U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality: Pharmaceutical Quality Update

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Generic Drug Forum
April 11, 2018

Outline

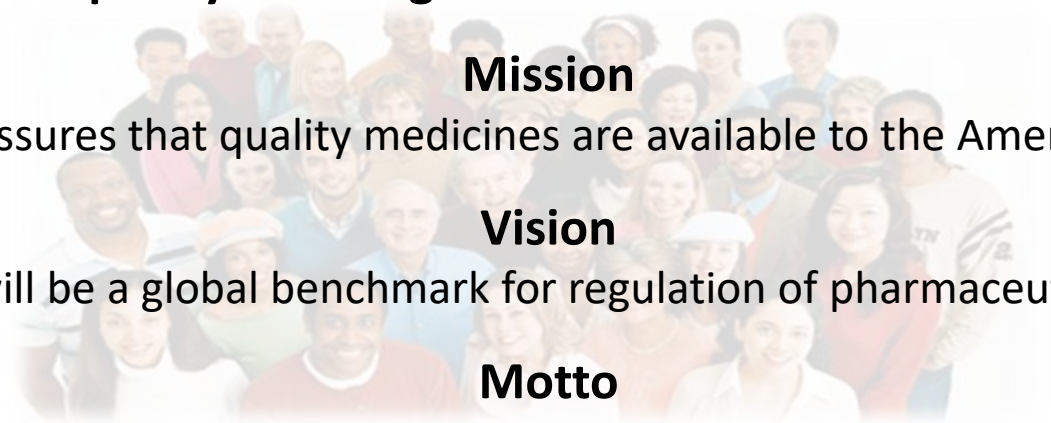
- OPQ Strategic Priorities
- OPQ Organization Updates
- Strengthen OPQ's Collaborative Organization
- Promote Availability of Better Medicines
- Elevate Awareness and Commitment to the Importance of Pharmaceutical Quality
- Strengthen Partnerships and Engage Stakeholders
- Engaging Stakeholders on Quality
- Conclusions

OPQ Strategic Priorities

Office of Pharmaceutical Quality

Pharmaceutical quality is our *shared* goal of assuring consistently safe and effective drugs are available to patients and consumers.

Pharmaceutical quality is what gives them confidence in their *next* dose.



Mission

OPQ assures that quality medicines are available to the American public

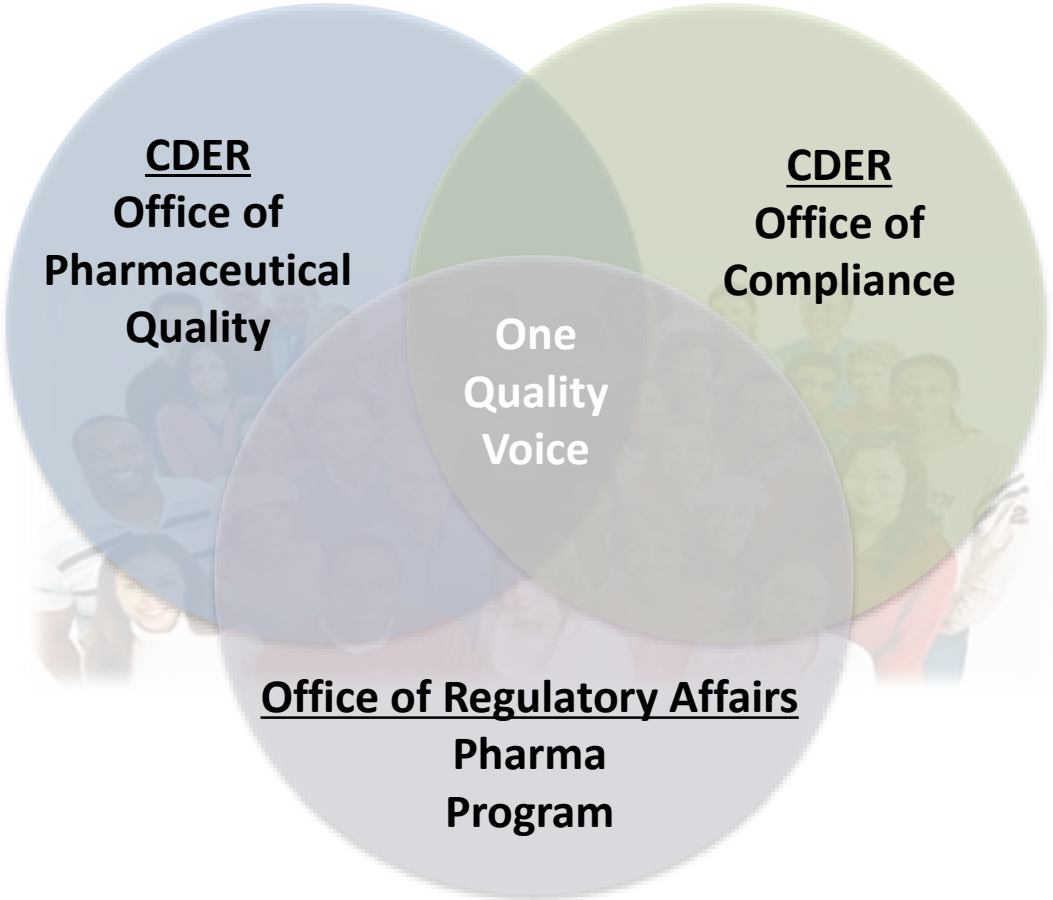
Vision

OPQ will be a global benchmark for regulation of pharmaceutical quality

Motto

One Quality Voice

One Quality Voice



Office of Pharmaceutical Quality

OPQ Strategic Priorities: 2018-2022

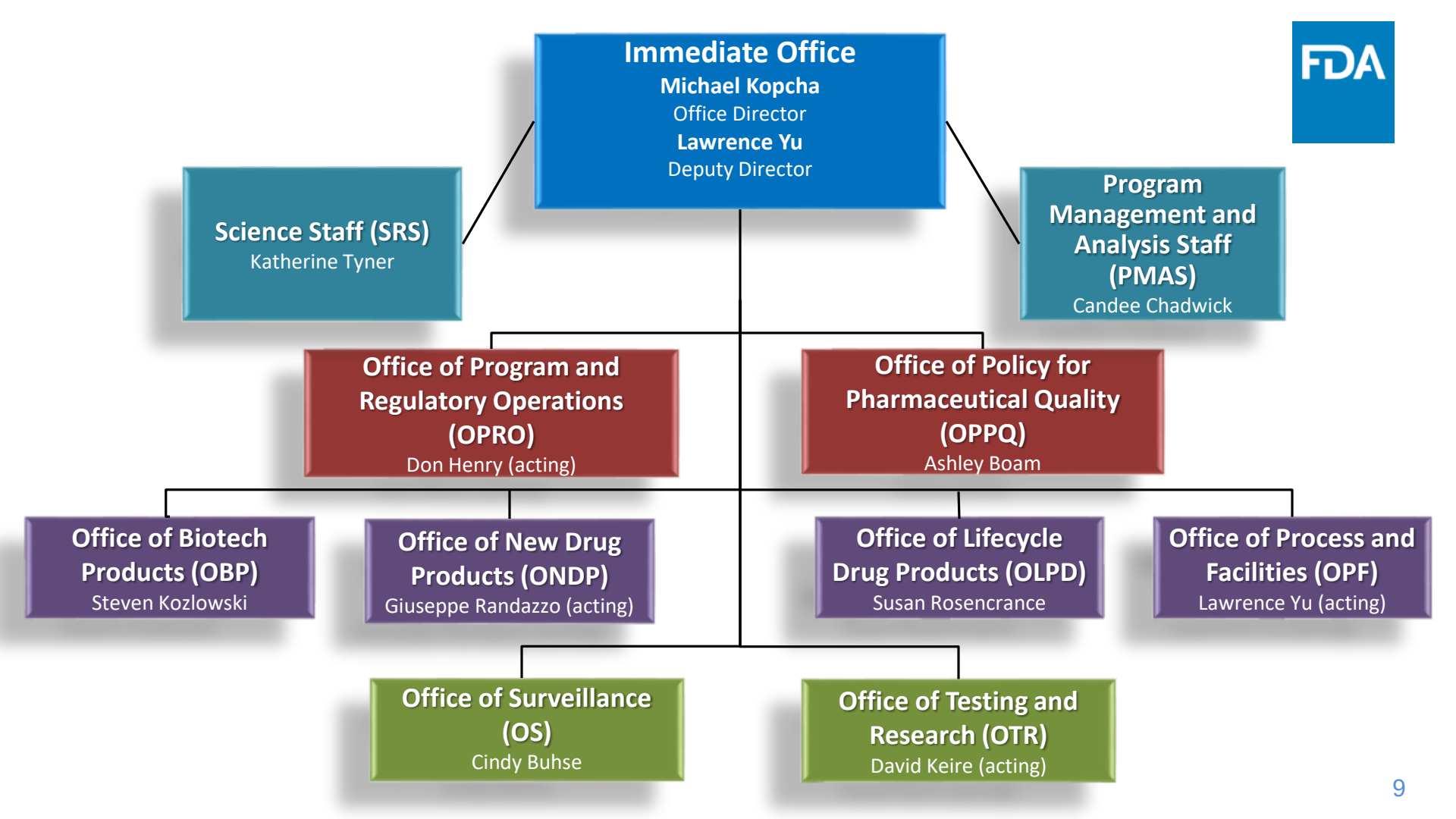
1. **Strengthen OPQ's collaborative organization**
   - Leverage a collaborative culture, an engaged and empowered workforce, streamlined processes, and effective teaming to ensure an efficient, high-performing, innovative, and results-oriented organization

2. **Promote availability of better medicines**
   - Minimize barriers to encourage innovation within FDA and in the manufacturing sector through sensible oversight, research, risk-based decision-making, and continuous process improvement

3. **Elevate awareness and commitment to the importance of pharmaceutical quality**
   - Effectively communicate the importance of quality and that the American public can trust their drugs

4. **Strengthen partnerships and engage stakeholders**
   - Build productive relationships with business partners within and outside FDA and jointly foster effective stakeholder engagement to meet the needs of the American public

OPQ Organization Updates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Office of Process and Facilities (OPF)
Lawrence Yu (acting)
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Quality Changes Related to GDUFA

GDUFA II

- All original ANDAs and ANDA amendments fall within a single assessment scheme (90% goals)
- Creation of a new pre-ANDA program for complex products
  - Product development, pre-submission and mid-cycle meetings for complex ANDAs
- Restructuring of the user fee program to provide resources commensurate with the workload
- Inclusion of elements to address small businesses concerns (e.g., facility fees for pending, tiers, CMOs)

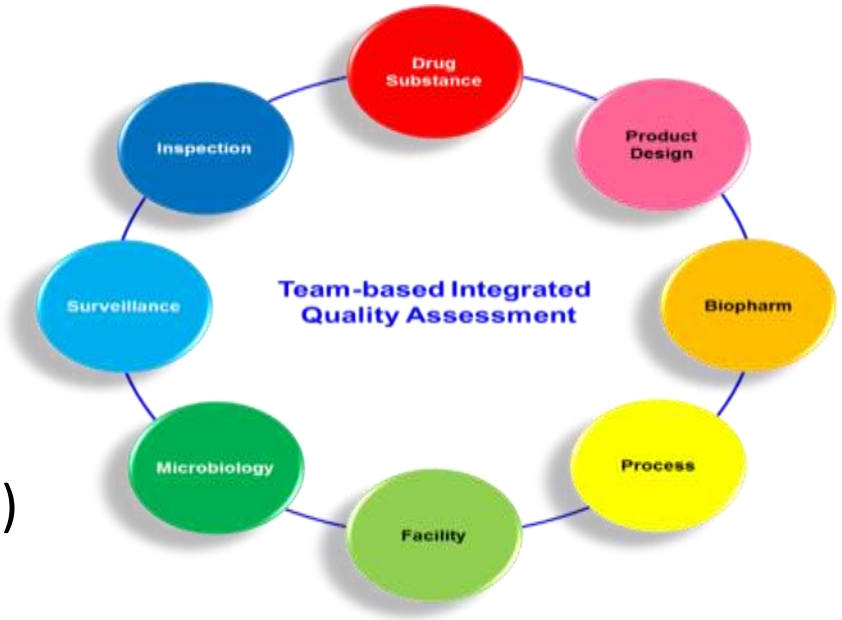
Standard Original	• **10 months**
Priority Original	• **8 months w/ PFC*** • **10 months w/o PFC**
Standard Major Amendment	• **8 months w/o inspection** • **10 months w/ inspection**
Priority Major Amendment	• **6 months w/o inspection** • **8 months w/ inspection & PFC unchanged** • **10 months w/ inspection & no/changed PFC**
Standard/Priority Minor Amendment	• **3 months**

***Pre-submission Facility Correspondence (PFC)** lists all facilities for manufacturing (including labs, etc.) with confirmation the facility is ready for inspection, plus sites for BE/clinical studies

Strengthen OPQ's collaborative organization

Integrated Quality Assessment (IQA)

- A team of subject-matter experts perform quality assessment of an application
- IQA Teams consist of:
  - Application Technical Lead (ATL)
  - Regulatory Business Process Manager (RBPM)
  - Discipline Reviewers (includes ORA)
- IQA integrates review and inspection functions



Quality Assessment Enhancements

OBJECTIVE: Develop tools to modernize quality assessment and knowledge management throughout the drug product lifecycle

- Piloted a **dashboard interface**, centered around:
  - Quality risks for critical quality attributes and corresponding mitigation strategies
  - Control strategies for drug substance and drug product
- Designed a **computer-aided interface** for lifecycle knowledge management and standardization of ANDA quality assessment
- Developing a **benefit-risk assessment framework** that balances clinical context with potential product quality issues

Quality Policy in 2017

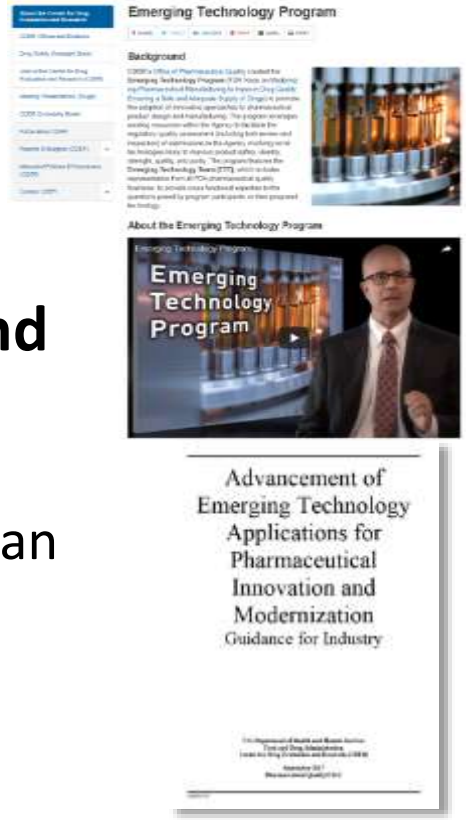
- Published **7 MAPP documents**
- Responded to **220 external inquiries**
- Responded to **527 controlled correspondence***
- Published **10 guidance documents**
  - ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications
  - Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization (Final)
  - CMC Post-approval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports
  - Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products
  - Child-Resistant Packaging Statements in Drug Product Labeling
  - Current Good Manufacturing Practice for Medical Gases
  - Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles
  - Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System
  - Drug Products, Including Biological Products, that Contain Nanomaterials
  - Gluten in Drug Products and Associated Labeling Recommendations

***None* missed GDUFA date**

Promote availability of better medicines

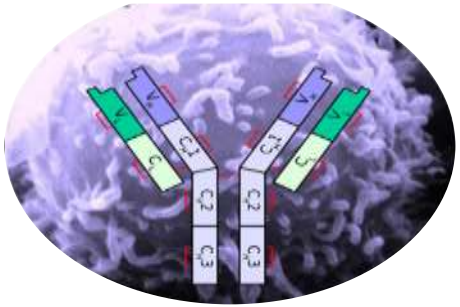
Emerging Technology Program

- Supports industry's development and implementation of innovative approaches in **pharmaceutical design and manufacturing**
- Identifies and **resolves potential scientific and policy issues** related to new approaches
  - Enabled the approval of the first switch from batch to continuous manufacturing process for an approved drug
- A website and Guidance for Industry were posted in 2017



OPQ Science and Research

Immunology

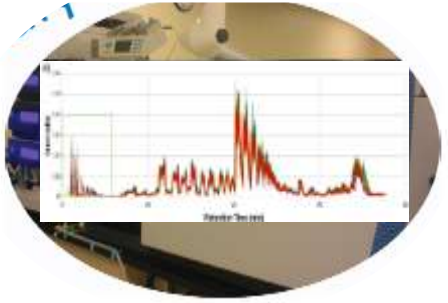


Manufacturing Science & Innovation

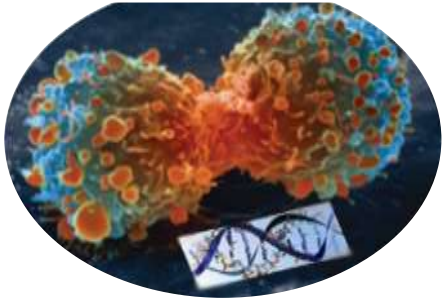
Manufacturing and Controls for Small Molecule Drugs

Manufacturing and Controls for Biological Products

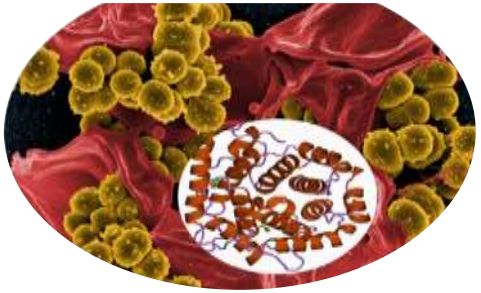
Pharmaceutical Analysis & Characterization



Tumor Biology



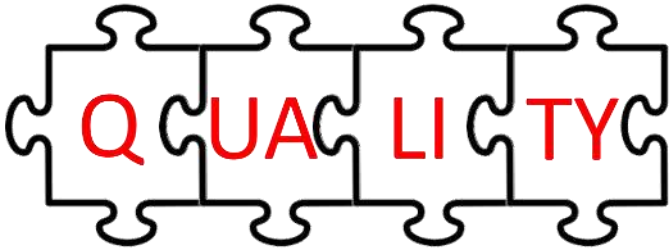
Infectious Disease & Inflammation



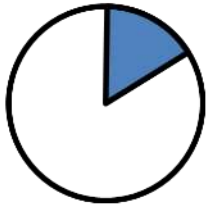
Elevate awareness and commitment to the importance of pharmaceutical quality

Quality Overall Summary

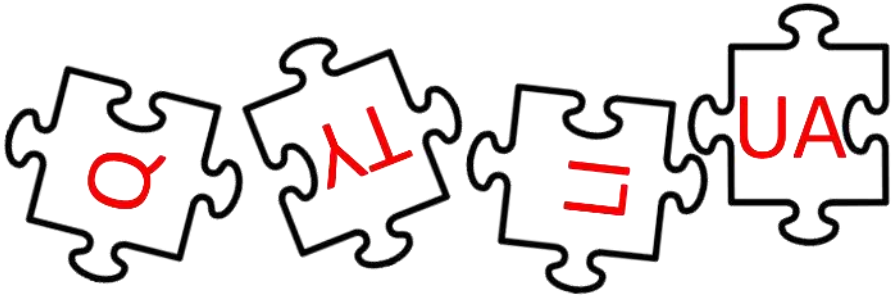
WHAT APPLICANTS TRY TO COMMUNICATE:

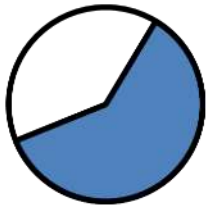


ASSESSMENT TIME:



WHAT REGULATORS SEE IN APPLICATIONS:





Quality Overall Summary

- **Published white paper** in Jan 2018 describing key considerations when creating a QOS
    1. Explain product and process development in a **patient-focused** context
    2. Effectively summarize the **overall control strategy**
    3. **Guide the regulator** through the submission
- Many generic applicants have effectively used a QOS based on Question-based Review (QbR) and may continue to do so in the future

OPQ 2017 Annual Report

- Highlights major accomplishments in assessment, inspection, surveillance, policy, and research
- Crosses all human drug User Fee programs and reaches across the drug product lifecycle
- Communicates the importance of quality and shares the message that the American public can trust their drugs
- Highlights the approval or tentative approval of a record **1,027 generic drug applications**

Strengthen partnerships and engage stakeholders

Organizations OPQ Regularly Engages

- U.S. Pharmacopeial Convention (USP)
- ASTM International (ASTM)
- The Pharmaceutical Research and Manufacturers of America (PhRMA)
- Association for Accessible Medicines (AAM) [formerly Generic Pharmaceutical Association (GPhA)]
- Biotechnology Industry Organization (BIO)
- International Pharmaceutical Excipients Council (IPEC)
- American Association of Pharmaceutical Scientists (AAPS)
- International Society for Pharmaceutical Engineering (ISPE)
- Parenteral Drug Association (PDA)
- Product Quality Research Institute (PQRI)
- US National Institute of Standards and Technology (NIST)
- Bulk Pharmaceutical Task Force (BPTF)
- Drug Information Association (DIA)
- Pharma and Biopharma Outsourcing Association (PBOA)
- International Forum on Process Analytical Chemistry (IFPAC)
- Personal Care Products Council (PCPC)

Engaging Stakeholders

FDA-USP

- In 2017 FDA had **135 liaisons** to USP Expert Committees and Expert Panels

International Collaboration

- Identifying best practices in foreign regulatory agencies: Australia (TGA), Japan (PMDA), Europe (EMA), Canada (Health Canada)

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

- Harmonizing inspections and sharing timely quality information (e.g., product quality defects, recalls)
- FDA hosting PIC/S Annual Seminar in Chicago, September 2018

ICH

- Q12 “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”
- M9 “Biopharmaceutics Classification Based Biowaivers”

Mutual Recognition Agreement

- 12 Member states now recognized: Austria, Croatia, France, Italy, Malta, Spain, Sweden, United Kingdom, Greece, Hungary, Czech Republic, Romania

Concept of Operations for Facility Evaluations and Inspections

- A collaboration between ORA, OC, and OPQ
  - Outlines the workflow processes for **Pre-Approval**, **Post-Approval**, **Surveillance**, and **For-Cause** Inspections
  - Defined and clarified the roles and responsibilities of CDER and ORA
- CDER and ORA began implementation of the ConOps in the fall of 2017
- Includes a commitment to communicate Surveillance Inspection classifications to facility owners within 90 days of the end of an inspection (90% of the time)
- Ongoing updates to related documents:
  - Manuals of Policies and Procedures (MAPPs)
  - Compliance Program Guidance Manuals (CPGMs)
  - Investigations Operations Manual (IOM)
  - Regulatory Procedures Manual (RPM)

Engaging Stakeholders on Quality

Many Establishments Use Quality Metrics

Indicators of Quality Metrics Program Maturity

- Minimal program (e.g., bare minimum information in the Annual Product Review)
- React to existing problems
- Only general, non-specific metrics

- Predictive analytics
- Thoughtful metrics selection
- Assess quality culture and overall commitment to quality
- Senior management and staff commitment to overall quality
- Continual improvement of product and process, the pharmaceutical quality system, and the metrics program

Why Are Quality Metrics Important to FDA?

- FDA CGMPs for drugs require manufacturers to have **an ongoing program** to maintain and evaluate product and process data related to product quality
- Facilitate **continual improvement** and meet **the expectations of ICH Q10** requires measurement of quality indicators
- Provide **quantitative and objective insight** into the state of quality for product and facility
  - Enhance risk-based surveillance inspection scheduling model (When?)
  - Improve effectiveness of inspections (What?)
  - Help to identify factors leading to supply disruption (Why?)

2016 Draft Guidance Revision

Metrics FDA intended to collect as part of a voluntary program

Robustness of Commercial Manufacturing Process

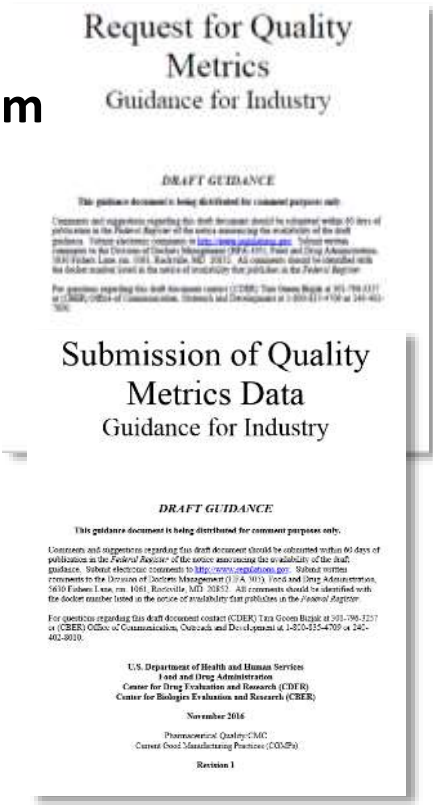
Lot Acceptance Rate

Robustness of Laboratory Operation

Invalidated Out-of-Specification Rate

Voice of the Patient/Customer

Product Quality Complaint Rate



Request for Quality Metrics
Guidance for Industry

DRAFT GUIDANCE

Submission of Quality Metrics Data
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

November 2016

Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Revision 1

2016 Draft Guidance Revision

Current Status:

Quality Metrics for Drug Manufacturing

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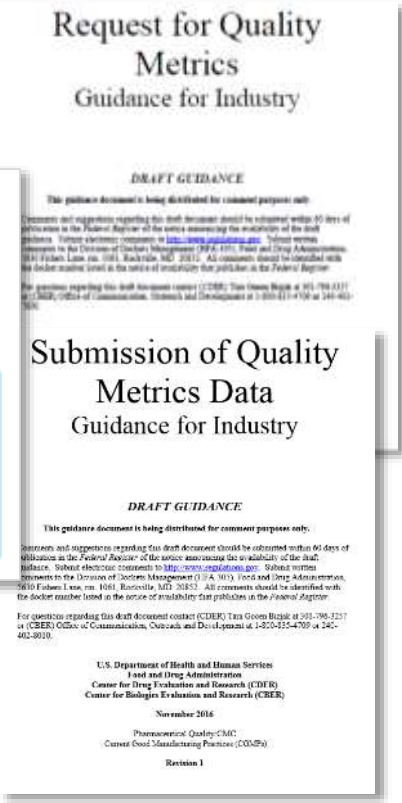
Update:

The portal is not opening in January 2018 for widespread, voluntary reporting. Stay tuned for additional updates.



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November 2016

Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Revision 1

Continuing the Discussion on Quality Metrics

- Quality metrics remain important to FDA and an expectation of modern manufacturing
  - We encourage firms to refine an existing program or initiate a new program as an important step toward building a quality culture
- FDA wants to understand industry concerns and suggestions to move the program forward
  - Contact us at CDER-OPQ-Inquiries@fda.hhs.gov
- Portal development near completion
  - We still plan to request voluntary testing using dummy data
- More to come in the future

Conclusions

OPQ Priorities and Related Actions

1. **Strengthen OPQ's collaborative organization**
   - Using tools to modernize the quality assessment of applications and knowledge management
2. **Promote availability of better medicines**
   - Supporting the development and implementation of innovative approaches in pharmaceutical product design and manufacturing
3. **Elevate awareness and commitment to the importance of pharmaceutical quality**
   - Emphasizing the importance of product and process development in a patient-focused context
4. **Strengthen partnerships and engage stakeholders**
   - Continuing the discussion on quality metrics

A Shared Responsibility

With a focus on patients, together we can provide them confidence in their *next* dose.


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ADMINISTRATION

Quality Changes Related to the UFAs

- FDA Reauthorization Act, signed into law 8/18/17, reauthorizes:
  - The Generic Drug User Fee Amendments (GDUFA) for the first time
  - The Prescription Drug User Fee Act (PDUFA) for the fifth time
  - The Biosimilar User Fee Act (BsUFA) for the first time
- User fees provide critical resources to conduct product assessments in a timely fashion and help ensure the quality, safety, and effectiveness of drug products
- The new UFAs bring some changes impacting our quality assessment, some more significant than others

Quality Changes Related to PDUFA

PDUFA VI

- Current practices regarding Program flexibility for expedited assessments are now part of PDUFA VI
- Advisory Committee Meetings will be no later than 2 months ~~3 months~~ (standard) or no later than 6 weeks ~~2 months~~ (priority) prior to the goal date
- Discipline Review Letters are no longer part of the performance under PDUFA VI
- All original applications and supplements are expected to include a comprehensive and readily located list of ALL manufacturing facilities
- If there is a need to inspect a facility that was not included on the list, FDA may extend the goal date
  - **3 months** for an original application or efficacy supplement
  - **2 months** for a manufacturing supplement
  - Only one extension permitted per assessment cycle (e.g., either major amendment clock extension or facilities clock extension)

Quality Changes Related to BsUFA

BsUFA II

- Assess 90% of applications within 10 months of the *60-day filing date*
  - Date when an applicant is notified if the application has been accepted by FDA for assessment
  - BsUFA I was within 10 months of *receipt*
- 60 days allows for additional communications and interactions between FDA assessment teams and biosimilar applicants
- Establishes an assessment model similar to “the Program” for new drugs
  - Promotes the first cycle assessment process
  - Minimizes the number of assessment cycles
- If there is a need to inspect a facility that was not included on the list of facilities, the FDA may extend the goal date, consistent with PDUFA VI
- Fee structure is more reflective of workload and resources needs for BsUFA
  - Financial predictability and transparency