CDER Emerging Technology Program and Quality Related Regulatory Science Activities

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Outline

• Emerging Technology Program
• Continuous Manufacturing
• OPQ Regulatory Science Program
CDER’s Office of Pharmaceutical Quality

OPQ Objectives:

• Provide seamless integration of review, inspection, surveillance, and research across the product lifecycle

• Assure that all human drugs meet scientifically-sound quality standards to safeguard clinical performance

• Enhance science- and risk-based regulatory approaches

• Transform product quality oversight from a qualitative to a quantitative, expertise-based assessment

• Encourage development and adoption of emerging pharmaceutical technology
Emerging Technology

• What is an Emerging Technology?
  - Technology with which the FDA has limited review or inspection experience, but that has the potential to modernize the body of knowledge associated with pharmaceutical development
  - New technology (or technology not previously applied to pharmaceutical applications) intended to support more robust, predictable, and/or cost-effective processes or novel products
  - Innovative or novel products, manufacturing processes, or analytical technology subject to CMC review

• Examples of Emerging Technology include:
  - Continuous manufacturing of drug substances and drug products
  - “On-demand” manufacturing of drug products
  - Aseptic filling closed system
  - 3-D printed tablets
  - New container and closure systems for injectable products
The Emerging Technology (ET) Program provides a centralized collaborative platform for FDA and industry to accelerate the development and adoption of emerging technologies.
Emerging Technology Team (ETT)

- A small cross-functional team with representation from all relevant CDER and ORA review and inspection programs
  - Chair: Sau (Larry) Lee, Associate Director of Science, OPQ
  - PM: Cheryl Kaiser (OPQ/OPRO)
  - Members: Thomas O’Connor (OPQ/IO-SRS), Celia Cruz (OPQ/OTR), Mohan Sapru & Ray Frankewich (OPQ/ONDP), Geoffrey Wu (OPQ/OLDP), Kurt Brorson (OPQ/OBP), Grace McNally, Sharmista Chatterjee & Bryan Riley (OPQ/OPF), Tara Gooen (OPQ/OPPQ), Rebeca Rodriguez & Susanne Richardson (ORA)
  - Other subject matter experts as needed
Emerging Technology Team Functions

• Serve as a centralized location for external inquiries on novel technologies

• Provide a forum for firms to engage in early dialogue with FDA to support innovation

• Ensure consistency, continuity, and predictability in review and inspection
  – ETT member(s) plays an active or leadership role in the OPQ quality assessment team for applications containing an emerging technology

• Identify and evaluate roadblocks relating to existing guidance, policy, or practice

• Help establish quality standards and policy, as needed

• Long-term goals:
  – Facilitate knowledge transfer to relevant CDER and ORA review and inspection programs
  – Engage international regulatory agencies to share learnings and approaches

Contact us: CDER-ETT@fda.hhs.gov
Draft Emerging Technology Guidance

Provides recommendations to companies interested in participating in a program involving the submission of CMC information containing emerging manufacturing technology to FDA.

Applicable to companies that intend the technology to be included as part of an: investigational new drug application (IND) or original or supplemental new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) reviewed by the Center for Drug Evaluation and Research (CDER), and where that technology meets other criteria described in this guidance.
What is Continuous Manufacturing?

In a continuous manufacturing process, the material(s) and product(s) are continuously charged into and discharged from the system, throughout the duration of the process.¹

(1) Batch

(2) Hybrid

(3) End-to-End

¹ Lee S. et. al. J Pharm Innov. 2015 10:191-199
Why Continuous Manufacturing?

- FDA recognizes that continuous manufacturing (CM) has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
  - Integrated processing with fewer steps
    - No manual handling, increased safety
    - Shorter processing times
  - Smaller equipment and facilities
    - More flexible operation
    - Lower capital costs, fewer work-in-progress materials
    - Reduced environmental foot print
    - Feasible for manufacturing small batch sizes
  - On-line monitoring and control for increased product quality assurance in real time
    - Amenable to Real Time Release Testing approaches
Coordination Across Federal Agencies

- CM for pharmaceuticals identified as a current priority for the Federal Government

- In the White House report CM is defined at a high level, major technical challenges and opportunities are outlined, and a sampling of current and planned Federal programs and initiatives is highlighted

- Workshop is being planned with NSF, NIH, NIST, DoD, BARDA, and FDA to improve coordination of Federal programs in this technical area

ADVANCED MANUFACTURING:

A Snapshot of Priority Technology Areas Across the Federal Government

PRODUCT OF THE
Subcommittee for Advanced Manufacturing
OF THE NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

April 2016
Continuous Manufacturing – Emerging Technology

- FDA has identified CM as an emerging technology
  - CM is a new manufacturing approach for pharmaceutical application in comparison with other industries (e.g., food and chemicals)
  - Adoption and advancement of system engineering tools (e.g., model-based design and optimization and advanced process control) may be needed to maximize potential benefits
  - There is a general lack of experience within both the industry and regulatory agencies with this technology
  - CM has a great deal of potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing, and thus have a huge impact on product quality
  - CM could provide benefits to both patients and industry
Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

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Abstract The Food and Drug Administration (FDA) regulates pharmaceutical drug products to ensure a continuous supply of high-quality drugs in the USA. Continuous processing has a great deal of potential to address issues of agility, flexibility, cost, and robustness in the development of pharmaceutical manufacturing processes. Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These investments along with the adoption of the quality-by-design (QbD) paradigm for pharmaceutical development and the advancement of process analytical technology (PAT) for designing, analyzing, and controlling manufacturing have progressed the scientific and regulatory readiness for continuous manufacturing. The FDA supports the implementation of continuous manufacturing using science- and risk-based approaches.

Keywords Continuous processing • Quality by design • Process analytical technology • Control strategy • Traceability efficient, agile, flexible pharmaceutical sector that reliably produces high-quality drugs without extensive regulatory oversight [1]. The pharmaceutical manufacturing sector is in transition, but overall processes, which are largely batch in nature, remain relatively inefficient and less understood as compared with those in other chemical process industries [2].

The lack of agility, flexibility, and robustness in the pharmaceutical manufacturing sector poses a potential public health threat as failures within manufacturing facilities that result in poor product quality can lead to drug shortages [3]. Drug shortages are a critical health care issue, affecting individual patients across the USA. Recognizing that shortages commonly begin with a supply disruption related to product or facility quality, FDA is focusing on encouraging and sustaining advancements in pharmaceutical manufacturing. Continuous manufacturing is one such innovation that has a great deal of potential to improve agility, flexibility, and robustness in the manufacture of pharmaceuticals. This article summarizes the potential advantages of continuous manufacturing for pharmaceutical products and highlights some unique quality aspects for consideration and how they may be addressed.
Trends in Continuous Manufacturing

• Orkambi (lumacaftor/ivacaftor)
  – 1st NDA approval for a continuous drug product manufacturing process for a new cystic fibrosis drug (July 2015)

• ~15 ETT-Industry meetings since the launch of ET program in early 2014 providing feedback on the development of CM processes
  – Drug substances
  – Drug products
  – Small molecules and biotechnology products
  – Facility visits

• Prezista (darunavir)
  – 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (April 2016)
Drug Quality Science & Research Needs

- Improving post-market data sources and their use in analyzing product quality
- Improving risk assessment and management strategies to reinforce the safe use of drugs
- Evaluating links between product quality attributes, manufacturing, and performance
- Developing predictive models of safety and efficacy in humans
- Enhancing individualization of patient treatment

*A subset of CDER’s identified science & research needs*
1. Manufacturing Science & Innovation
2. Product Quality Standards
3. Advanced Characterization of Biologic Products
4. Physicochemical Characterization of Complex Dosage Forms
5. Post Market Quality Assessment
6. Immunogenicity & Immunology
7. Linking Quality Attributes to Safety & Efficacy

*Word cloud of all OPQ research publication titles in 2015
Manufacturing Science and Innovation

- Utilize QbD approach to product development to aid effective assessment of scale-up approaches for commercial production
  - Evaluate complex batch processes for high-risk APIs and solid oral dosage forms across scales.

- Develop process modeling and simulation tools to facilitate quantitative initial risk assessment for product quality
  - Assess the effects of critical material attributes and process parameters on product quality attributes through sensitivity analysis.

- Advance manufacturing technologies to bring agility, flexibility and robustness in pharmaceutical manufacturing
  - Build knowledge platform to aid effective regulatory quality assessment of emerging manufacturing technology.
Drug Quality Standards

• Develop methods and standards to support efficient drug evaluation and lifecycle management
  – Establish quality standards for complex drug substances and products (e.g., heparin, iron-colloid products, and ophthalmic emulsion).
  – Evaluate abuse-deterrent properties of opioid products.
  – Develop a standardized analytical approach for testing the quality of products administered through a nasogastric (NG) tube.

Acid resistance test results (as % esomeprazole released) of Nexium 20mg and 40mg capsules delivered through NG tubes with 0 or 15 minute incubation in DI or tap water
Advanced Characterization of Complex Mixtures and Biologics

• Develop “fingerprint-like” characterization to assess chemical structure of complex molecules
  – Assess equivalence amongst complex molecules that are heterogeneous (e.g., enoxaparin, conjugate estrogen, and glatiramer acetate).

• Develop quantitative analysis and modeling tools to assess equivalence between test and reference
  – Develop an integrated model for comparative characterization of complex molecules (e.g., pentosan polysulfate).
  – Develop chemometric methods in comparing analytical data of complex drug products (e.g., enoxaparin and glatiramer acetate).

LC-MS chromatographic alignment of glatiramer acetate samples. These data supplemented the regulatory review and helped to inform the decision to approve the first generic GA product.
Physicochemical Characterization of Complex Dosage Forms

• Develop integrated analytical approaches to support pharmaceutical and therapeutic equivalence for complex formulations and dosage forms
  – Evaluate the effect of formulation and process factors on the quality and performance of transdermals, drug products containing nanomaterials, drug-device combination products (e.g., nasal spray suspension and inhalation products), etc.

CytoViva Images of Restasis®

Applying a spectral library to map the location of cyclosporine in ophthalmic emulsion

Hyperspectral Images of Restasis®
Post-Market Quality Assessment and Public Health Issues

- Determine the underlying reasons when drug products lose efficacy or cause adverse events
  - Detect impurities or contaminants in drug products (e.g., OSCS in heparin)
  - Examine the quality of injectable products
  - Explore a set of “quality metrics” that have broad utility across industry segments in quality oversight of manufacturing facilities

Synthesis and detection of N-sulfonated oversulfated chondroitin sulfate (NS-OSCS) in marketplace heparin
Immunogenicity and Immunology

• Develop new methods to prospectively determine immunogenicity risk
  – Assess innate immune response modulating impurities in therapeutic peptides (test synthetic peptide vs. reference recombinant peptide).

Integration of data from animal models and in vitro studies to identify sensitive biomarkers and establish clinically relevant limits.
2015 OPQ Research Impact

2015 Research Impact*

% of OPQ Projects

Publication(s) | Informed Regulatory Decision/Review | External Presentation(s)/Training | Tech/Internal Report(s) | Regulatory Standards | Informed Guidance (or Draft) | General Advice or Warning Letter | Allowed Screening/Monitoring of Products | Technology Transfer Agreement

Future Research Impact*

% of OPQ Projects

Influence Decision Making/Review | Enhance Understanding | Development/Validation of Method | Define Biomarkers | Assay Development | Will Inform Guidance | Allow Screening/Monitoring of Products | Regulatory Standards | Medical Countermeasures | Evaluate Adverse Events | Surveillance/Understand Supply Chain | Training Program

*Preliminary analysis based on self-reported, uncategorized, narrative impact statements