FDA’s Evolving Approach to Pharmaceutical Quality

Lawrence Yu, Ph.D.
Deputy Director, Office of Pharmaceutical Quality
FDA Center for Drug Evaluation and Research

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Objectives:

- Encourage the early adoption of new technological advances
- Facilitate industry application of modern quality management
- Encourage implementation of risk-based approaches
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs
Quality Related Guidance and Initiatives

21st Century Initiative
Final Report
ONDQA CMC Pilot Program
OGD QbR
ICH IWG formed
OBP Pilot Program
EMA-FDA QbD Pilot Program
QbD Examples
IQA Pilot


PAT Guidance
ICH Q8 Finalized
ICH Q9 Finalized
Quality Systems Guidance Finalized
ICH Q10 Finalized
ICH Q8(R1) Finalized
ICH IWG Q&A’s
Process Validation Guidance Finalized
ICH IWG Points to Consider
ICH Q11 Finalized
OPQ QM 10 Guidance
Drug Shortages – State of Quality?

Figure 1. Number of New and Prevented Shortages by Dosage Form, 2005-2012

Source: Data from FDA’s internal drug and biologics shortages databases.

Figure 2. Drug Shortages by Primary Reason for Disruption in Supply in 2012

Risk to product quality
Benefit of availability

Source: Data from FDA’s internal drug and biologics shortages databases.
Delivering on the 21st Century Quality Goals

CDER’s Office of Pharmaceutical Quality (OPQ)

January 11, 2015

Advances FDA’s Quality Initiative to the next level
FDA OPQ Mission, Vision, and Slogan

**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: One Quality Voice

Value Statements

• Put patients first by balancing risk and availability

• Have one quality voice by integrating review and inspection across product lifecycle

• Safeguard clinical performance by establishing scientifically sound quality standards

• Maximize focus and efficiency by applying risk-based approaches

• Strengthen the effectiveness of lifecycle quality evaluations by using team-based processes
OPQ: One Quality Voice
Value Statements (cont.)

- Enhance quality regulation by developing and utilizing staff expertise
- Encourage innovation by advancing new technology and manufacturing science
- Provide effective leadership by emphasizing cross-disciplinary interaction, shared accountability, and joint problem solving
- Build collaborative relationships by communicating openly, honestly, and directly
OPQ: Objectives

1. Assuring that all human drugs meet the same quality standards to safeguard clinical performance

2. Enhancing science- and risk-based regulatory approaches

3. Transforming product quality oversight from a qualitative to a quantitative and expertise-based assessment

4. Providing seamless integration of review, inspection, surveillance, and research across the product lifecycle

5. Encouraging development and adoption of emerging pharmaceutical technology
Objective 1: Same Quality Standards for All Human Drugs

• Same quality standards for new and generic drugs
  – Impurities
  – Dissolution

• Clinically relevant specification
  – Connect quality to safety and efficacy
  – Relate quality to clinical performance, not process capability

• Support and develop quality standards by conducting internal and external research
2015 Quality Guidances

- Published unprecedented number of guidances
  - Quality Metrics
  - Established Conditions
  - BCS Biowaiver
  - Dissolution for BCS Class 1 and 3 Immediate Release Dosage Forms
  - Analytical Procedures and Methods
  - Size, Shape, and other Attributes
  - Near IR Analytical Procedures
  - Environmental Assessment
  - Allowable Excess Volume and Vial Fill Size
  - Botanicals
**Objective 2: Science- and Risk-based Regulatory Approaches**

- Put patients first by balancing risk and availability
- Implement risk-based approaches
  - Review
    - Plan, Do, Check, and Act
  - Inspection
- Advance regulatory science
  - FDA laboratory and sponsored research
  - Additional regulatory science efforts
Quality Management Maturity Levels

- **Initial**: Ad hoc and Chaotic
- **Managed**: Planned and executed in accordance with policy
- ** Defined**: Organization-wide standardization; well documented
- **Quantitatively Managed**: Managed based on Quant Objectives; Focus on Special Cause
- **Optimizing**: Continuous improvement Focus on Common Cause

- **Disciplined Process**
- **Standard Process**
- **Predictable Process**
- **Continually Improving Process**

**Quality**
- **Control**
- **Assurance**

**Performance Excellence**
Objective 3: Quantitative and Expertise-based Product Quality Oversight

- Product quality platform and informatics
- Comprehensive Quality Overall Summary/Question-based review
- Quality metrics and FDA lab-based surveillance
- New inspection protocol project (NIPP)
  - Pre-approval inspection, surveillance inspection, and for-cause inspection
  - Parity of domestic and international facilities
Product Quality Informatics

• Enabling an efficient science-driven assessment requires significant transformation in how OPQ collects, evaluates, and learns from the product quality data

• Core areas of Product Quality Informatics:
  – Structured data submission and collection
  – Knowledge management and communication
    • Established conditions
    • Risk mitigation
  – Post-market surveillance and quality monitoring
  – Intelligent data analysis
Question-based Review

- FDA Manual of Policies and Procedures (MAPP) 5015.10
  - Chemistry Review of Question-based Review (QbR) Submissions

- This MAPP clarifies how drug substance and drug product reviewers should assess drug applications (NDAs, ANDAs, and drug substance DMFs) that follow a Question-based Review format

Quality Metrics

• Vision
  - A more rigorous and comprehensive approach to quality surveillance that allows for improved monitoring of current status across the inventory of FDA-regulated drug products and manufacturing sites

• Goals: Objective measures
  - Quality of a drug product
  - Quality of a site
  - Effectiveness of systems associated with the manufacture of pharmaceutical products

• Draft Guidance published July 27, 2015
• **Metrics FDA Intends to Calculate**
  - Lot acceptance rate
  - Product quality complaint rate
  - Invalidated Out-of-Specification rate
  - Annual product review or product quality review on time rate
Optional Metrics

- Quality Culture
  - Senior management engagement
  - corrective action and preventive action effectiveness
  - percentage of your corrective actions involved re-training of personnel

- Process Capability/Performance
  - Process capability is a leading, useful indicator. However, its calculation is relative complex
Our Journey Started 10 Years Ago at a Management Review Meeting!

- **Leadership** decided to monitor manufacturing processes and product attributes using process capabilities.
- **Leadership** focused on poor performing manufacturing processes and product attributes leading to improvements.
- **Leadership** decided that any PpK less than 1.0 required a CAPA to drive continuous improvement.

Leadership relentlessly follow-up on these CAPAs at each Management Review Meeting.

*Since 2007, The Actual Number of Parameters Achieving 6 Sigma has Doubled*

- At the end of 2014,
  - 82% of the parameters were performing at a 6σ level
  - 14% of the parameters were performing between 3σ and 6σ levels
  - 4% of the parameters had CAPA’s open to improve performance
New Inspection Protocol Project

- Goal: To develop a new paradigm for inspections and reports that will advance pharmaceutical quality
  - Standardized approach to inspection
  - Data gathering to inform “quality intelligence” of sites and products
  - Risk-based and rule-based process, using expert questions
  - Semi-quantitative scoring to allow for comparisons within and between sites
  - More common inspection report structure
  - Recognize and reward positive behaviors in cases where facilities exceed basic compliance
New Inspection Protocols Project (NIPP) Steering Committee
CDER ORA

**Pre-Approval Inspection Subgroup**
Observations to inform premarket review decisions

**Surveillance Inspection Subgroup**
Observations on state of quality in a facility to assess quality risk

**For Cause Inspection Subgroup**
Evidence of cGMP violations to support enforcement

Escalation/transition to “For Cause” when conditions indicate
Objective 4: Integration of Review, Inspection, Surveillance, Policy, and Research

- Team-based integrated quality assessment
- Program alignment across FDA
- Lifecycle management; establish parity of NDAs and ANDAs
Team-based Integrated Quality Assessment (IQA)

A team of experts performing a quality assessment of an application (NDA, BLA, ANDA) based on risk and knowledge management
Previous Review Process

- No formal risk assessment process to define scope and extent
- Discipline reviewers worked in isolation
- Independent reviews (or assessments)
- Separate review templates
- Rare communications between review functions and facility inspections

Team-based Integrated Quality Assessment

- Formal risk assessment process to enhance efficiency and effectiveness of review and inspection
- Team of discipline reviewers with constant communication
- A single collaborative review (or assessment)
- Consolidated review template
- Integration of review with inspection for more informed decisions on facility acceptability and application approvability
The Review Team

**Discipline Reviewers**

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

- ‘One Quality Voice’

**Technical Advisors**

- OPQ Laboratories
- Policy Surveillance
- Others as needed

**Application Technical Lead (ATL)** – oversees the scientific content of the assessment

**Business Process Manager (BPM)** – manages the process, adhering to the established timelines
Program Alignment across FDA

- Transition to distinct commodity-based and vertically-integrated regulatory programs with:
  - Well-defined leads
  - Coherent compliance policy and enforcement strategy development
  - Well-designed and coordinated implementation
  - Investigators, compliance officers, import reviewers, laboratory personnel, and managers who are more specialized in a particular regulatory program
Lifecycle management

- Establish parity of NDAs and ANDAs
  - OLDP leads the evaluation of post-approval changes of ANDAs, as well as NMEs and 505b(2) NDAs 3 and 1 year after approval, respectively
  - OBP leads the evaluation of post-approval changes of BLAs
  - OPF undertakes responsibilities essential for the evaluation of process and facility changes
Objective 5: Development and Adoption of Emerging Technology

- Formed emerging pharmaceutical technology team
- Drafted emerging pharmaceutical technology guidance
- Continuous manufacturing
  - Sponsored research
  - Published scientific review
  - Planned FDA Science Board presentation
  - Policy
What is the FDA Emerging Technology Team (ETT)?

• A small cross functional team with representation from all relevant CDER and ORA review and inspection programs

• Vision
  • Encourage and support the adoption of emerging technology to modernize pharmaceutical development and manufacturing where the FDA has limited review or inspection experience
ETT Objectives

- Serve as a centralized location for external inquiries on novel technologies
- Provide a forum for firms to engage in early dialog with FDA to support innovation
- Ensure consistency, continuity, and predictability in review and inspection
- Help establish review and inspection standards and policy, as needed
- Identify and evaluate roadblocks relating to existing guidance, policy, or practice
- Long term goals:
  - Engage international regulatory agencies to share learnings and approaches
  - Modernizing pharmaceutical development and manufacturing
- Contact us: CDER-ETT@fda.hhs.gov
U.S. Approves First 3D Printed Pill

• TIME, Aug. 4, 2015. “U.S. Approves First 3D Printed Pill…The pill is better for children and elderly users who find it difficult to swallow large tablets…”


• The Washington Post, Sept. 22, 2015. “For the first time ever, the FDA has approved a 3D-printed prescription pill for consumer use…”
FDA Approves ORKAMBI™ (lumacaftor/ivacaftor) - the First Medicine to Treat the Underlying Cause of Cystic Fibrosis for People Ages 12 and Older with Two Copies of the F508del Mutation

Vertex, J&J, GSK, Novartis all working on continuous manufacturing facilities

FDA supports the move as a way to improve quality in manufacturing

February 9, 2015 | By Eric Palmer

Vertex Pharmaceuticals ($VRTX) is building a $30 million, 4,000-square-foot continuous manufacturing facility in Boston in anticipation that it will get approval for a new cystic fibrosis drug. It is one of a handful of projects from GlaxoSmithKline ($GSK), Novartis ($NVS), Johnson & Johnson ($JNJ) and others that are moving the industry out of its decades-old processes into a new realm in which some drugs can be manufactured without using the time-consuming, chemical heavy batch processes.