Pharmaceutical Quality – Opportunities and Expectations

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Quality Is the Foundation

QUALITY

SAFETY  EFFICACY
Our primary stakeholder
Expectations for Quality

• Quality expectations/standards are the same irrespective of approval process
  – Accelerated vs. Regular, Brand vs. Generic

• Willing to accept inherent risk as long as benefit outweighs the risk

• Expectations for safety, efficacy, AND quality
  – Package insert has no section for quality-related risk
Quality Is a Shared Responsibility

• **FDA’s Goal:** Ensure industry can manufacture products that consistently safely deliver their intended benefit to the patient.

• **Industry:** Understand and manage their manufacturing processes and expand the product/process body of knowledge to facilitate continual improvement (ICH Q10).
Getting There Requires...

• **FDA and industry:**
  – Commitment to a culture of innovation, efficiency, and continual improvement
  – Transparent, risk-informed decisions
  – Communication/cooperation

• **A strategic approach informed by potential quality risks**
  – Information enables confidence in the quality of drug products
  – FDA can allow industry more flexibility, while prioritizing resources towards areas of greater risk
A Culture of Innovation...

Innovation in FDA regulatory approaches:

• Advancing emerging technologies

• Understanding relationships between quality attributes and clinical performance
  – Setting clinically relevant specifications

• Regulatory decisions regarding quality that are well-informed, risk-based, and patient-focused

• A lifecycle approach - structure and processes in OPQ facilitate learning
  – IND to NDA, NDA to NDA supplement, NDA to ANDA
Focus on Emerging Technology

• Recognition that emerging manufacturing technology may lead to improved product quality throughout a product’s lifecycle

• Formation of the Emerging Technology Team
  – Team of subject matter experts available to:
    • Answer questions from industry about planned submissions
    • Help address policy issues related to new manufacturing technology
    • Serve as lead or co-lead on quality assessment team for marketing applications
  – Described in “Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base: Guidance for Industry” (December 2015)
  – Both the guidance and a corresponding MAPP are being finalized
2015  Approved the first 3D printed drug product
   – Spritam (levetiracetam) for treatment of epilepsy

2015  Approved the first NDA for a breakthrough treatment to treat cystic fibrosis; first continuous manufacturing (CM) process
   – Orkambi (ivacaftor and lumacaftor)

2016  Approved the first Prior Approval Supplement for switching from a batch to a continuous process
   – PREZISTA® (darunavir) Oral Tablets for treatment of HIV-1 infection

• ETT has engaged with numerous companies:
  – Container closure systems, continuous manufacturing, 3D printing, aseptic filling

• For more, visit OPQ’s Emerging Technology Program website
  (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm)
Applying Clinical Relevance to Quality

• A high quality drug product reproducibly delivers the therapeutic benefit to the patient stated in the label, free of defects and undeclared risks (e.g., contamination)

• **Attributes**
  – Begin with the end in mind
    • Design the product to meet patients’ needs and the intended performance
  – Develop the Quality Target Product Profile (QTPP)
    • Characteristics of a drug product that ideally ensure the desired quality, taking into account safety and efficacy - ICH Q8(R2)
  – Identify “clinically relevant” CQAs
    • Characteristics impacting product quality

• **Specifications**
  – Such as: Dissolution, Impurities, Size/Shape/Delivery/Design
Clinical Relevance and Risk Communication

• Frequent interfaces for risk communication in all stages of Quality Risk Management

• Risk communication should follow ICH Q9
  – With a focus on risk to quality and ultimately risk to clinical performance

• Risk communication also applies to:
  – OPQ communication of quality concerns to OND and OGD for overall risk-benefit assessment
  – OPQ communication to applicants regarding application and inspection concerns
Performing team-based quality assessments of applications inclusive of drug substance, drug product, manufacturing, and facilities.

OPQ - Seamless Integration of Review, Inspection, Surveillance, Policy, and Research

- Drug Substance Experts
- Product Experts
- Process Experts
- Facility Experts

‘One Quality Voice’

Technical Advisors
- OTR
- OPPQ
- OS

Others as needed
Knowledge Management Across the Product Lifecycle

- An integrated **Knowledge Base** allows for:
  - Parity in the quality assessment of brand and generic drugs
  - Consistent quality standards for brand and generic drugs
  - Clearer identification of product and process risks
  - Quick addressment of quality issues
Efficiency in Regulatory Oversight

OPQ is:

• Exploring ways to streamline review documentation to speed application review

• Implementing more frequent review communication
  – Particularly for complex products
  – Learning from experience with new drugs

• Supporting ICH Q12
  – Tools to reward premarket development and post-market continual improvement with regulatory flexibility

• Developing and using multiple surveillance tools to focus resources on facilities and products of highest risk
A Two-Way Street

An agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight

• CDER’s 2004 vision will take more than just changes at FDA

• Changes must be embraced by industry as well
Increasing Regulatory Efficiency

• When industry demonstrates a commitment to quality (an effective pharmaceutical quality system – ICH Q10):
  – FDA can use that information to inform regulatory decisions
  – Opportunities arise for reduced regulatory burden (submission and inspection)

• A key element of an effective PQS is communication across facilities involved in manufacturing the product (knowledge management, change management)
  – Active communication between applicants and contract facilities can minimize problems for application approval
Increasing Regulatory Efficiency Through Harmonization

- Flexibility in post-approval CMC change management promised by ICH Q8, Q9, and Q10 has not been fully realized

- Different requirements around the world are a disincentive to making improvements to increase process robustness
  - A single manufacturing change can take 3-5 years to gain regulatory approval across all markets
  - Significant implications for product inventory management and cost

- Ideal state: manufacturers encouraged to consistently pursue continual improvement
  - Leads to better assurance of supply and opportunities for innovation
ICH Q12 “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”

**Science- and risk-based approaches for assessment of changes across the product lifecycle**

- **Expects**
  - Effective change management, especially across supply chain
  - Enhanced transparency and trust between manufacturer and regulator

- **Encourages use of harmonized tools (new and existing)**
  - Established conditions
  - Proactive product lifecycle management strategy document
  - Post-approval change management protocols
  - Application of Q12 approaches for currently marketed products

- **Goal:**
  - Recognize product and process knowledge (development, experience) by allowing the manufacturer to manage more CMC post-approval changes without the need for prior approval or with only on-site documentation
Understanding the State of Quality and Improving Surveillance

• Better understanding the inventory of pharmaceutical manufacturing facilities

• Robust analytics to guide risk-based scheduling for inspections
  – Inspection history, including inspections by trusted regulatory partners
  – Field Alert Reports/Biologic Product Defect Reports
  – Information on risk specific to product type (e.g., sterile products, narrow therapeutic index drugs)

• Monitoring factors that might predict drug shortage situations
  – Intelligence on firm, facility, product
  – Market share/available alternatives
  – Mechanisms to engage proactively
Transparency and Communication

• OPQ aims to provide clear guidance to set transparent expectations regarding applications and CGMPs

• Transparency in inspections
  – New Inspection Protocol Project
    • New approaches to quantify findings of inspection
    • Documents deficiencies and areas exceeding minimum expectations
  – More timely communication to facility owners post-inspection
    • Possible by Program Alignment & CDER/ORA Concept of Operations
    • More timely remediation of problems
    • More timely decision-making regarding the potential need for an alternate facility
Transparency and Communication

INDUSTRY  FDA

• Frequency of FDA surveillance inspections is based on various risk factors
  – Inspectional history, time since last inspection, product or process complexity

• What is the state of quality *between* inspections?
  – An effective PQS provides a foundation for regulatory flexibility
  – Inspection reports from capable regulatory partners under Mutual Recognition Agreement
  – Quality metrics
    • Provide insight regarding the state of quality for product and facility
    • Assessing next steps for the QM program based on stakeholder feedback
Patients/Consumers are the ultimate beneficiaries of a focus on quality

Fewer recalls, fewer quality-related shortages
Final Thoughts

**FDA seeks a future state in which...**
- Manufacturers are incentivized to:
  - Develop and maintain an effective pharmaceutical quality system
  - Seek continual improvement
  - Implement modern and innovative manufacturing technologies
  - Commit to a culture of quality

- FDA’s approach to regulatory oversight:
  - Achieves more effective quality assessment through risk-based approaches and knowledge management
  - Routinely considers risk in the context of clinical performance
  - Has in-depth insight into the state of manufacturing
  - Uses robust analytics and surveillance techniques to proactively engage with firms to minimize drug shortages and recalls
THANK YOU