:
  o Specificity
  o Accuracy
  o Precision
    ❑ Repeatability
    ❑ Intermediate precision
  o LOD and LOQ
  o Linearity
  o Range
  o 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
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.
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