How CDER is Encouraging Adoption of Emerging Technologies in Pharmaceutical Industry

Moderator: Lawrence Yu
Speakers: Thomas O’Connor & Sharmista Chatterjee
Emerging Technology: A Key Enabler for Modernizing Pharmaceutical Manufacturing and Advancing Product Quality

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AAPS 2016 Annual Meeting and Exposition
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Outline

• Office of Pharmaceutical Quality (OPQ) and Quality Trends
• Drivers for the Adoption of Emerging Technologies
• OPQ Programs and Initiatives
  – Emerging Technology Team
CDER’s Quality Journey

2002: Pharmaceutical cGMPs for the 21st Century

2004: PAT Guidance

2006: ICH Q9

2008: ICH Q10

2009: ICH Q8

2011: Process Validation Guidance

2012: ICH Q11

2015: Stand-up OPQ

Building the Science and Risk Based Foundation for the Regulation of Pharmaceutical Quality
Office of Pharmaceutical Quality (OPQ)

Mission
OPQ assures that quality medicines are available to the American public

Vision
OPQ will be a global benchmark for regulation of pharmaceutical quality

Slogan
‘One Quality Voice’
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
OPQ Structure

Immediate Office
Director: Michael Kopcha
Deputy Director: Lawrence Yu

Office of Program and Regulatory Operations
Director: Giuseppe Randazzo

Office of Policy for Pharmaceutical Quality
Director: Ashley Boam

Office of Biotech Products
Director: Steven Kozlowski

Office of New Drug Products
Director: Sarah Pope Miksinski

Office of Lifecycle Drug Products
Director: Susan Rosencrance

Office of Process and Facilities
Director: Robert Iser

Office of Surveillance
Acting Director: Sarah Pope Miksinski

Office of Testing and Research
Director: Cindy Buhse
Drivers for Modernizing Pharmaceutical Manufacturing

- Quality issues account for 2/3 of drug shortages
- Surge in drug product recalls due to quality issues
- The supply chain is globalized at an unprecedented level
- Major advances in the scientific landscape are pressuring existing regulatory paradigms, especially around biosimilars, precision medicine, combination products and the use of real-world data
Emerging Technologies Key to Addressing Pharmaceutical Manufacturing Challenges

• Address the underlying causes of product recalls and drug shortages
  – Two thirds of drug shortages resulted from product-specific quality failures or general manufacturing facility issues
  – Product recalls has surged over the past couple of years

• Facilitate new clinical development – precision medicines
  – Enable a wider range of novel dosage forms, a wider range of doses without extensive alterations of the process, and convenient fixed-combination dosage forms

• Improve manufacturing efficiency
  – Increase process robustness
  – Lower manufacturing costs for pharmaceutical products
  – Increase supply chain flexibility
The Desired State

The Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
OPQ Programs and Initiatives

• Emerging Technology Team

• Advancing Regulatory Science

• Stakeholder Engagement and Communication
Emerging Technology

• What is an Emerging Technology?
  – Technology with the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty
  – Innovative or novel product, manufacturing process, or analytical technology subject to CMC review

• Examples of Emerging Technology include:
  – Continuous manufacturing of drug substance and drug product
  – “On-demand” manufacturing of drug products
  – Use of robots in pharmaceutical manufacturing
  – 3-D printed tablets
  – New container and closure system for injectable products
**CDER Emerging Technology Program**

**OPQ Priority**: A collaborative approach with manufacturers that encourages innovation and the adoption of new technologies.

Emerging Technology Team (ETT)

• Vision
  – Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience

• A small cross-functional team with representation from all relevant FDA quality review and inspection programs (OPQ/CDER & ORA)
  – 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), Rapti Madurawe, Sharmista Chatterjee & Bryan Riley (OPQ/OPF), Grace McNally & Tara Gooen (OPQ/OPPQ), Thomas Arista & Susanne Richardson (ORA), Rick Friedman (OC)
  – Other subject matter experts as needed:
FDA ETT Objectives

- To serve as a centralized location for external inquiries on novel technologies
- To provide a forum for firms to engage in early dialog with FDA to support innovation
- To ensure consistency, continuity, and predictability in review and inspection
- To identify and evaluate roadblocks relating to existing guidance, policy, or practice
- To help establish review and inspection standards and policy, as needed
- To facilitate knowledge transfer to relevant CDER and ORA review and inspection programs
- To engage international regulatory agencies to share learnings and approaches
Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry

**DRAFT GUIDANCE**

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to [http://www.regulations.gov](http://www.regulations.gov). Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sue L. Lee 240-256-9136.

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

December 2015
Pharmaceutical Quality/CMC

• 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.
Meeting Requests

• Submit electronically to CDER-ETT@fda.hhs.gov

• Request should include:
  1) A brief description of the proposed technology;
  2) A brief explanation why the proposed technology is substantially novel;
  3) A description of how the proposed technology could modernize pharmaceutical manufacturing and thus improve quality;
  4) A summary of the development plan and any perceived roadblocks to implementation (e.g., technical or regulatory);
  5) A timeline for a submission (IND, ANDA, BLA, NDA, original or supplemental)

• Meeting request should generally not exceed 5 pages
  – If accepted, more detailed information can provided in a separate meeting package along with specific questions to the Agency
Application Specific Emerging Technology Inquiries

• OPQ review leads will conduct technical triage and evaluation of meeting requests or regulatory applications following appropriate established procedures
• If a potential ET is identified during the process, the review lead will submit a consult request to the ETT Chair
• If the ETT chair confirms that the meeting request or regulatory application contains an ET, he or she will assign an appropriate ETT Member(s) to be part of the OPQ review team.

ETT is a champion for the adoption of novel technologies that have the potential to positively impact product quality for patients
Integrated Quality Assessments under the Emerging Technology Program

• **Early Engagement (Pre-submission)**
  – Face-to-face meeting(s) with ETT involvement – provided upfront scientific input under the Emerging Technology Program

• **Pre-Operational Visit (POV) if needed**
  – 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 a Co-Application Technical Lead

• **Pre-Approval Inspection (PAI)**
  – Conducted by team members from OPQ (including the ETT Member(s)) and ORA.
ETT Industry-Interactions

• Number of requests to participate in program:
  – 2015: 10
  – 2016: 20

• Number of meetings/t-cons:
  – 2015: 11
  – 2016: 15

• ETT has provided feedback on wide range of emerging technologies:
  – “On-demand” manufacturing of drug products
  – Use of robots and other technologies in pharmaceutical manufacturing of sterile products
  – 3-D printed tablets
  – New container and closure systems for injectable products
  – Innovative dosage forms
ETT Trends

• Continuous Manufacturing
  – Drug product
  – Drug Substance
  – Biotechnology products
  – Facility visits

• Sterile Manufacturing/Injectable
  – Robotics
  – New container closure systems

• Biotechnology Process/Analytics
  – On demand production
  – Multi-attribute methods
  – Model based control

• Other
  – 3D printing
  – New dosage forms
Notable Approvals

• Aprecia’s SPRITAM (levetiracetam)
  – 1\textsuperscript{ST} NDA approval for using 3D printing technology for production of a epilepsy drug (tablet) (August 2015)\textsuperscript{1}

• Prezista (darunavir)
  – 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (tablet) (April 2016)\textsuperscript{2}

\textsuperscript{1}https://www.aprecia.com/pdf/2015_08_03_Spritam_FDA_Approval_Press_Release.pdf
\textsuperscript{2}http://www.pharmtech.com/fda-approves-tablet-production-janssen-continuous-manufacturing-line
Working Together We Will Achieve the Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
Implementation of Emerging Technologies: Case Studies

Sharmista Chatterjee, Ph.D.
Division Director(Acting), Division of Process Assessment II, Office of Process & Facilities (OPF)/OPQ/CDER/FDA
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• Case Study 1: 3 D Printing
• Case Study 2: Continuous Manufacturing
• Conclusion
FDA APPROVES THE FIRST 3D PRINTED DRUG PRODUCT

Aprecia Introduces its First Product Using the ZipDose® Formulation Platform for the Treatment of Epilepsy

BLUE ASH, Ohio, August 3, 2015 – Aprecia Pharmaceuticals Company today announced that the U.S. Food and Drug Administration (FDA) has approved SPRITAM® levetiracetam for oral use as a prescription adjunctive therapy in the treatment of partial onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures in adults and children with epilepsy.¹ SPRITAM utilizes Aprecia’s proprietary ZipDose® Technology platform, a groundbreaking advance that uses three-dimensional printing (3DP) to produce a porous formulation that rapidly disintegrates with a sip of liquid.¹ While 3DP has been used previously to manufacture medical devices, this approval marks the first time a drug product manufactured with this technology has been approved by the FDA.
3-D Powder-Bed Printed Drug Products

• Product considerations
  – What should be the dosage form name? Technology is ‘invisible’
    • Labeling
  – Can tablets withstand shipping/handling? No compression. Friable?
  – Indicators for clinical performance?
    • Dissolution, content uniformity, impurities, form stability

• Manufacturing Process/Control Strategy considerations
  – Control of raw materials for even layers, printability, binding, etc.
    • Particle (powder bed) and print fluid properties
  – Manufacturing Process
    • Manufacturing risks: E.g., Layer thickness, printing, binding, de-dust, recycling
    • Process parameters: E.g., Powder feed rate, roller speed, print head speed, print head liquid fill height, layer drying time/temp, # of powder recycles
    • Identification of high risk unit operations and risk mitigation strategy
  – PAT/In-Process Controls
ETT Role in the 3D Printed application

- **Integrated Quality Assessment (IQA)**
  - ETT member served as a Co-Application Technical Lead
  - ETT members facilitated resolution of policy issues, e.g. labeling
    - Led cross functional discussions within CDER

- **Pre-Approval Inspection (PAI)**
  - Participation of ETT member
Case Study 2

FDA Allows First Switch From Batch to Continuous Manufacturing for HIV Drug

Posted 12 April 2016
By Zachary Brennan (/SearchRegFocus.aspx?name=Zachary Brennan)

The US Food and Drug Administration (FDA) for the first time in its history allowed a manufacturer to switch from the more antiquated batch manufacturing process to a continuous manufacturing process – a move that FDA is seeking to encourage among more pharmaceutical manufacturers.

The manufacturing change, announced last Friday, is for Janssen’s HIV-1 treatment Prezista (darunavir). And although Janssen isn’t the first manufacturer to use continuous manufacturing (Vertex’s cystic fibrosis drug Orkambi [lumacaftor/ivacaftor] has been using the continuous manufacturing process since its approval in July 2015), FDA is keen on pushing more manufacturers to this newer, more efficient process that can enable faster production and more...

Some Considerations when Switching from Batch to Continuous

- **Defining a batch for a CM process**
  - Based on run time and mass flow rate
  - Batch size defined by manufacturer prior to start of manufacture
  - Stability requirements

- **Formulation & Incoming material considerations**
  - Any change in formulation
  - Impact on label
  - Any additional specifications needed for in-coming materials

- **In-process controls**
  - Establishing state of control
  - Methods to detect and remove non-conforming product

- **Release specifications**
  - If RTRT (Real Time Release Testing) is used, are proposed acceptance criteria statistically supported
  - Any models used for release?

- **Establishing equivalency to marketed product**
  - BE study or can biowaiver be granted?
ETT Role in the CM application

- Pre-submission meeting
  - Face-to-face meeting with ETT involvement – discussions on control strategy, bioequivalence, batch definition

- Pre-Operational Visit (POV)
  - Participation by ETT members – understand proposed quality system, control strategy implementation considerations

- Integrated Quality Assessment (IQA)
  - ETT member served as a Co-Application Technical Lead
  - ETT members facilitated resolution of policy issues

- Pre-Approval Inspection (PAI)
  - Participation of ETT member
Concluding Remarks

- Emerging technologies offer the promise of novel therapies for patients and modernizing pharmaceutical manufacture.
- FDA supports the implementation of innovative technologies using a science and risk-based approach.
- Early and frequent discussion with the Agency during technology development facilitates first cycle approval.
- The Emerging Technology Program enables early FDA-Industry interactions, even before IND submission.
- ETT member(s) played an active reviewer as well as leadership role in the OPQ quality assessment team for these applications.
Plug for Some Related AAPS sessions

Fast-Tracking Innovation: Using Emerging Technologies to Facilitate Speed to Market
Emerging technologies are paving the way to higher quality manufacturing of drugs. Technologies that enable continuous manufacturing processes, e.g., use of extrusion techniques for continuous manufacturing of drug products, have become commercially feasible. Antibody-drug conjugation technologies allow for more consistent drug payload, more stable chemical linkers, lower cytotoxicity, and higher production efficiency. And 3D printing has come a long way, with the Food and Drug Administration approving the first drug manufactured by 3D printing, SPRITAM. This session aims to examine learnings from these examples to illustrate the importance of innovation toward enhancing patient lives.

This symposium will be held on Tuesday, November 15, from 1:20 pm to 3:40 pm.

A New Chapter in Pharmaceutical Technology: 3D Printing for Solid Oral Dosage Forms
This session will discuss the motivation for developing 3D-printed drug products for oral administration and the process and regulatory considerations for drug manufacturers and regulators. In August 2015, the Food and Drug Administration approved the first 3D-printed drug product (for oral administration) and observed that research interest in this area is growing. In this session, there will be focused discussion on the scientific progress with 3D-printed drug products, process development, and uptake of this promising technology for developing medicines for the 21st century.

This symposium will be held on Thursday, November 17, from 9:40 am to noon.

Continuous Manufacturing of Drug Product: Technical and Regulatory Challenges
Technology advances have opened the door for continuous manufacturing of drug products. Several major pharma-ceutical companies are developing continuous manufacturing processes for either existing or new products. This symposium will focus on: (1) regulatory and quality considerations of continuous manufacturing, particularly when transitioning from batch to continuous for an existing product; (2) case studies highlighting challenges associated with developing continuous manufacturing process for existing products; and (3) role of enabling process analytical technology to demonstrate process control in a continuous manufacturing process.

This symposium will be held on Tuesday, November 15, from 9:40 am to noon.
Thank you!