U.S. FOOD & DRUG ADMINISTRATION

OPQ Update

Ashley B. Boam, MSBE
Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality

OPQ Strategic Priorities

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

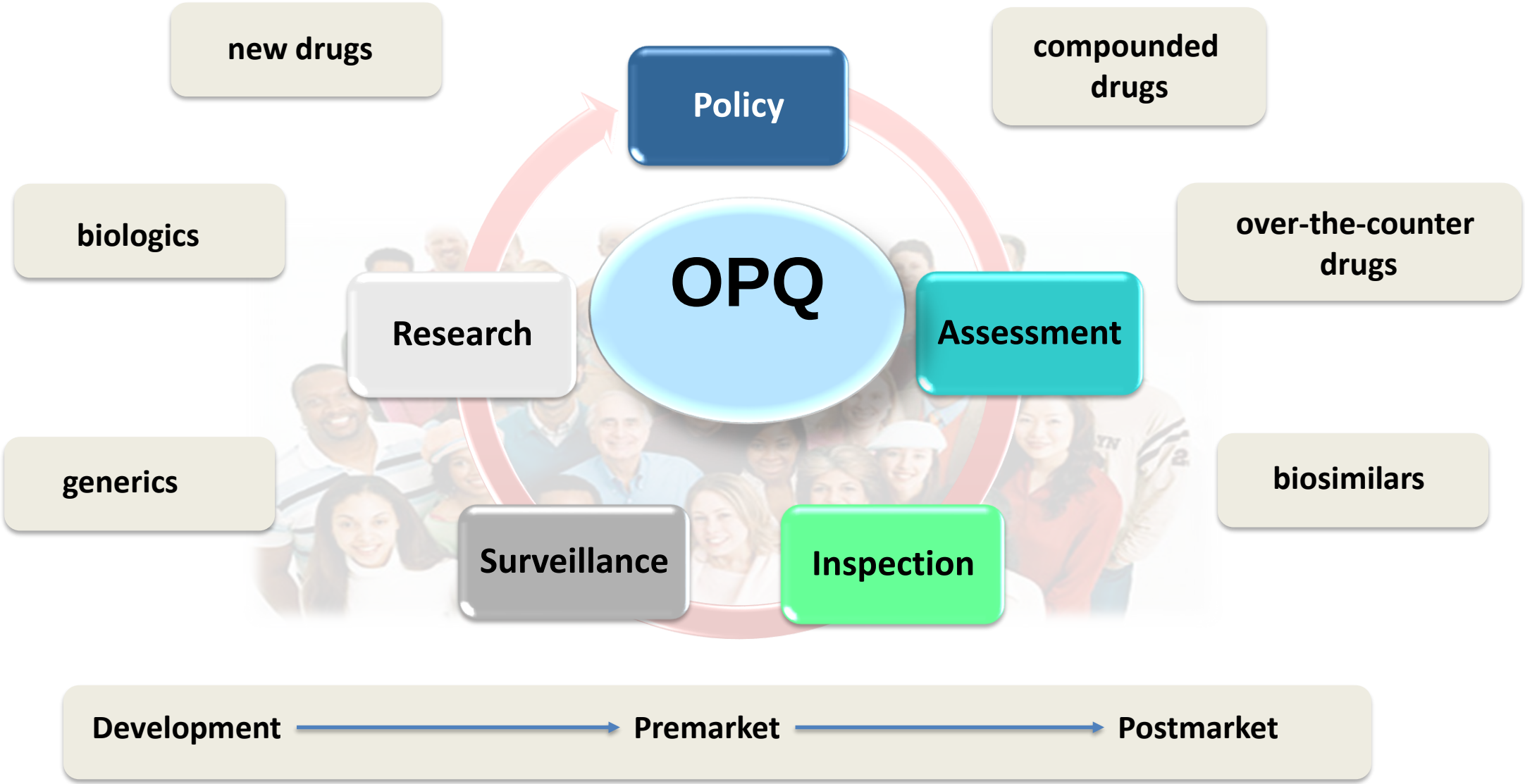
2. **Promote availability of better medicines**
   - Minimize barriers to encourage innovation within FDA and in the manufacturing sector through sensible oversight, research, risk-based decision-making, and continuous process improvement

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

Strengthen OPQ's collaborative organization

Office of Pharmaceutical Quality



Drug Quality Assessment Enhancements

Develop tools to streamline product, process, facility, and benefit-risk assessments

- Developed and piloting a dashboard interface, centered around:
  - Quality risks for critical quality attributes and corresponding mitigation strategies
  - Control strategies for drug substance, drug product

Drug Quality Assessment Enhancements

- Developing the next generation – Knowledge-aided Assessment and Structured Application (KASA):
  - Promote issue-based regulatory and technical assessment
  - Use rules and algorithms based on datasets available to FDA to perform risk assessments and to evaluate applicant's risk mitigation strategies consistently across applications
  - Attain and manage data during the lifecycle of a drug product to facilitate regulatory assessment and decision-making; and
  - Create a knowledge management tool to objectively compare quality across drug product lines and facilities

Drug Quality Assessment Enhancements

- Developing a benefit-risk assessment framework that balances clinical context with regard to potential product quality issues
  - Improve risk communication to business partners and applicants

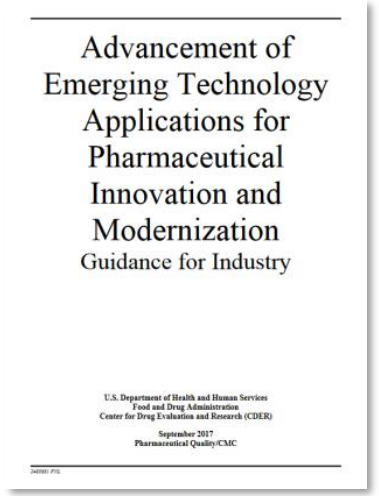
Implementing the Concept of Operations

- Signed in Summer 2017; implementation began Fall 2017 – 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
- Ensures **consistency, efficiency, and transparency** in facility evaluations, inspections, and regulatory decision-making for marketing applications
- Improves **strategic alignment** and **operational capacity** by enhancing collaboration across CDER and ORA
- Ongoing updates to related documents such as:
  - Manuals of Policies and Procedures (MAPPs)
  - Compliance Programs (e.g., Compliance Program 7356.002 for Drug Surveillance Programs)
  - Investigations Operations Manual (IOM)
  - Regulatory Procedures Manual (RPM)

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



Emerging Technology Program

ETT in the news…

- April 2018: Modernizing Pharma Manufacturing (PharmTech.com)
- April 2018: Pallone & FDA Commissioner Gottlieb Visit Rutgers University to Discuss Innovative Pharmaceutical Manufacturing (Congressman Frank Pallone, Jr.)
- April 2018: Continuous Processing (American Pharmaceutical Review)
- February 2018: Facilities of the Future Conference Highlights New Tech (ISPE.org)


› FDA In Brief

FDA supports critical research to spur innovation for continuous manufacturing technology to support and advance drug and biologics development

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August 1, 2018

FDA awarded three grants, using its authority under the 21st Century Cures Act, to:

- Rutgers University (Piscataway, N.J.), Industry 4.0 Implementation in Continuous Pharmaceutical Manufacturing
- The Massachusetts Institute of Technology (Cambridge, M.A.), Smart Data Analytics for Risk Based Regulatory Science and Bioprocessing Decisions
- Georgia Institute of Technology (Atlanta, G.A.), Continuous Synthesis, Crystallization, and Isolation (CSCI) of an API: Process Model-Controlled Enzymatic Synthesis of Beta-Lactam Antibiotics

Innovation through ICH – Q12

ICH Q12 guideline published in draft May 31, 2018; docket open for public comment until December 15, 2018.

Objectives:

- …**Harmonize change management**…in a more transparent and efficient manner…across ICH regions
- …Facilitate **risk-based regulatory oversight**…
- Emphasize…**control strategy** as a key component of the…dossier
- Support **continual improvement** and facilitate introduction of **innovation**
- Enhance use of regulatory tools for **prospective change management**…enabling **strategic management of post-approval changes**…

Innovation through ICH – New Topics

- Q13 – Continuous Manufacturing

- Q2(R2) and Q14 – Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

- *Meeting:* September 20, 2018
- *Agenda:* The meeting will focus on two topics related to OPQ's priority of promoting the availability of better medicine
  - the modernization of assessing drug applications through a Knowledge-Aided Assessment and Structured Application (KASA) initiative. FDA will seek input on the potential enhancement of a submission format consistent with KASA to improve the efficiency and consistency of regulatory quality assessment.
  - in-vitro/in-vivo relationship standards, and will seek input on establishing patient-focused dissolution standards for oral solid modified-release dosage forms.

Industry attendance and participation are encouraged!

Elevate awareness and commitment to the importance of pharmaceutical quality

Communicating the Importance of 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.

Outreach to Patients and Consumers

- **July/August WebMD "Check Up" on Drug Quality 101**
- **Study on Consumer Knowledge of Drug Quality**
  - Gain insight into consumers' current understanding of quality

EXPERT Q&A

Drug Quality 101

Curious about the quality of your medications?

→ **Here or There** The FDA has the same quality standards for drugs made in the U.S. and abroad.

PATIENTS AND CONSUMERS EXPECT SAFE AND EFFECTIVE DRUGS WITH every dose they take. **Michael Kopcha, PhD, RPh,** director of the Office of Pharmaceutical Quality at the FDA, answers some common questions about drug quality.

Q What does drug quality mean?
KOPCHA A quality product of any kind consistently meets the expectations of the user. Drugs are no different. They must be manufactured using standards that ensure every dose is safe, effective, and able to provide its intended benefit. The FDA assesses all drugs before approval to assure they meet established quality standards.

Q How does drug quality impact me?
KOPCHA Quality is what ensures every dose of your drug is of the appropriate strength—not too weak and not too strong—and free of contamination and defects. It gives you confidence in the next dose you take. Also, problems with drug quality can create shortages, which may make your drug unavailable when you need it.

Q Does the FDA have the same expectations for the quality of a drug made in the U.S. vs. abroad? Brand-name vs. generic?
KOPCHA Yes. The FDA has the same expectations for quality whether a drug is made in the U.S. or abroad and whether a drug is brand name or generic. You can have confidence knowing that all FDA-approved drugs have been held to consistent quality standards regardless of the source.

Q What should I do if I suspect a problem with the quality of a drug?
KOPCHA Even when manufacturers are very vigilant, sometimes quality issues arise after drug approval. You can report suspected quality issues with a drug directly to the FDA using the MedWatch system. Visit www.fda.gov/medwatch to easily find the online reporting form for consumers and patients.

You can also discuss any concerns you have with your doctor or pharmacist.

BY THE NUMBERS

Nearly 1 in 3	90%	More than 1,300	More than 1,000
Number of drug shortages caused by quality issues related to manufacturing.	Percentage annual reported drug shortages have dropped since 2011.	Number of people who staff the FDA's Office of Pharmaceutical Quality, one of the largest offices at the FDA.	Number of generic drugs approved by the FDA in 2017, an all-time high.

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Patient-Focused Quality Standards

- Can be defined as the set of criteria to which a drug product should conform in order to achieve the intended performance
- Ensure that the product can reproducibly deliver the therapeutic benefit to the patient, safely, as stated in the label, whether that benefit has been newly established through clinical trials or is based on a reference listed drug or reference product
- What is intended:
  - Increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on relevance to intended performance, instead of process capability or manufacturing process control
- What is not intended:
  - Conducting additional clinical studies to set acceptance criteria
- Example - OPQ MAPP 5017.2 “Establishing Impurity Acceptance Criteria As a Part of Specifications for NDAs, ANDAs and BLAs Based on Clinical Relevance

Patient Focus and the Control Strategy

- Manufacturers should pursue development of a patient-focused, risk-based, overall control strategy
- **Published white paper** in Jan 2018 describing key considerations when creating a Quality Overall Summary (QOS) that should:
  - explain product and process development in a patient-focused context
  - effectively summarize the overall control strategy
  - guide the regulator through the submission
- Regulator should be able to use the QOS to initiate the assessment of potential risk to the patient, and the control of such risk, in the commercially manufactured product.


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A Regulatory Perspective on the Quality Overall Summary: Putting the Pieces Together


FDA Drug Information
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The Office of Pharmaceutical Quality Releases White Paper with Key Considerations for the Quality Overall Summary of Human Drug Applications: go.usa.gov/xnfxK.

12:18 PM - 23 Jan 2018

6 Retweets 11 Likes

BRIEF

FDA debuts paper on quality standards, aiming to decrease review times

FDA White Paper: A Regulatory Perspective on the Quality Overall Summary: Putting the Pieces Together, January 2018

Strengthen partnerships and engage stakeholders

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”
- Q13 “Continuous Manufacturing”
- Q14 “Analytical Procedure Development and Revision of Q2(R1) Analytical Validation”

Mutual Recognition Agreement

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

Recently Published Guidance and MAPPs

- Quality Attribute Considerations for Chewable Tablets Guidance for Industry (8/20/18)
- Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (8/8/18)
- Elemental Impurities in Drug Products (8/7/18)
- Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments (Draft; 7/24/18)
- Field Alert Report Submission: Questions and Answers (Draft; 7/18/18)
- Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Draft; 5/30/18)
- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations (Draft; 4/18/18)
- Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (4/4/18)
- Regulatory Classification of Pharmaceutical Co-Crystals (2/4/18)

- MAPP 5014.1 – Understanding CDER's Risk-Based Site Selection Model (9/5/18)
- MAPP 5310.3 Rev.1 – Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes (4/26/18)

Improving Transparency for Facility Inspections Outcomes – Preapproval

- Preapproval inspections
  - Objectives:
    - Assure readiness for manufacturing
    - Evaluate adherence to application commitments
    - Assess the authenticity and accuracy of data submitted in applications
  - A “withhold” recommendation holds up approval of the application until remediated
  - If issues identified that could impact approvability of a new drug application, FDA will communicate this through an information request, discipline review letter, or complete response letter (GDUFA II Commitment Letter)

Improving Transparency for Facility Inspections Outcomes – Surveillance

- Surveillance inspections
  - Objectives:
    - Determine compliance with CGMP requirements; provide evidence for action as necessary
    - Provide an assessment of firms' conformance to CGMP requirements for Agency decisions
    - Provide feedback to firms to improve their compliance;
    - Better understand current practices in drug manufacturing for the purpose of updating the CGMP requirements, regulatory policy, and guidance documents
  - FDA generally issues a letter to the facility with the inspection outcome within 90 days of the inspection – Official Action Indicated (OAI), Voluntary Action Indicated (VAI), No Action Indicated (NAI)
  - Violative inspection (OAI) will generally preclude application approval

Identifying Facilities for Surveillance Inspections

- MAPP 5014.1 – Understanding CDER's Risk-Based Site Selection Model – published September 5
  - Outlines the risk factors FDA uses in the Site Selection Model (SSM) to generate the Site Surveillance Inspection List that prioritizes sites for surveillance inspection; higher risk sites assigned to ORA for inspection that fiscal year
    - One goal of the SSM is to achieve parity in inspection frequency = equal frequency for sites with equivalent risk, regardless of geography (e.g., foreign vs. domestic) or product type (e.g., originator, generic/biosimilar, OTC monograph)
  - Risk factors consistent with section 510 of the FD&C Act
  - Annual review and approval process – CDER and ORA
    - Risk factors, weights, and methodology assessed, areas for improvement or modification identified

MAPP 5014.1 – Understanding CDER's Risk-Based Site Selection Model

Current risk factors included in the SSM:

- Site type (e.g., manufacturer, packager only, control lab only)
- Time since last surveillance inspection (or if the site was never previously inspected)
- FDA compliance history
- Foreign regulatory authority inspectional history (with authority deemed capable under section 809 FD&C Act)
- Patient exposure
- Hazard signals (such as FARs, BPDRs, MedWatch reports, recalls, etc.)
- Inherent product risk:
  - Dosage form
  - Route of administration
  - Products intended to be sterile
  - API load (concentration of API in dosage form or unit dose)
  - Biologic drug substance or drug product
- Therapeutic class
- Narrow Therapeutic Index (NTI) drugs
- Emergency use drugs

Sharing Inspection Outcomes

Inspection Classification Database

- Provides the most recent classifications of inspections of manufacturing facilities conducted for routine CGMP surveillance purposes or inspections of sites conducting bioequivalence/ bioavailability studies.
- Provides transparency to the industry, the general public, and other regulators.
- Database also updated to build on our progress implementing the Mutual Recognition Agreement with the European Union, and now supports inclusion of facility status based on classification of inspection reports from foreign regulatory authorities.
- Updated every 30 days

Strengthen partnerships and engage stakeholders

Furthering a Commitment to Quality

Meeting the Expectations of ICH Q10

- Q10 Objectives:
  - Achieve product realization
  - Establish and maintain a state of control
  - Facilitate continual improvement
- "Management should:
  - (1) Participate in the design, implementation, monitoring, and maintenance of an effective pharmaceutical quality system

  …
  - (5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system
  - (6) Advocate continual improvement"

Requires measurement of quality indicators

And…FDA CGMPs for drugs require manufacturers to have an ongoing program to maintain and evaluate product and process data that relate to product quality

Many Establishments Use Quality Metrics

Indicators of Quality Metrics Program Maturity

- Predictive analytics
- Thoughtful metrics selection
- Assess quality culture and overall commitment to quality
- Senior management and general staff commitment to overall quality
- Metrics are used for continual improvement of product and process, the pharmaceutical quality system, and the metrics program

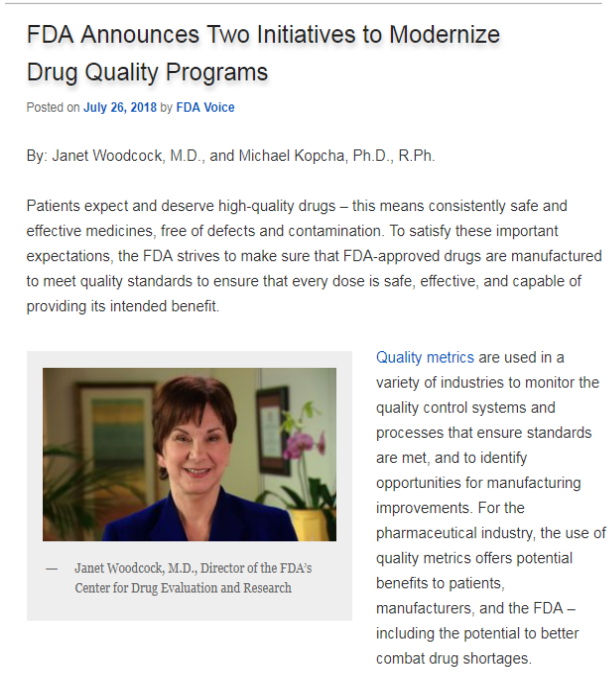
Research Indicates Quality Metrics Programs Are a Good Business Practice

- Collaborative research with St. Gallen University (Switzerland) and FDA
- Developing a model for Pharmaceutical Quality System (PQS) Excellence
- Implications from Year 1
  - Research supports alignment of reporting of quality performance metrics with internal operational excellence programs
  - Fostering Quality Maturity will have a positive impact on the *Quality Behavior* at a firm, leading to superior Cultural Excellence and subsequently providing the *foundation of PQS Excellence*

Report can be obtained at: http://tectem.ch/institute/opex/fda

Why Are Quality Metrics Important to FDA?

- Additional insight into the state of quality for product and facility
- More quantitative and objective measure of quality at the product, site, and system levels
- Enhance risk-based surveillance inspection scheduling model
  - When should we inspect
- Improve effectiveness of inspections
  - What should our inspection focus be
- Help to identify factors leading to supply disruption



FDA Announces Two Initiatives to Modernize Drug Quality Programs

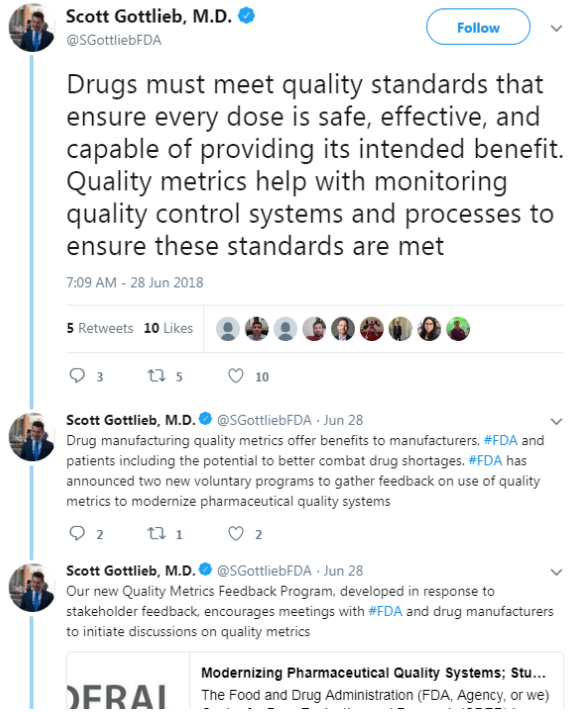
Posted on July 26, 2018 by FDA Voice

By: Janet Woodcock, M.D., and Michael Kopcha, Ph.D., R.Ph.

Patients expect and deserve high-quality drugs – this means consistently safe and effective medicines, free of defects and contamination. To satisfy these important expectations, the FDA strives to make sure that FDA-approved drugs are manufactured to meet quality standards to ensure that every dose is safe, effective, and capable of providing its intended benefit.

— Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research

Quality metrics are used in a variety of industries to monitor the quality control systems and processes that ensure standards are met, and to identify opportunities for manufacturing improvements. For the pharmaceutical industry, the use of quality metrics offers potential benefits to patients, manufacturers, and the FDA – including the potential to better combat drug shortages.



Scott Gottlieb, M.D. @SGottliebFDA Follow

Drugs must meet quality standards that ensure every dose is safe, effective, and capable of providing its intended benefit. Quality metrics help with monitoring quality control systems and processes to ensure these standards are met

7:09 AM - 28 Jun 2018

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3 5 10

Scott Gottlieb, M.D. @SGottliebFDA · Jun 28

Drug manufacturing quality metrics offer benefits to manufacturers, #FDA and patients including the potential to better combat drug shortages. #FDA has announced two new voluntary programs to gather feedback on use of quality metrics to modernize pharmaceutical quality systems

2 1 2

Scott Gottlieb, M.D. @SGottliebFDA · Jun 28

Our new Quality Metrics Feedback Program, developed in response to stakeholder feedback, encourages meetings with #FDA and drug manufacturers to initiate discussions on quality metrics

Modernizing Pharmaceutical Quality Systems; Stu...

The Food and Drug Administration (FDA, Agency, or we)

FDA's Quality Metrics Journey - Next Steps

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–1903]

Modernizing Pharmaceutical Quality Systems; Studying Quality Metrics and Quality Culture; Quality Metrics Feedback Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) Center for Drug Evaluation and Research (CDER) is announcing two new efforts to gather feedback on the use of quality metrics to modernize pharmaceutical quality systems and advance innovation based on stakeholder feedback. These efforts include Type C formal meeting requests and pre-abbreviated new drug application (pre-ANDA) meeting requests, and a pilot study to gain feedback from those establishments for which Type C formal meetings or pre-ANDA meetings do not apply (*e.g.*, active pharmaceutical ingredients (API)

Quality Metrics for Drug Manufacturing

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Update:

- June 2018 – FDA announces the **Quality Metrics Feedback Program** and **2018 Quality Metrics Site Visit Program**.

What are Quality Metrics?

Quality metrics are used throughout the drugs and biologics industry to monitor quality control systems and processes. Modern manufacturing includes robust quality metrics programs as a foundation for continual improvement of product and process quality. Quality metrics are one element of companies' commitment to quality culture.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–1896]

Quality Metrics Site Visit Program for Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Staff; Information Available to Industry

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in the Food and Drug Administration (FDA or Agency) are announcing a 2018 CDER and CBER staff experiential learning site visit program specific to FDA's Quality Metrics Program. FDA is proposing this program, in part, in response to input from a variety of stakeholders over the past couple of years. The purpose of this 2018 Quality Metrics Site Visit Program is to provide experiential and firsthand learning opportunities to FDA staff involved in the development of the FDA Quality Metrics Program and to provide stakeholders with an opportunity to explain the advantages and challenges associated with implementing and managing a robust Quality Metrics Program. This notice invites

FDA's Quality Metrics Feedback/ Site Visit Programs - Clarifications

- Feedback Program
  - For application holders, use of existing meeting mechanisms is for convenience only; no impact on pending or planned applications
  - Any data shared is for demonstration/informational purposes only
    - Data will not be considered part of an application, for any type of assessment, or to influence inspection planning
  - Format and duration of meetings are flexible
  - Firms may request to participate in both the feedback program and the site visit program
- Site Visit Program
  - Window for proposals extended to December 17, 2018 (83 FR 41080)

Conclusions

- OPQ is committed to assuring availability of safe, effective, quality medicines.
- We are:
  - Taking steps to modernize our programs, and enhance our regulatory assessments to be more effective and efficient
  - Strengthening our internal and external collaborations to better assure the availability of quality drugs
  - Improving transparency regarding inspection outcomes
  - Participating in global harmonization efforts to reduce barriers to innovation and continual improvement in manufacturing


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