Advanced technology for manufacturing process control

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What is 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.
Advanced Manufacturing

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

Four major points to consider:

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

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