Office of Pharmaceutical Quality (OPQ)

Susan Rosencrance, Ph.D.
Sarah Pope Miksinski, Ph.D.
Christine Moore, Ph.D.
Giuseppe Randazzo, M.S.

June 9, 2015
2015 GPhA CMC Workshop
Advances FDA’s Quality Initiative to the next level

CDER’s Office of Pharmaceutical Quality (OPQ)

January 11, 2015
OPQ
A single units within CDER dedicated to product quality
Objectives of OPQ

• A single unit in CDER dedicated to drug product quality
  - Across all drug product areas
    • new drugs, generic drugs, biotechnology products, and over-the-counter drugs
  - Across all sites of manufacture
    • domestic and foreign
Objectives of OPQ

• The creation of ‘one quality voice’ streamlining quality oversight throughout the lifecycle of a drug product
  – Aligns review, inspection, and research functional areas
  – Spans pre- and post-approval for brand and generic drugs
  – Strengthens surveillance and inspections of facilities globally
Objectives of OPQ

- Encourages use of modern, more efficient manufacturing technologies
- Establishes consistent quality standards and clear expectations for industry
- Balances potential quality risks with the risk of a patient not getting a drug
Objectives of OPQ

• Anticipates quality problems before they develop to help prevent drug shortages
• Emphasizes quality metrics and surveillance techniques to help monitor quality across facilities
Seamless Integration of Review, Inspection, Surveillance, Policy, and Research

- Performing team based quality assessments of applications inclusive of drug substance, drug product, manufacturing, and facilities

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

‘One Quality Voice’

Technical Advisors
- OTR
- OPPQ
- OS
- Others as needed
The Integrated Quality Assessment

A single integrated quality assessment that captures OPQ’s overall recommendation on approvability
OPQ

- Office of Lifecycle Drug Products (OLDP)

• Assures drug product quality during the lifecycle of both brand and generic drug products
OPQ - OLDP

– Pre-Marketing Divisions

• An evaluation and assessment of ‘product quality’ aspects of an ANDA

1. Formulation/product design
2. Identifying potential failure modes
3. Risk assessment
4. Quality standards
5. Clinically-relevant specifications
6. Product characterization
7. Method validation
8. Control strategy related to product attributes
9. Container/closure system
10. Stability
OPQ - OLDP

− Pre-Marketing Divisions

• Work with subject matter experts across OPQ to perform team-based reviews and provide risk-informed recommendations on approvability to stakeholders

• Creates opportunities for knowledge management across offices

• Participate, as needed, in scientific investigations to evaluate and access any drug product quality problems that may arise.
– Post-Marketing Divisions

• Responsible for monitoring the lifecycle of:
  1. Generic (ANDA) drug products
  2. Brand (NDA) drug products, after a limited time frame (1 or 3 years) in the Office of New Drug Products

• Perform collaborative evaluations and assessments of supplements and annual reports using risk-management practices

• Participate, as needed, in scientific investigations to evaluate and access any drug product quality problems that may arise.
OLDP Stakeholders

- **ONDP**
  - DMF & Biopharm

- **OPF**
  - Process, Facility & Microbiology

- **OPRQ**
  - Policy

- **OS**
  - Surveillance Inputs & Outputs

- **OTR**
  - Research, Support & Advice

- **OPRO**
  - Project Management

- **OGD**

- **OND**

Other Stakeholders:
- OC/ORA
- Regulated Industry
The Office of New Drug Products (ONDP)
In the Establishment of OPQ:

- Multiple offices (including ONDP) adopted cross-program responsibilities for GDUFA and PDUFA
- OLDP adopted primary responsibility for lifecycle management, following a short post-approval duration
- ONDP adopted DMF and Biopharmaceutics review functions (NDAs and ANDAs)
- Existing staff experience leveraged across OPQ sub-offices as needed
- Opportunities created for knowledge management across offices
ONDP Functions - Summary

• Convey **risk-informed** recommendations on product quality to CDER offices and industry

• **Communicate product risk** in the pre-marketing stage of assessment

• **Collaborate** with other OPQ offices to conduct **integrated** quality assessments

• Serve as **quality liaison** to the Office of New Drugs

• **Participate** in inspections as needed

• **Assess** multiple components of applications, including drug substance and biopharmaceutics
ONDP Stakeholders

Other Stakeholders:
- OC/ORA
- Regulated Industry
Office of New Drug Products

Office of the Director

- Division of Lifecycle API
  - Generally, GDUFA-driven DMF, DS info for ANDAs

- Division of New Drug API
  - Generally, PDUFA-driven Biopharm info

- Division of Biopharmaceutics
  - Generally, PDUFA-driven DMF, DS, info for NDAs and INDs

- Division of New Drug Products 1
  - Generally, PDUFA-driven OND-aligned branches

- Division of New Drug Products 2

[Image of FDA logo and Office of Pharmaceutical Quality]

[Image of FDA logo and Office of Pharmaceutical Quality]
Drug Substance Review (ONDP)

Division of Lifecycle API
- David Skanchy (Division Director)
- Review of API information supporting ANDAs, including review of DMFs supporting ANDAs
- Heavily involved in GDUFA-driven reviews

Division of New Drug API
- Ali Al Hakim (Acting Division Director)
- Review of API information supporting NDAs, including review of DMFs supporting NDAs
- Heavily involved in PDUFA-driven reviews
Biopharmaceutics/Drug Product

Division of Biopharmaceutics
- Paul Seo (Acting Division Director)
- Review of Biopharmaceutics information supporting NDAs and ANDAs
- Involved in both PDUFA- and GDUFA-driven reviews

Division of New Drug Products 1/2
- Tom Oliver (Acting Division Director, 1)
- Eric Duffy (Division Director, 2)
- Review of drug product information supporting NDAs
“Link to the Patient”
Key ONDP Initiatives

- Improving overall Drug Substance review efficiency
- Exploration of innovative knowledge management strategies in the pre- and post-approval spaces
- Establishing new and creative partnerships in CDER and OPQ
- Patient-Centric Quality Review
  - Clinical Relevance
  - The translation of technical to the patient
- Risk Communication
Risk Communication

• How do we **intentionally** and **explicitly** link the risks identified in our quality assessment to patient outcomes?

• How do we communicate our findings and recommendations to our stakeholders outside of OPQ?
  - Internal: OND, OGD
  - External: e.g., industry, patients
Linking to the Patient

- Focus/align on “Why does it matter to the patient?” or “What is the impact on overall quality?”
- Most effective when discussions are *timely* and transparent
- Multiple partners involved (e.g., clinical review division, Applicants, other offices)
- Collaboratively framed
- Occurs within the appropriate regulatory framework
- End result – using sound science and technical expertise to identify/discuss major risks to quality, while communicating effectively regarding necessary mitigation and/or potential impact to the patient
Additional Considerations

• Are we having the right conversation at the right time?
• Determining communication gaps and clarification needs from actual scientific disagreements
• Generating One Quality Voice within the appropriate regulatory framework
• Embracing a “culture of curiosity”
• Utilizing resources effectively (e.g. combined IRs)
• Building proactive communication into review process
• Building formalized risk assessments into review process and team staffing decisions
• Improving overall risk communication to stakeholders
Introduction to Office of Process and Facilities (OPF)

Christine M. V. Moore, Ph.D.
Acting Director, OPF
FDA/CDER/OPQ
What is OPF?

The Office of Process and Facilities is:

- A large, diverse organization
  - Staffed by chemists (all types), pharmaceutical scientists, engineers, microbiologists, biologists, and others
- Responsible for a wide range of process related review and inspection aspects
  - Process review
  - Microbiology review
  - Preapproval inspection oversight
- Involved in nearly all application types
  - All original NDAs, ANDAs and BLAs
  - All site change sNDA, sANDA and sBLA
  - Certain complex drug substances
  - Some INDs, meeting packages, process change supplements
Office of Process and Facilities

- OPF ensures that quality is built into manufacturing processes and facilities over the product lifecycle.
- OPF will use risk-based approaches for efficient assessment of the following application-related aspects:
  - Manufacturing facilities, processes, and controls for certain drug substances and intermediates, and for all ANDA and NDA drug products.
  - Microbiological aspects for drug substances and drug products.
  - Facility and manufacturing process suitability for commercial manufacturing and consistency with the principles of CGMP.
- Additionally, OPF partners with other offices internal and external to OPQ to establish standards for OPF-related review and inspectional activities.
Office of Process and Facilities (OPF)

Office of Process and Facilities
Christine Moore (Acting Director)
Dave Doleski (Acting Deputy Director)
Bob Iser (Acting Sr Scientific Advisor)

Process Assessment Divisions I, II, III:
- 6 branches solid drug products
- 2 branches for liquid drug products
- 1 branch for complex drug substances

Microbiology Division:
- 3 branches for sterile small molecule drug product and substance
- 1 branch for biotech drug substance and product

Division of Process Assessment I
Rapti Madurawe (acting)

Division of Process Assessment II
Naiqi Ya

Division of Process Assessment III
Bob Iser

Division of Microbiology Assessment
Lynne Ensor (acting)

Division of Inspectional Assessment
Dave Doleski

Onboard ~180
Ceiling = 215
Why OPF?

• OPF has been designed to provide the necessary specialization and expertise to provide oversight to manufacturing processes and facilities
• Traditionally, process review has been isolated from facility inspections
• A higher degree of integration between the field and center is needed to deal with modern challenges
• Manufacturing technologies are becoming more complex and critical to drug product quality
OPF Role in Review

• Conduct reviews of drug product (and some drug substance) manufacturing processes, facilities and microbiological assurance for BLAs, ANDAs, NDAs, supplements, and certain DMFs

• Communicate the risks related to manufacturing process, facilities and microbiological aspects to the IQA team, including ORA investigators

• Provide manufacturing process, facility and microbiological recommendations, comments and deficiencies for information requests or complete response letters
OPF Role in PAI Oversight

• Evaluate need for pre-approval inspection (PAI) for manufacturing sites for all original applications and certain supplements

• Communicate the risks related to process and facilities to IQA team, including investigators

• Facilitate coordination of inspection with application timelines

• Frequently participate on PAIs as subject matter experts

• Make final site recommendation (Acceptable, Withhold) based on investigation recommendation and data from the application
OPF Initiatives

• Build an organization with employee engagement and continual improvement

• Cross train OPF staff across disciplines and to develop staff expertise in inspection

• Develop and implement risk-based pre-approval inspection models

• Develop and implement New Inspection Protocol Project for PAIs
Risk Based PAI Model (in development)

- **Facility Risk:**
  Are there manufacturing risks associated with the inspectional history and current operations at this facility that impact the application?

- **Process Risk:**
  What are the manufacturing risks associated with the proposed unit operations in this application?

- **Product Risk:**
  Is there limited knowledge about the manufacture of this product? What’s the connection between manufacturing with clinical efficacy and patient safety?
New Inspection Protocol Project (in development)

- 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
OPF Stakeholders

Other Stakeholders:
- OND
- OGD
- Regulated Industry
Introduction to Office of Program and Regulatory Operations (OPRO)

Giuseppe Randazzo M.S.
Acting Director, OPRO
FDA/CDER/OPQ
OPRO’s Mission

A customer-oriented, regulatory-focused, and process-centered organization which empowers OPQ with an operational framework that fosters collaboration, efficiency, and quality.

OPRO’s Vision

To be the model organization for regulatory and business operations across FDA centers.
What is OPRO?

• A centralized regulatory project management staff:
  - Pharmacists, Chemists, Regulatory scientists, PMPs, Educational experts, Quality system experts, and others

• OPRO consists of:
  - Immediate office with specialized project managers
  - Three division
    • Innovators products
    • Generic Products
    • Organizational Excellence and Learning and Professional Development

• Involved in all application types, including:
  - All original and supplemental NDAs, ANDAs and BLAs
  - INDs, industry meetings
  - Preoperational facility meetings
OPRO is responsible for

• Leading and managing all processes associated with drug quality reviews and facility inspections, in collaboration with OPQ functional office leadership

• Monitoring, reporting, and leading corrective and preventive actions relating to the performance of internal processes, as defined by standard procedures

• Designing, developing, and implementing OPQ-specific training and developmental programs to ensure the skill sets and competencies of staff are maintained and continually improved

• Serving as the conduit to regulated industry and internal stakeholders

• Serving as the regulatory expert on the review team
OPRO – what do we really do?

• Ensures review team is aware of the UFA timelines and timelines are met
• Serves as change agents as we continue to improve processes
• Adapts to external and internal changes and evolving customer needs while maintaining consistency in practices/approaches.
• Applies innovative approaches to solve new challenges
• Provides efficient and continuous learning adapting to regulatory and changing environment
• Manages product quality application process
• Facilitates regulatory work/work products
• Provides program and project management functionality
• Facilitates the learning development of OPQ staff
Onboard ~70
Ceiling = 100

Office of Program and Regulatory Operations
Giuseppe Randazzo (Acting Director)
Mike Smedley (Deputy Director)

Associate Director for Business Operations  Don Henry (Acting)
Associate Director for Science & Comm.  Angeline O’Shea (Acting)
Associate Director for Regulatory Affairs  Michael Folkendt

Regulatory & Business Process Mgmt. – Division I
Tanya Clayton (Acting)

Regulatory & Business Process Mgmt. – Division II
Robert Gaines

Org. Excellence, Learning & Professional Dev. – Division III
Lloyd Ballou (Acting)

Branch 1
Branch 2
Branch 3
Branch 4
LPD
OE

Generally, PDUFA - driven
NDA, BLA and DMF

GDUFA - driven

Post Marketing PDUFA and GDUFA - driven
RBPM – Division I

• Branch I:
  – Manages pre-marketing activities for NDAs/BLAs
    • Original applications
    • All INDs
  – Houses discipline specific PMs for:
    • DMF PMs to handle DMF reviews outside of the application (ANDAs)

• Branch II:
  – Manages pre-marketing activities for ANDAs
    • Cohorts I, II, and III
RBPM – Division II

• Branch III:
  - Manages pre-marketing activities for ANDAs
    • Cohorts I, II, and III

• Branch IV:
  - Manages all post-marketing activities for NDAs, BLAs, ANDAs
OE/LPD – Division III

Organizational Excellence (OE):

• The OE branch manages:
  - The Feedback and Change Management process, Registry, Reporting, and communication
  - OPQ cross-office process documentation (SOPs, work aids, process maps)
  - The document management framework for all OPQ offices (in collaboration with OPQ offices)
  - OE-assigned process improvement projects from “issue identification” or root-cause analysis through the implementation of a solution, for all OPQ offices

• The OE branch provides support on:
  - Using proven methodologies (six sigma, lean TQM, theory of constraints) OE supports process design and process improvement projects that are internally led by OPQ offices’ staff
  - Process documentation for internal processes to each OPQ office (SOP writing, process mapping, root cause analysis)
OE/LPD – Division III (cont.)

Learning and Professional Development (LPD):

• This branch coordinates with all OPQ offices to identify training, development and certification needs and requirements for all job functions.
  - Developing internal training and development programs.
  - Facilitating and tracking the training for all staff within OPQ relative to OPQ policy and standards.
  - Working closely with the other divisions in OPRO, as well as the other OPQ functional offices to identify additional training opportunities and requirements based on the professional needs of OPQ staff.
  - Determining, developing and implementing all certification requirements within OPQ.
  - Working closely with other offices in OPQ in designing, developing, implementing and monitoring staff individual development plans (IDPs).
OPRO Stakeholders

Other Stakeholders:
- OC/ORA
- Regulated Industry
Objectives of OPQ

• OPQ working in concert with its stakeholders (ORA, OC), and its internal customers (OND, OGD), better positions the FDA to respond to current challenges and achieve the goals laid out in FDA’s Pharmaceutical Quality for 21st Century Initiative

Vision: “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.” – Dr. Woodcock