Advanced technology for manufacturing process control

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US FDA Center for Drug Evaluation and Research

USP Biologics Stakeholder Forum

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What is Pharmaceutical Quality?

FDA

- 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.

Advanced Manufacturing

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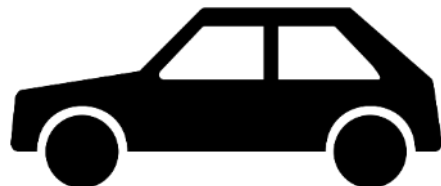
Produce better quality medicine. A transition to advanced manufacturing technology can facilitate operation above a six-sigma level, meaning manufacturers would see no more than 3.4 defects per million opportunities.

Develop drugs rapidly. Advanced manufacturing technology speeds the development of novel or patient-focused therapeutics (e.g., orphan drugs, oncology drugs, breakthrough therapies).

Prevent drug shortages. FDA found 62% of drug shortages were associated with manufacturing or quality problems. Advanced manufacturing can proactively reduce today's quality-related manufacturing issues.

Improve emergency preparedness. More agile and flexible manufacturing technology can help manufacturers pivot quickly to address unanticipated demands in a public health emergency.

Emerging Technology Program

Mission

To encourage and support the adoption of **innovative technology** to modernize pharmaceutical development and manufacturing through **close collaboration** with industry and other relevant stakeholders
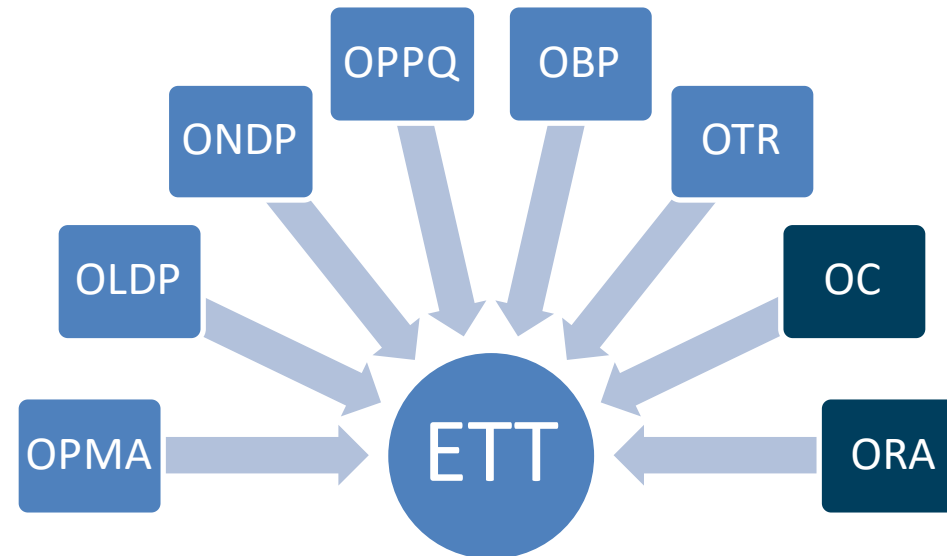
Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization
Guidance for Industry

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

September 2017
Pharmaceutical Quality/CMC

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


4

Current Trends in Biotech

- Continuous and semi-continuous manufacturing processes
  - First approval of semi-continuous drug substance process for a biotech product (2020)
  - Several other biotech CM processes under development admitted to the ETP

- Implementation of increasing complex process analytical technology (PAT)
  - Feedback and feedforward control mechanisms

- Multi-attribute methods (MAM)
  - Traditional off-line testing
  - On-line and in-line PAT tools
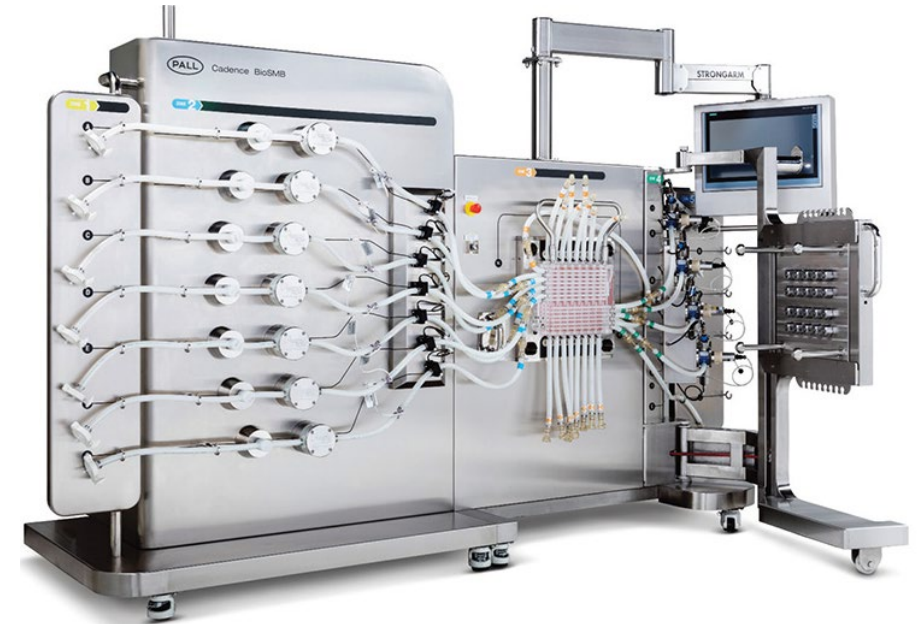
PAT in biotech manufacturing

- Common for small-molecules and simple biotech applications (e.g., pH, in-line UV flow cells, etc.)
- Moving beyond Level 3 control of bioreactors
  - Biocapacitance: monitor cell growth kinetics in real-time to enable automated feed additions
  - Raman spectroscopy: automated glucose feedback control
- Proposed for downstream process control and RTRT
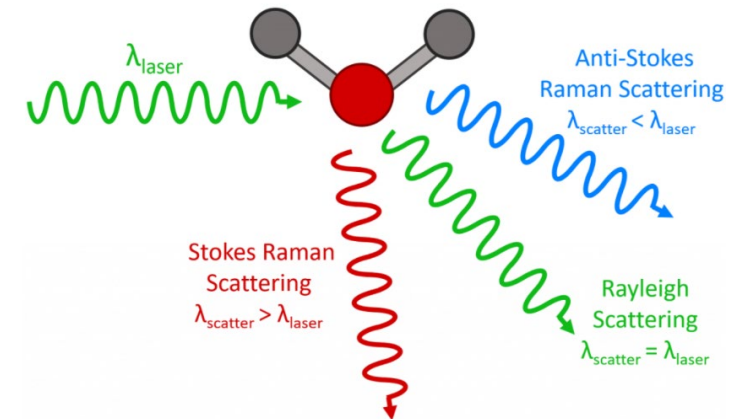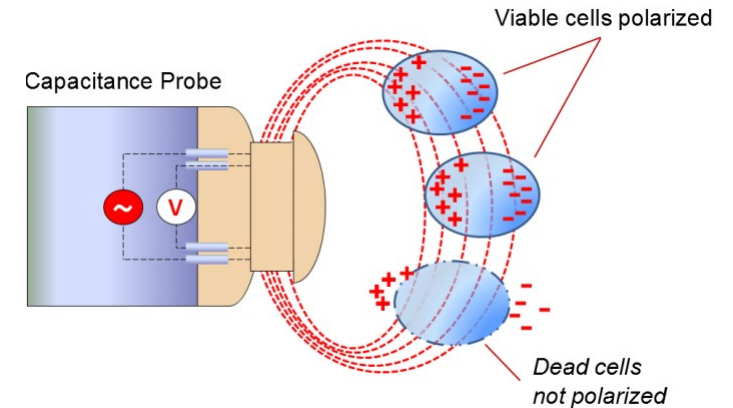
Multi-Attribute Method (MAM)

- Recent improvements in instrumentation have led to development of MS for control of therapeutic proteins

- MAM proposed for control biotech processes
  - Multiple products at different stages of product development
  - Conventional method sunset strategy for one applicant

- Applications inspired in-house assessment of MAM methodology focusing on reproducibility, robustness, and applicability vs conventional methods

LC-MS based peptide mapping
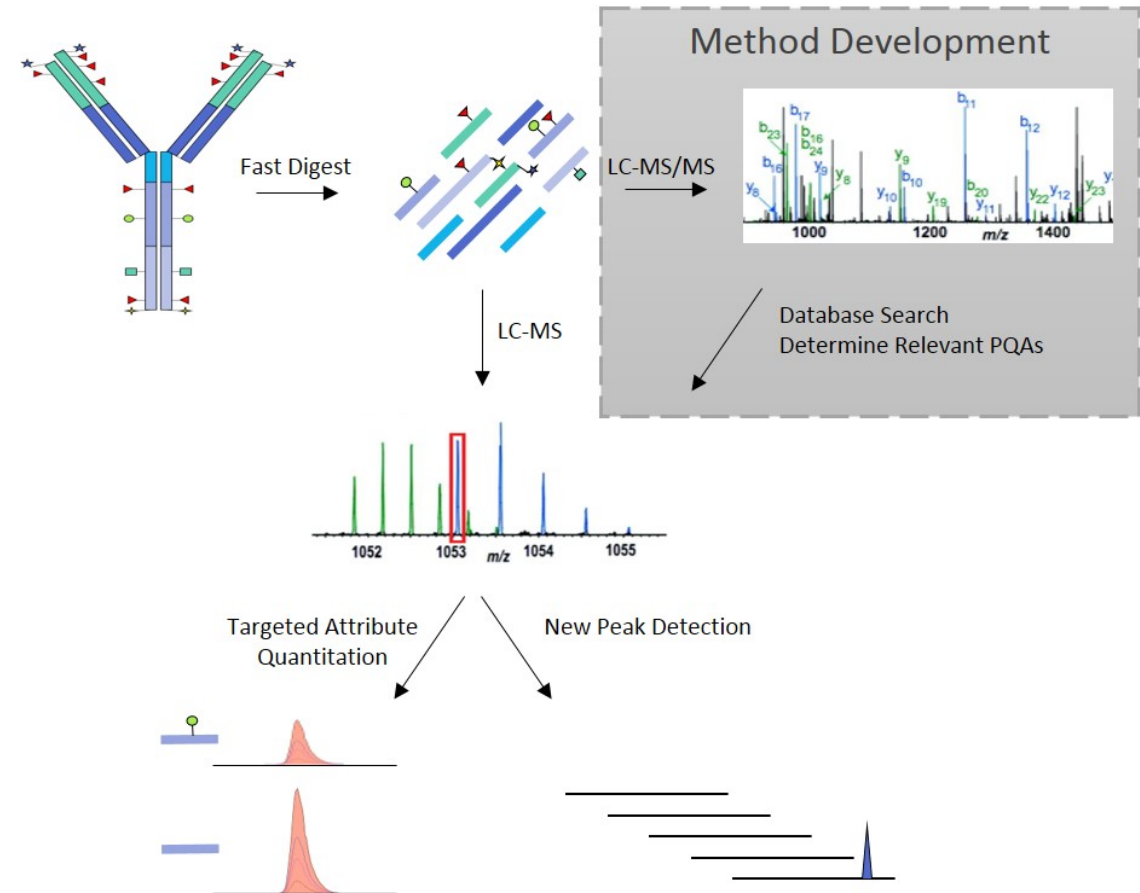
MAM Development

Four major points to consider:

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

Multi-Attribute Method for Quality Control of Therapeutic Proteins

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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.
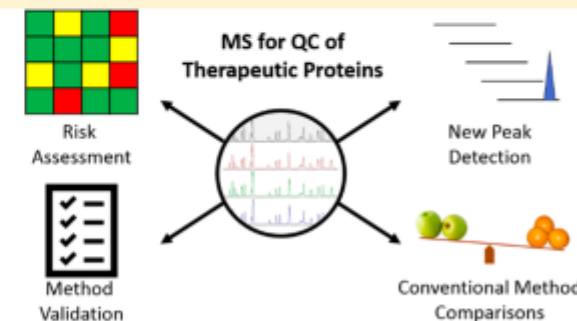
Current Trends in Biotech

- Increasing role for models in biotech control strategies
  - Models have already been implemented or proposed for process monitoring in both batch and continuous processes
    - In silico process development
    - Glucose control during cell culture
  - CM also uses models (e.g., RTD models) for:
    - Process development (e.g., supporting feeder limits)
    - Material traceability and propagation of disturbances
    - Material diversion
  - Models could potentially be used as part of process control if they:
    - Consider all relevant factors and their variations (e.g., potential variability generated by raw/input materials)
    - Reflect commercial operating conditions
    - Show adequate predictive power for the intended purpose through proper validation

Tian, G. *et. al*. Comp. & Chem. Eng. 2019
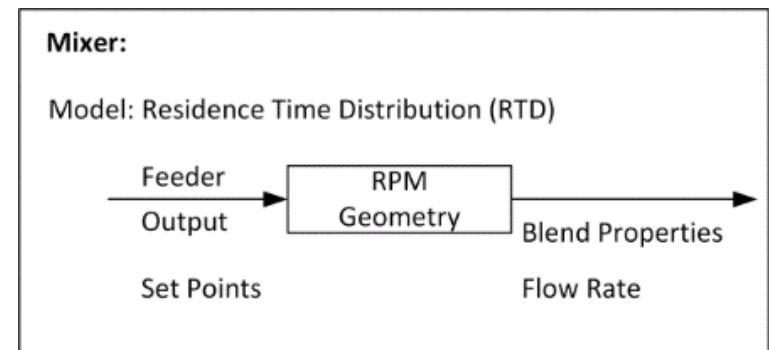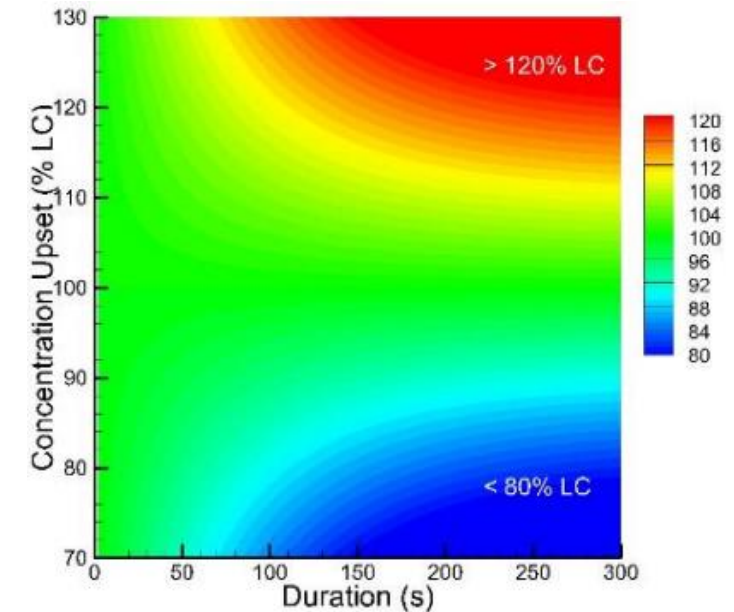
Model impact

- Low impact: These models are typically used to support product and/or process development (e.g., formulation optimization).

- Medium impact: Such models can be useful in assuring quality of the product but are not the sole indicators of product quality (e.g., most design space models, many in-process controls).

- High impact: A model can be considered high impact if prediction from the model is a significant indicator of quality of the product (e.g., a chemometric model for an assay, a surrogate model for dissolution).

Additional information: Guidance for Industry Q8, Q9, & Q10 Questions and Answers

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8-q9-q10-questions-and-answers-appendix-qas-training-sessions-q8-q9-q10-points-consider

Implementation of modeling

Hypothetical scenario: Model used during in silico process development to support proven acceptable ranges for chromatography
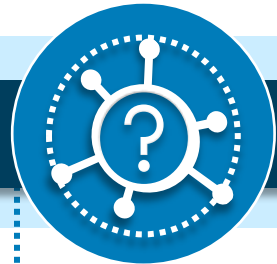
- Likely considered a medium impact model because it supports the control strategy
  - Model risk assessed by considering the influence of the model relative to other contributing evidence for making a quality decision. For example:
    - based solely on model predictions
    - model predictions and small-scale experiments
    - model predictions and limited commercial-scale experiments
- Regulatory filing should include information and data to support model development, calibration, and validation such as:
  - model assumptions
  - a summary of model inputs and outputs and their respective ranges
  - relevant model equations
  - a comparison of model prediction(s) with measured data
  - statistical analyses

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Implementation of modeling

Hypothetical scenario: Model used during in silico process development to support Proven Acceptable Ranges for chromatography

- Factors to consider for validating and supporting implementation
  - The role of the model relative to other experimental data in setting PARs
  - Purpose of the specific unit of operation
  - Product experience and applicable prior knowledge
    - CQAs evaluated by the model
    - Applicable product attributes/variants thoroughly characterized?
  - Supporting that a model is predicative of the commercial-scale process
    - Are small- and/or commercial-scale data available from either product under development or a representative product and unit operation to empirically understand impact of the process on CQAs?
  - Validation based on risk to process performance and/or product quality and should describe:
    - Number of samples and range of conditions tested
    - Comparative assessment to empirical process development and associated acceptance criteria
    - Uncertainties and sensitivities between the model predictions and the comparative experimental measurement
- Approach for monitoring model performance either on a routine basis or after a process change, as applicable for the model's context of use
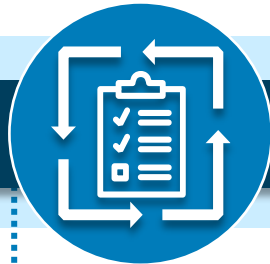
ETP Program Objectives

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

To engage international regulatory agencies to share learnings and approaches

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

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

To ensure consistency, continuity, and predictability in review and inspection
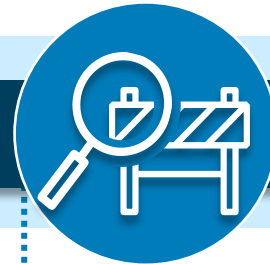
To identify and evaluate potential roadblocks relating to existing guidance, policy, or practice

To help establish scientific standards and policy, as needed

ETT Collaborative Approach

Early Engagement (Pre-submission)

Face-to-face meeting(s) with ETT involvement – provided upfront scientific input under the Emerging Technology Program

Emerging Technology Site Visit

Participation by OPQ (including the ETT member(s)) and/or ORA members

Integrated Quality Assessment (IQA)

Interdisciplinary team with experts in Drug Substance, Drug product, Process/Facility, Biopharm, and/or Inspection

ETT member as an Application Technical Lead (ATL) or co-ATL to lead the IQA team when the ET impacts most part of a CMC section

Pre-Approval Inspection (PAI)

Conducted by team members from OPQ (including the ETT Member(s)) and ORA.

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

Getting Ready for ETT Meetings

Regulatory Agencies

- Willing to learn / understand and recognize potential of new technologies with an open mind

- Make science- and risk-based assessments and decisions

- Be transparent to industry and not afraid to ask questions

- Multi-disciplinary approach (collaborative)

Industry

- Be transparent and willing to share with the agency early

- Not afraid to receive and answer many questions from the agency

- View regulators as part of your team

Right Mindset and Culture

Moving Forward...

- Enhancement of Emerging Technology Program (ETP 2.0)
  - Refine the operating model to meet increasing workload
  - Strengthen knowledge management and transfer

- Advanced manufacturing regulatory framework
  - If necessary, make changes to our current regulatory framework or create a new regulatory framework to facilitate the adoption of advanced manufacturing

- Collaborate with other CDER/OPQ efforts or initiatives to improve the effectiveness and efficiency of regulatory oversight of drug quality
  - Quality Surveillance Program (e.g., quality maturity, quality metrics)
  - ICH Q12 – Pharmaceutical Product Lifecycle Management

Thank You!