Office of Pharmaceutical Quality
Key Quality Initiatives

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Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
FDA 21st Century Initiative

Objectives:

• Encourage the early adoption of new technological advances by the pharmaceutical industry

• Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches

• 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
Desired State of Manufacturing

• Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
• Manufacturers strive for continuous improvement
• FDA role: Initial verification, subsequent audit
• Minimal or no manufacturing supplements needed (for application-based products)
Initial Successes...

- Initial successes:
  - ‘Enabling’ of modern technology (e.g., PAT and Continuous Manufacturing)
  - Updates to CGMP regulations and guidances (e.g., Aseptic Processing, Process Validation)
  - Multiple ICH documents:
    - Pharmaceutical Development and Quality by Design (QbD) (ICH Q8(R2))
    - Quality Risk Management (ICH Q9)
    - Quality Systems (ICH Q10)
  - Formation of Pharmaceutical Inspectorate
  - Risk-based selection of facilities for inspection
...But We’re Not There Yet

• Drug shortages
  – Regulators have limited ability to predict quality problems and potential shortages or supply disruptions
  – Majority of drug shortages in the US are due to a quality problem

• Outdated manufacturing technology
  – Regulatory oversight/uncertainty is a factor limiting adoption of modern manufacturing technology

• Postapproval change management
  – Time required for regulatory approval in US and globally delays or blocks facility improvements, e.g., site changes, major upgrades
The path forward...

Building on the goals of the 21st Century Initiative:

• Establish **consistent quality standards** and clear expectations for industry regarding both review and inspection
• Use **risk-based approaches** to drive more efficient and effective quality evaluations (application review and facility assessment)
• Evaluate risk focusing on **clinically relevant product attributes**, which may include attributes that impact delivery and human factors
• Encourage use of **modern, more efficient manufacturing technologies**
• Develop approaches to **increase regulatory flexibility** for postapproval changes
• Focus on **robust analytics and surveillance techniques** to monitor the state of manufacturing in the pharmaceutical industry.
Achieving these Goals Requires

• New organizational structure
• Changing policies and procedures
• Developing new tools
Office of Pharmaceutical Quality

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Deputy Director: Lawrence Yu

Office of Program and Regulatory Operations
Director: Giuseppe Randazzo

Office of Policy for Pharmaceutical Quality
Director: Ashley Boam

Office of Biotechnology Products
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Office of New Drug Products
Director: Sarah Pope Miksinski

Office of Lifecycle Drug Products
Director: Susan Rosencrance

Office of Process and Facility
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Office of Testing and Research
Director: Lucinda Buhse

Office of Surveillance
Acting Director: Sarah Pope Miksinski
CDER OPQ

Mission
The Office of Pharmaceutical Quality assures that quality medicines are available to the American public

Vision
The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality

One Quality Voice
Formation of the Office of Pharmaceutical Quality

• Implemented January 11, 2015
• OPQ combines drug quality functions into one super-office, creating “one quality voice” and improving our oversight of quality throughout the lifecycle of a drug product
• OPQ’s structure provides for centralized functions for administrative activities, project management, training, quality management systems, and policy.
• OPQ creates a uniform drug quality program across all sites of manufacture, whether domestic or foreign, and across all drug product areas – new drugs, generic drugs, biotechnology products, biosimilars, and over-the-counter drugs
KEY OPQ INITIATIVES
APPLICATION REVIEW
Prior to OPQ

- Single CMC reviewer for application review
- Original NDA and NDA supplement review separate from follow-on generics (ANDAs)
- Application review primarily conducted separate from facility assessment and inspection
- Missing:
  - Best use of reviewer expertise
  - Knowledge management over the lifecycle of the product (NDA to NDA supplement; NDA to ANDA)
  - Inspection focus informed by review of application
  - Application review informed by findings from inspection
  - Overall quality recommendation
Changing Processes and Culture

Team-based Integrated Quality Assessment (IQA)

A team of experts perform a quality assessment of an application (NDA, BLA, ANDA) based on risk and knowledge management.
The Integrated Review Team

**Discipline Reviewers**

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

**Technical Advisors**
- OPQ Laboratories
- Policy
- Surveillance
- Others as needed

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

**Regulatory Business Process Manager (RBPM)** – manages the process, adhering to established timelines
Knowledge Management

• The integrated **Knowledge Base** allows for:
  - Greater parity in the regulatory oversight and quality assessment of brand and generic drugs
  - Application of uniform and consistent quality standards for both brand and generics drugs
  - Clearer identification of product and process risks
  - Quickly addressing quality issues
POLICY DEVELOPMENT
Why Centralized Policy?

Historically:
• Policy development slow, uncertain, and inconsistent
• Different approaches to policy-setting in different offices
• Minimum looking backward for existing policies
• Lack of focus on USP and other standards setting organizations

Solution—Office of Policy for Pharmaceutical Quality (OPPQ)
• Strategic and coordinated policy development and evaluation; aligned with CDER and FDA
• Dedicated Office; dedicated staff
• Formal governance
  – OPPQ for centralized quality policy development and clearance
  – CDER Council for Pharmaceutical Quality (CPQ) for oversight of Center-wide quality initiatives
Approach to Policy-Making

Guiding principles

- Policies should be not only science- and risk-based, but feasible and valuable
- Policies should generally be considered as impacting “pre-market” and “commercial” (or “post-market”) phases
  - Not merely “review” vs. “inspection”
  - Policies are intended to shape quality activities
  - Documents should reflect that drug development, scale-up, production and process control strategies, and change management are all connected by the pharmaceutical quality system
- Policies should, to the extent possible, consider all products, not just application-based products
  - OTC Monograph, medical gases, 503B Outsourcing Facilities
OPPQ Work Products

• Policy Development and Evaluation
  – Regulations
  – Guidance for Industry
  – MAPPs
  – SOPs (policy-related)
  – Compliance Programs (CPGMs)

• Communicating with stakeholders
  – Citizen Petition consults/responses
  – Controlled correspondence (ANDA only)
  – External inquiries (NDA/BLA/CGMP/503B compounding)
  – Media inquiries
  – Legislative inquiries (Congressional inquiries, GAO, OIG)
  – Individual policy questions/issues

• Compendia and standards organizations
  – USP inquiries/PF review/USP liaison program
  – Coordination of CDER participation in voluntary consensus standards
Guidance Published in 2016

• Immunogenicity-Related Considerations for Low Molecular Weight Heparin Guidance for Industry (2/18/16)
• Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (3/4/16)
• Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry – Draft (4/19/16)
• Data Integrity and Compliance With Current Good Manufacturing Practice Guidance for Industry – Draft (4/14/16)
• Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products – Draft (4/22/16)
• Quality Attribute Considerations for Chewable Tablets Guidance for Industry – Draft (6/16/16)
• Elemental Impurities in Drug Products – Draft (6/30/16)
• Regulatory Classification of Pharmaceutical Co-Crystals – Draft (8/16/16)
Selected Forthcoming Draft Guidance*

- Drug Master Files – Revised Draft
- Harmonizing Compendial Standards with Drug Application CMC Approval Requirements Using the USP Pending Monograph Process
- Nanomaterials in Drug and Biologic Products
- Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products – Revised Draft
- Field Alert Report Submission
- Submission of Quality Metrics Data – Revised Draft

SURVEILLANCE
Developing New Tools
Understanding the State of Quality and Improving Surveillance

• Better understanding the inventory of pharmaceutical manufacturing facilities
  – New IT platform – single database to support surveillance

• Robust analytics to guide risk-based scheduling for inspections
  – Site inspectional 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
FDASIA 705: Risk-based Inspection

FDA “shall inspect establishments...in accordance with a risk-based schedule”

Risk factors:

(A) The compliance history of the establishment.

(B) The record, history, and nature of recalls linked to the establishment.

(C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment.

(D) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years.

(E) Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809.

(F) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources.
Current Surveillance Model Structure

Outcome is a score and relative priority ranking of entire inventory
- Absolute score not relevant (i.e., NOT “high,” “medium,” “low”)
Site Surveillance Model ➔ Site Surveillance Inspection List

- SSM reviewed annually per policy/procedure
  - Annual factors and weights documented
    - Reviewed and endorsed by CDER and ORA executive management
- Entire inventory processed through SSM annually
  - Excluding OAI firms (separated out for follow up by Office of Compliance)
  - Approximately 8K facilities in surveillance inventory
    - Not all segments are equal in terms of risk
      - Medicated shampoo vs. oral vs. sterile
  - ORA capacity for GMP/SSI inspections approximately 1700/year
A Two-Way Street

• Achieving that 2004 vision (an “...agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight” will take more than just changes at FDA

• Changes must be embraced by industry as well
McKinsey: “Flawless: From measuring failures to building quality robustness in pharma”

- “There’s...the challenge of shifting mind-sets across industry that has focused predominantly on compliance rather than on truly knowing the root causes and effects on quality issues”
Moving Beyond Compliance

• Quality metrics program
  – Based on information now required to be collected and evaluated under CGMP
  – Can provide insight into the state of quality for product and facility
  – One factor in risk-based inspection scheduling
  – Help to identify factors leading to supply disruption
  – Initial draft guidance issued in July 2015
  – Significant comments received
    • Technical comments re proposed metrics and definitions
    • Concerns regarding burden of data collection/formatting/submission
    • Legal concerns regarding proposed mandatory program
  – Revised draft guidance to issue by end of 2016
Moving Beyond Compliance

- Program alignment
  - Centers and ORA improving and streamlining inspection assignments and disposition
  - Vertical alignment on a commodity basis
  - Establishing joint cadre of compliance officers whose ultimate functions will include domestic and foreign activities
    - Create Specialized Investigators, Compliance Officers and First-line Managers
    - Expanding level of specialized investigators, compliance officers and 1st line managers
  - Developing performance based public health metrics for compliance / quality activities
Moving Beyond Compliance

• New Inspection Protocol Project
  – New approaches to quantify findings on inspection –
    documenting both the deficiencies and areas exceeding
    minimum expectations
  – Expert question-based inspection format with scoring for
    elements of each of the six systems
  – Customize further based on the type of product and unit
    operations being inspected
  – Exploring ways to reward firms that move beyond
    compliance
    • Regulatory flexibility commensurate with state of the pharmaceutical
      quality system and product/process knowledge
More than just a business case...

Patients 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
    • Increase process robustness by implementing modern and innovative manufacturing technologies
    • Commit to a culture of quality
  – FDA’s approach to regulatory oversight:
    • Achieves more efficient and effective quality assessment through application of risk-based approaches and knowledge management
    • Has in-depth insight into the state of manufacturing and uses robust analytics and surveillance techniques to proactively engage with firms to minimize drug shortages and quality-related recalls
Thank you for your attention!