

The U.S. FDA's Generic Drugs Regulatory Program

A Joint Keynote:

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Director, Office of Generic Drugs

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Center for Drug Evaluation and Research

U.S. Food and Drug Administration

2019 Generic + Biosimilars Medicines Conference

November 5, 2019

Generic Drugs Regulatory Program



The Generic Drug Program: Collaborating for Success

Sally Choe, Ph.D.

Director, Office of Generic Drugs

The State of Compliance

Donald Ashley, J.D.

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Join Us in a Commitment to Quality

Michael Kopcha, Ph.D., R.Ph.

Director, Office of Pharmaceutical Quality

The Generic Drug Program: Collaborating for Success

Generic Drugs Benefit the Public Health



Dr. Ned Sharpless
@FDACommissioner

Follow

FDA approved an additional generic naloxone product after announcing in April that we would start granting priority review to all abbreviated new drug applications for products indicated for the emergency treatment of known or suspected opioid overdose.

go.usa.gov/xVJFc

FDA approves additional generic for emergency treatment of known or suspected opioid overdose



Embracing the Future



The changing generic landscape impacts us all

Enhanced, timely collaboration is key to success of the Generic Drug Program

GDUFA Regulatory Science

Guidance on complex products

Internal alignment on complex issues

Confidence in generic substitution

Review tool development

Faster and smarter generic drug
development and review



Highlighted FY2019 Workshops

- **Generic Drug Forum**, hosted by CDER Small Business & Industry Assistance (SBIA)
- **Generic Drug Regulatory Science Initiatives**, public workshop
- **Complex Generic Drug Product Development Workshop**, hosted by SBIA
- **Complex generic drug-device combination products workshop**, co-hosted by FDA and the Drug Information Association
- **“Flight simulator” workshop on complex generic drug products**, hosted by the American Association of Pharmaceutical Scientists
- **PBPK Modeling for the Development and Approval of Locally Acting Drug Products pre-conference workshop**, hosted by the American Society for Clinical Pharmacology and Therapeutics



Collaboration on Generic Drug Product Development

- Pre-ANDA program
 - FDA’s pre-submission process shows early collaboration helping longer term success
 - **Controlled correspondence** inquiries that address specific development questions from potential generic applicants
 - **Pre-ANDA meeting requests for complex generics**
- Guidances
 - Enhanced communications with and transparency to industry through PSGs and guidance documents = **significant improvement in the adequacy of applications on receipt**
 - **Industry can engage in ideas for guidance development**

FY2019 Highlighted Guidances for Industry

Draft guidances for industry

- Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations
- Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs
- Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs
- Bioavailability Studies Submitted in NDAs or INDs – General Considerations

Final guidances for industry

- ANDA Submissions – Content and Format of Abbreviated New Drug Applications
- Post Complete Response Letter Meetings Between FDA and ANDA Applicants Under GDUFA

Assessment is a Collaborative Opportunity

Mutual commitment to the assessment process has shown clear value

More clear communications from FDA, and complete, timely responses from applicants significantly enhances process

Maximizing GDUFA II mechanisms is critical

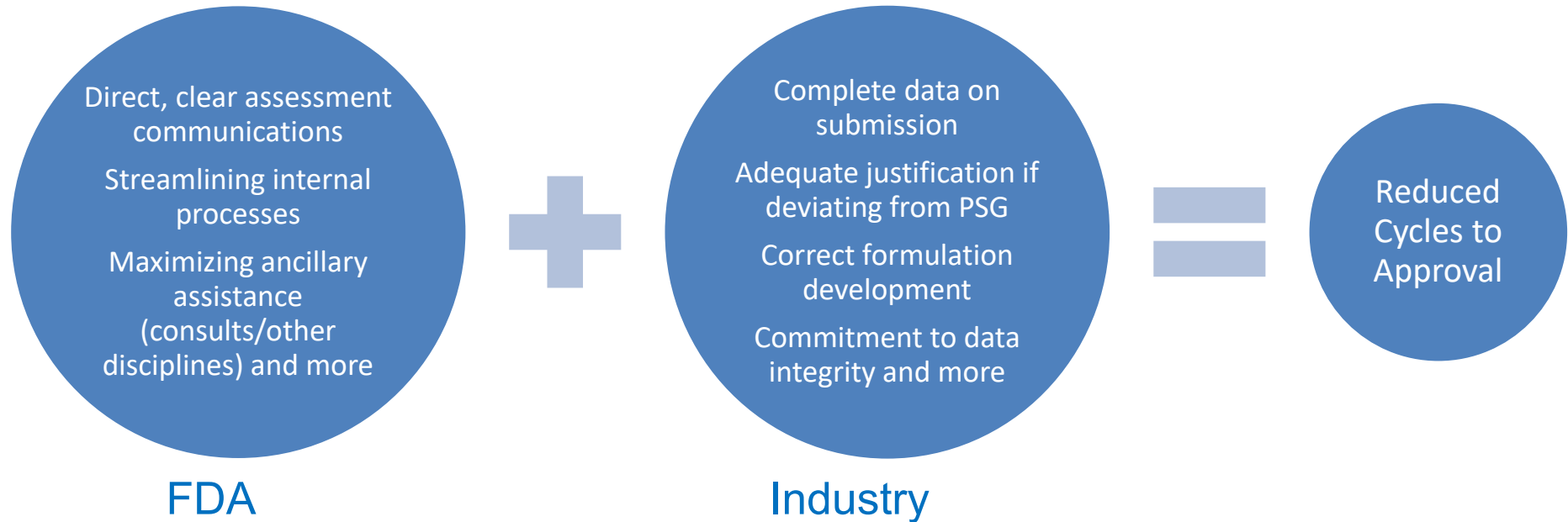


Assessment Success through Sustained Commitment to Process

- Launched [Upcoming Product-Specific Guidances \(PSGs\) for Complex Drug Product Development](#)
- Updates to
 - [List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic](#)
 - [Patent Certifications and Suitability Petitions](#)
 - [Reference Listed Drug Access Inquiries](#)
- Final Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application
- Draft Guidances for Industry:
 - ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs
 - CDER’s Program for the Recognition of Voluntary Consensus Standards Related to Pharmaceutical Quality
 - Designation, Submission, and Review of ANDAs for Competitive Generic Therapies
 - Harmonizing Compendial Standards with Drug Application Approval Using the USP Pending Monograph Process
 - Using the Inactive Ingredient Database
- Maximizing mechanisms in GDUFA II

We are not done!

Example: Mutual Commitment to Maximizing Best Practices for First-Cycle Approval



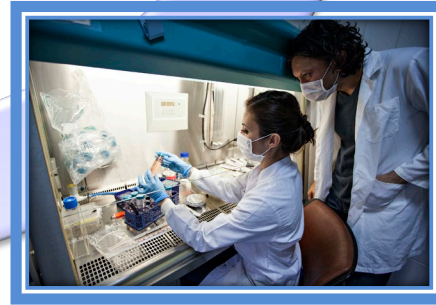
An icon representing a document or checklist, showing a grid of lines and a checkmark.

Best Practices Include Timely Actions by Industry

- Timely responses to communications, e.g., Information Requests, Complete Response Letters
- Proactively update to reflect changes resulting from RLD, changes to patent and exclusivity information
- Withdraw ANDAs industry does not intend to pursue



Generic Drug Program



The State of Compliance

Concept of Operations

Goal: Create and implement a formalized and streamlined facility evaluation and inspection program

90-day Classification Letter

- Rate of classification letters issued by FDA in 90 days from close of inspection

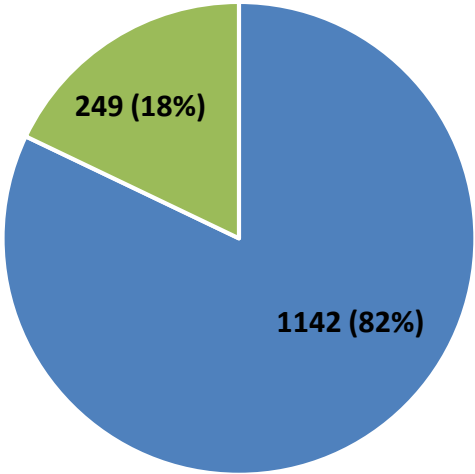
OAI Regulatory Actions

- Rate of OAI regulatory actions completed in 6 months from the closing of the inspection

Key Performance Indicators

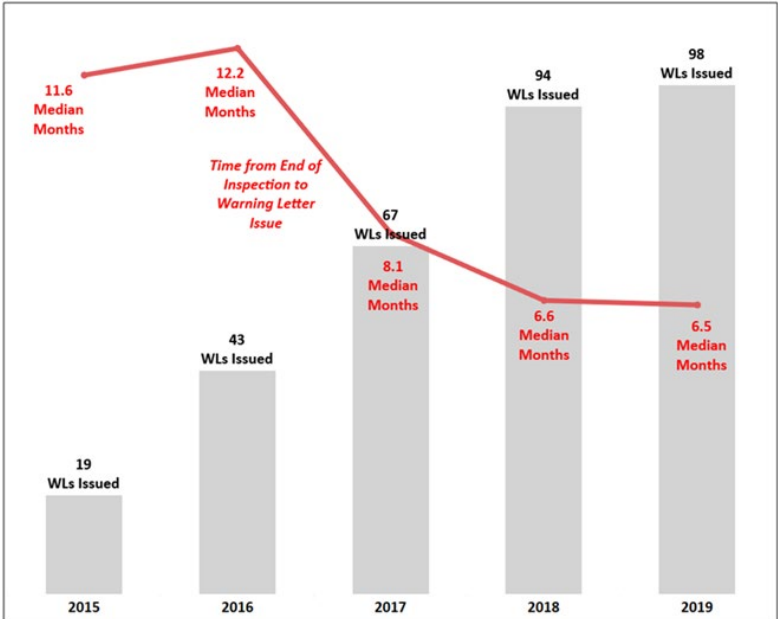
90-day Classification Letters in FY 2018

1,391 classification letters issued in FY18



■ Met 90-day target ■ Missed 90-day target

FY 2015-2019: Overall median 58% improvement in time to issue warning letters from the end of inspection



Total CGMP Warning Letters by Country: FY 2015 to FY 2019



© 2019 Mapbox © OpenStreetMap

Total CGMP Warning Letters by Region: FY 2019



© 2019 Mapbox © OpenStreetMap

Non-compliance trends for API



- Obfuscation of Supply Chain Information
- Data integrity
- Impurities



Regulatory Authority for API

- Statutory authority for API CGMP is the Food, Drug and Cosmetic Act, Section 501(a)(2)(B)
- FDA considers the expectations outlined in ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients in determining whether APIs are manufactured in conformance with CGMP

Obfuscation of Supply Chain

- Failure to maintain traceability of API throughout the supply chain
 - Failed to obtain and retain documents with the identity of the original manufacturer and certificate of analysis
- Distributed API, including opioids, with inadequate certificates of analysis
 - This compromises supply chain accountability and traceability and may put consumers at risk
 - Customers included compounding pharmacies

ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

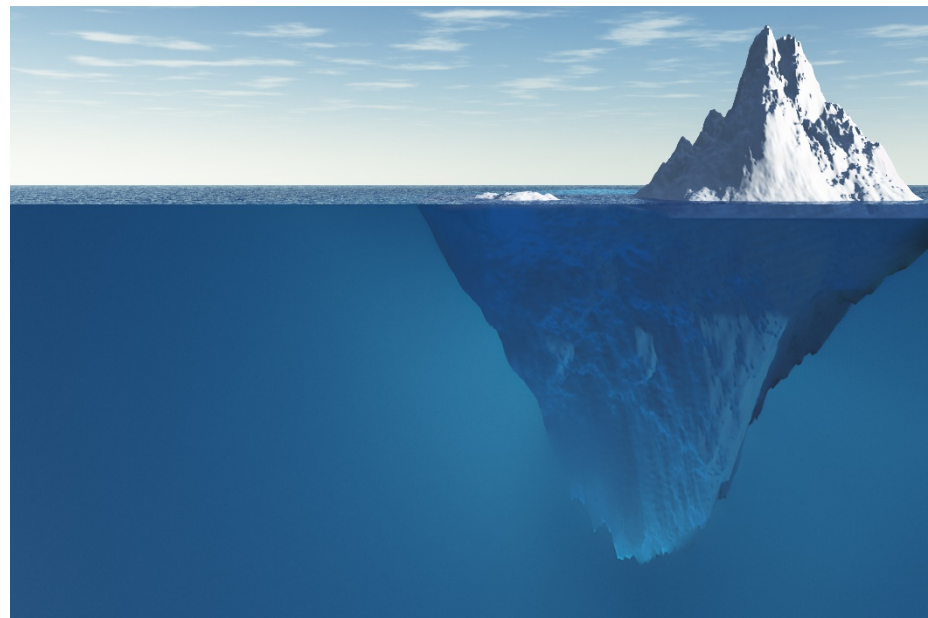
Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer. (17.60)

ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied. (17.61)

Data Integrity

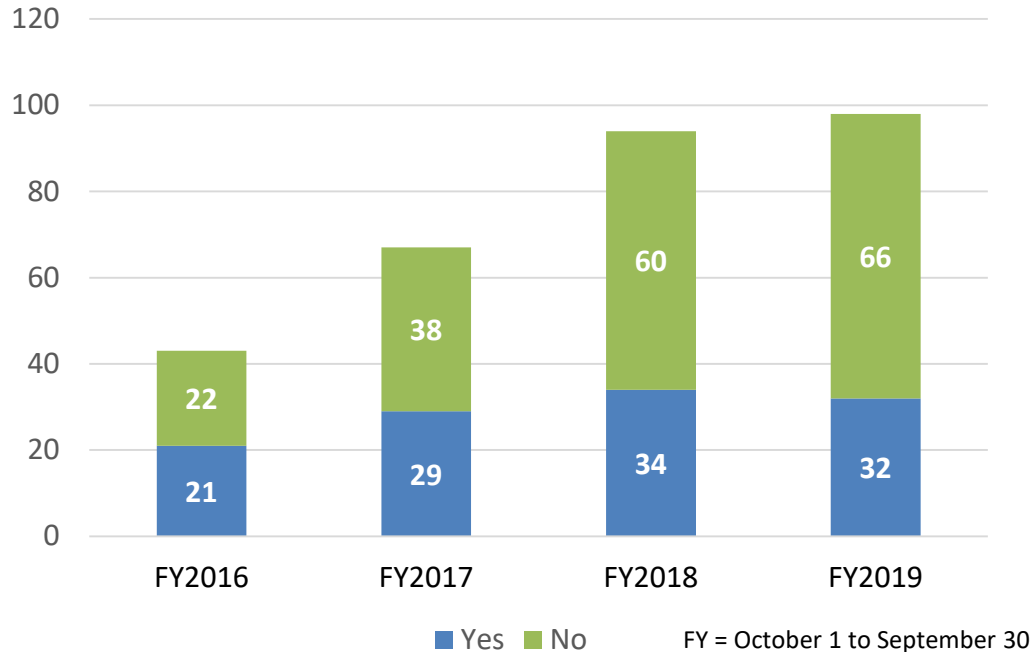
- Data integrity is evidence that data are complete, consistent, and accurate
- CGMP is the minimum requirement
- Data integrity underpins CGMP
- Lapses obscure other problems



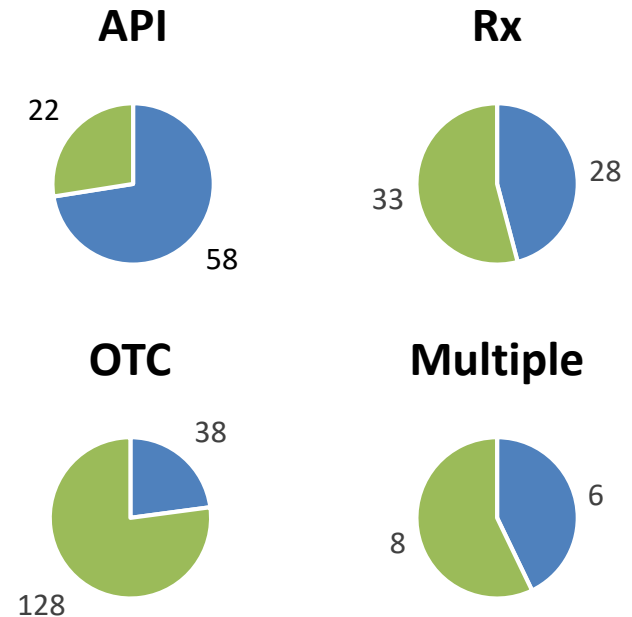
Data integrity problems you can see are the tip of the iceberg.

Data Integrity

Warning letters issued containing data integrity charges



Distribution of data integrity charges by drug type



Data Integrity



From a recent warning letter:

“Your firm failed to implement adequate controls to ensure the integrity of data generated at your facility.”

“...your firm admitted to routinely deleting recovered solvents gas chromatography data older than three months permanently, without any backup.”



FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

“The FDA is committed to maintaining our gold standard for safety and efficacy. That includes our efforts to ensure the quality of drugs and the safe manner in which they’re manufactured. When we identify lapses in the quality of drugs and problems with their manufacturing that have the potential to create risks for patients, we’re committed to taking swift action to alert the public and help facilitate the removal of the products from the market.”

- Scott Gottlieb, MD
Former FDA Commissioner

Impurities



From a recent warning letter:

“Your firm failed to implement procedures to evaluate and control impurity risks associated with your solvent recovery operations done under contract to API manufacturers. This includes adequate testing to confirm their suitability for manufacturing processes in which they may be use, establishing an impurity profile for solvents to ensure that they meet appropriate standards and maintaining an ongoing program for monitoring process controls to ensure stable manufacturing and prevent unanticipated impurities.”

Statement on new testing results, including low levels of impurities in ranitidine drugs



“Americans deserve to have confidence in the quality of drugs the U.S. Food and Drug Administration regulates – from the prescription medicines they take to the over-the-counter (OTC) products they use in their daily lives. Helping assure the quality and safety of these products is one of our greatest responsibilities. Over the past several weeks, the FDA has been [investigating](#) the detection of a contaminant known as N-Nitrosodimethylamine (NDMA) in ranitidine medications, commonly known by the brand name Zantac.”

- Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

FDA guidance on impurities

- ICH **Q3A** Impurities in New Drug Substances
- ICH **Q3B(R2)** Impurities in New Drug Products
- ICH **Q3C** Impurities: Residual Solvents
- ICH **Q3D** Elemental Impurities
- ICH **M7(R1)** Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Guidance for Industry

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)
September 2016
ICH

Revision 1

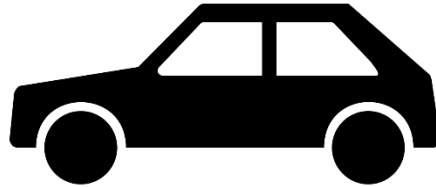
- Provides guidance regarding CGMP for the manufacturing of APIs under an appropriate system for managing quality
- Intended to help ensure APIs meet the quality and purity characteristics that they purport, or are represented, to possess

Join Us in a Commitment to Quality

Pharmaceutical Quality

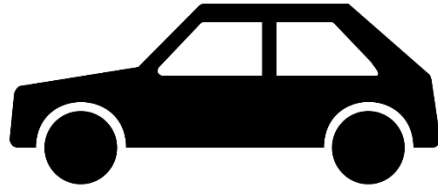


A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's arm in a light blue sleeve.

**Patients expect safe and effective
medicine with every dose they take.**

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's arm in a blue sleeve.

**It is what gives patients confidence
in their *next* dose of medicine.**

A History of Quality Events



Congress and FDA have acted because companies failed to adequately ensure quality

1938

>100 deaths from elixir sulfanilamide

1938 Food, Drug, and Cosmetic (FD&C) Act

Safety studies required for new drugs

1962

Children born with severe birth defects from thalidomide

1962 Kefauver-Harris Amendments to the FD&C Act

Need to prove that drugs are safe and effective

2015

Serious injuries and deaths from global heparin crisis

FDA establishes Office of Pharmaceutical Quality

Integrates functions and elevates FDA's commitment to quality



Congressional Hearing April 29, 2008

I watched my husband and my best friend slip away before my eyes.

As a nurse, I thought that I would be there to save my husband from any errors, but I guess I was naïve.

I never thought the life-saving medication we were relying on might be contaminated.

Office of Pharmaceutical Quality



Across the life cycle...





Performs all administrative operations

Performs regulatory operations, scientific standards/quality assessments, and investigational operations, including research and development, quality control, and quality products (e.g., NDAs, ANDAs, BLAs, supplements)

The State of Pharmaceutical Quality



Key findings from FY 2018:

- **More regulated sites** manufacture products¹ for both NDA & ANDA products than for either NDAs or ANDAs alone
- **Over a quarter** of all recalls were attributed to manufacturers described as re-packers and re-labelers
- The Top 2 applicants by submission volume had **more Complete Responses than Approvals**
- **63%** of all drugs in shortage are ANDA products

¹ "Product" refers to both drug product and drug substance/active pharmaceutical ingredient

The Shortage Issue



Drug Shortages:

Root Causes and Potential Solutions

2019



To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality – Not Just Medicine

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Content reviewed as of 10/24/2019

Regulated Products/ Drugs

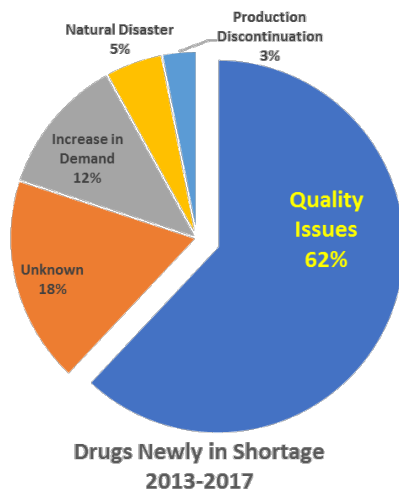
By: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

You might not always shop based solely on the lowest price. For instance, if you highly value your time, you may choose a car from a manufacturer with a great reputation for reliability, even though similar cars cost a bit less. Choices based on what you value are common in everyday life. But, unfortunately, when it comes to prescription medications, buyers may not have that option. And in the view of the U.S. Food and Drug Administration, this lack of transparency is contributing to ongoing drug shortages, a critical health care issue that reduces treatment options, limits access to medications, and can threaten the well-being of patients in need of important therapies. Let's take a closer look.

All drug manufacturers that sell their medications in the United States must adhere to the FDA's Current Good Manufacturing Practice (CGMP) requirements. Adherence to CGMP requirements is intended to make sure the drug itself is of adequate quality.

But there's another element to quality in manufacturing – the ability to reliably make the product in sufficient quantities and with sufficient speed to ensure that supply consistently meets demand over sustained periods of time. This is especially true in the pharmaceutical industry, where the product is often life-sustaining – and ongoing access is critical.

Purchasers of prescription drugs such as drug distributors, hospitals, and pharmacies can be assured that FDA-approved medications have been shown to be safe and effective for their labeled uses. Since these purchasers have tight budgets, they may select the lowest-priced product, in



Root causes for drug shortages:

- Lack of incentives for manufacturers to produce less profitable drugs
- **Market does not recognize and reward manufacturers for “mature quality systems”**
- Logistical and regulatory challenges make it difficult to recover from a supply disruption

Enduring solutions:

- Understanding the impact of drug shortages and the contributing contracting practices
- **A ‘rating system’ to incentivize quality management maturity**
- Sustainable private sector contracts for a reliable supply of medically important drugs

ENGAGE

Strengthen Partnerships and Engage Stakeholders

WE WANT YOU



**TO JOIN US IN A
COMMITMENT TO QUALITY**

YOU



PAYORS
PURCHASERS
PROVIDERS
STUDENTS
COMPOUNDERS
REGULATORS

PATIENTS
CONSUMERS
TEACHERS
MANUFACTURERS
PHARMACISTS
HOSPITALS

Engaging Stakeholders



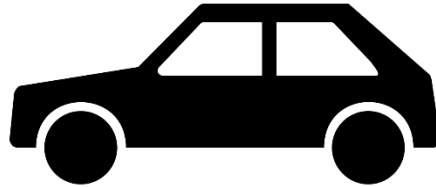
On Quality Metrics

- [Quality Metrics Programs](#)

Quality Metrics Programs

Quality Metrics

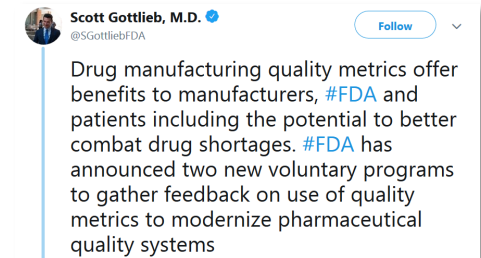
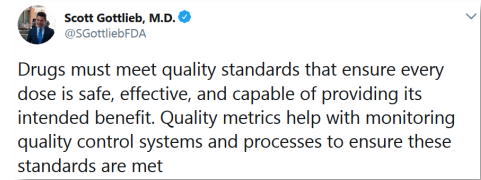
Many products are made using *Quality Metrics* to monitor quality control and continually improve quality.



Drugs should be no different.

FDA's Quality Metrics Programs

- **Quality Metrics are just one part of Quality Management Maturity**
- **Feedback Program (still open until Dec 30, 2019)**
 - Solicits information from drug manufacturers that are currently using quality metrics programs
 - Any data shared is for demonstration/ informational purposes only
- **Site Visit Program**
 - Provided on-site learning opportunities for FDA staff involved in the FDA Quality Metrics Program
 - Well-received program with over 15 site visits



FDA's Quality Metrics Programs

- **Quality Metrics alone will not be the 'ratings system' for manufacturers**
 - Will use different criteria than the quality metrics model

- **Increasing acknowledgement of the value of quality metrics programs**
 - **ISPE Culture Excellence Report, PDA Quality Culture Maturity Model and Tool**
 - *“PhRMA also supports the current voluntary and pilot program approach to the Quality Metrics program, as well as the on-going research...”*
 - Public Comments to Docket No. FDA-2018-N-3272

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.

Emerging Technology Program

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 first switch from batch to continuous manufacturing (CM) for an approved drug
- A [website](#) and [Guidance for Industry](#) are posted

Advanced the Center for Drug Evaluation and Research

CDER Offices and Divisions

Drug Safety Oversight Board

Jobs at the Center for Drug Evaluation and Research (CDER)

Meeting Presentations (Dmgp)

CDER Exclusivity Board

FAQs about CDER

Reports & Budgets (CDER)

Manual of Policies & Procedures (CDER)

Contact CDER

Emerging Technology Program

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Background

CDER's Office of Pharmaceutical Quality created the Emerging Technology Program (FDA Voice on Modernizing Pharmaceutical Manufacturing to Improve Drug Quality: Ensuring a Safe and Adequate Supply of Drugs) to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. The program leverages existing resources within the Agency to facilitate the regulatory quality assessment (including both review and inspection) of submissions to the Agency involving novel technologies likely to improve product safety, identity, strength, quality, and purity. The program features the Emerging Technology Teams (ETTs), which includes representation from all FDA pharmaceutical quality functions, to provide cross-functional expertise to the questions posed by program participants on their proposed technology.

About the Emerging Technology Program

Emerging Technology Program

Emerging Technology Program

Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry

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

September 2017
Pharmaceutical Quality CMC

Small text at the bottom of the page.

Emerging Technologies

Small Molecules

Biological Molecules



A generic manufacturer using Continuous Manufacturing is engaged with our Emerging Technology Program

- Model-based control strategy for continuous manufacturing
- Continuous aseptic spray drying
- 3D printing manufacturing
- Ultra long-acting oral formulation

- Continuous manufacturing for a downstream process
- End-to-end integrated bioprocess
- Pharmacy-on-demand

Pre-ANDA Program

Complex Products

COMPLEX...	Example	Products
Active ingredients	Peptides, complex mixtures, natural source products	Glatiramer acetate
Formulations	Liposomes, emulsions	Liposomal formulations
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	PLGA microspheres
Drug-Device Combinations	Dry powder inhalers, nasal sprays, transdermal systems	Mometasone nasal spray
Other products	Complexity or uncertainty concerning the approval pathway that would benefit from early scientific engagement	Abuse deterrent opioid formulations

ANDA Program for Complex Products

- Clarifies regulatory expectations for prospective applicants early in product development



138 complex generic drugs were approved in FY 19

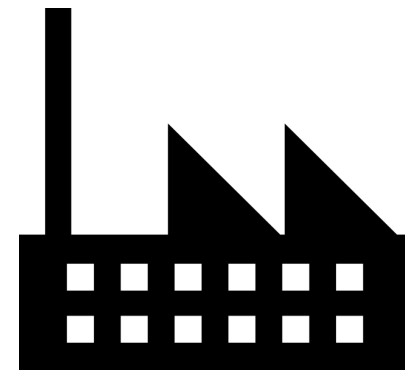
- Mid-Review Cycle Meetings

Site Engagement Program

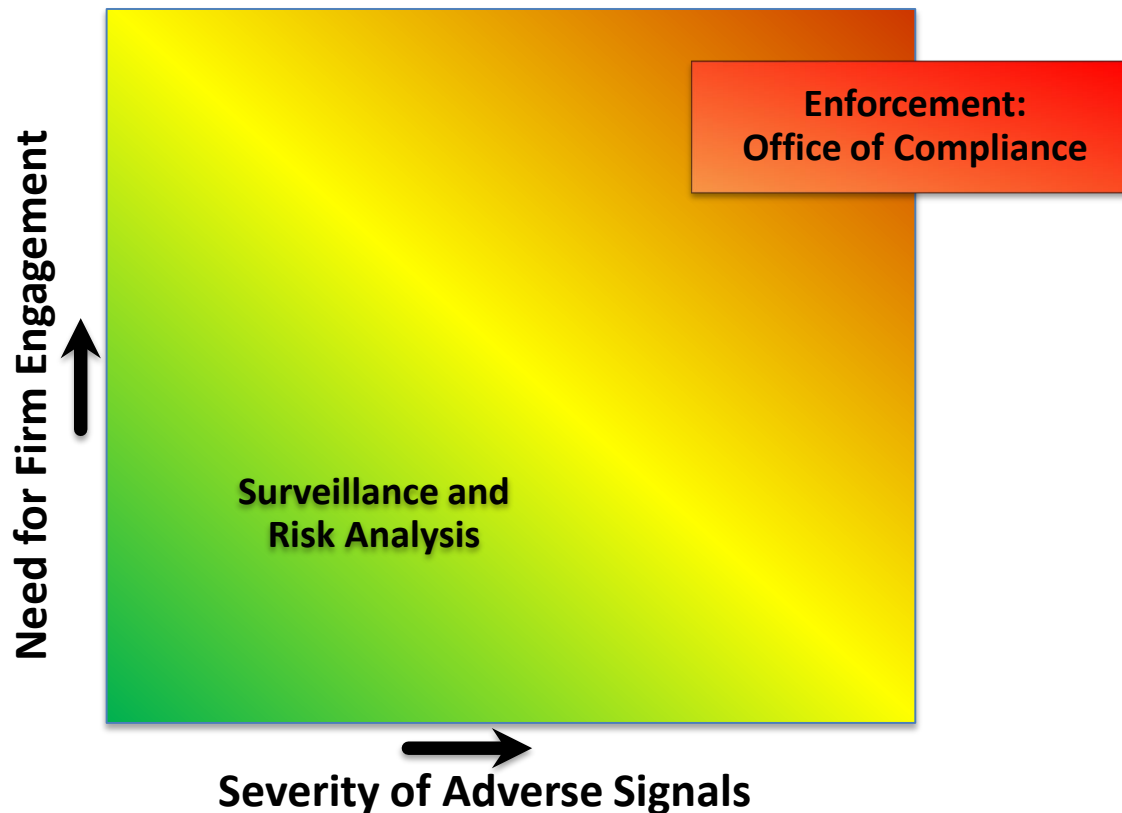
Site Engagement Program



- **An open discussion and collaboration on manufacturing issues that could impact patients**
 - Helps mitigate or prevent future production problems
- **This is a voluntary program**
- **Initial focus is sites where quality issues could potentially disrupt availability**
 - Not for sites “on the cusp of failure”



Surveillance vs. Enforcement



Benefits of Site Engagement Program



- **An opportunity for open discussion and collaboration on manufacturing issues**
 - May lead to effective corrective or preventive actions
 - May result in reduced frequency and/or duration of on-site surveillance inspections



Conclusions

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted downwards. A white label is partially visible on the bottle, with some text and a yellow rectangular area. The right hand is open, palm up, holding three white, oval-shaped pills. The background is softly blurred, showing more of the person's hands and skin.

We can't do this alone

**Join us in a commitment to
pharmaceutical quality**

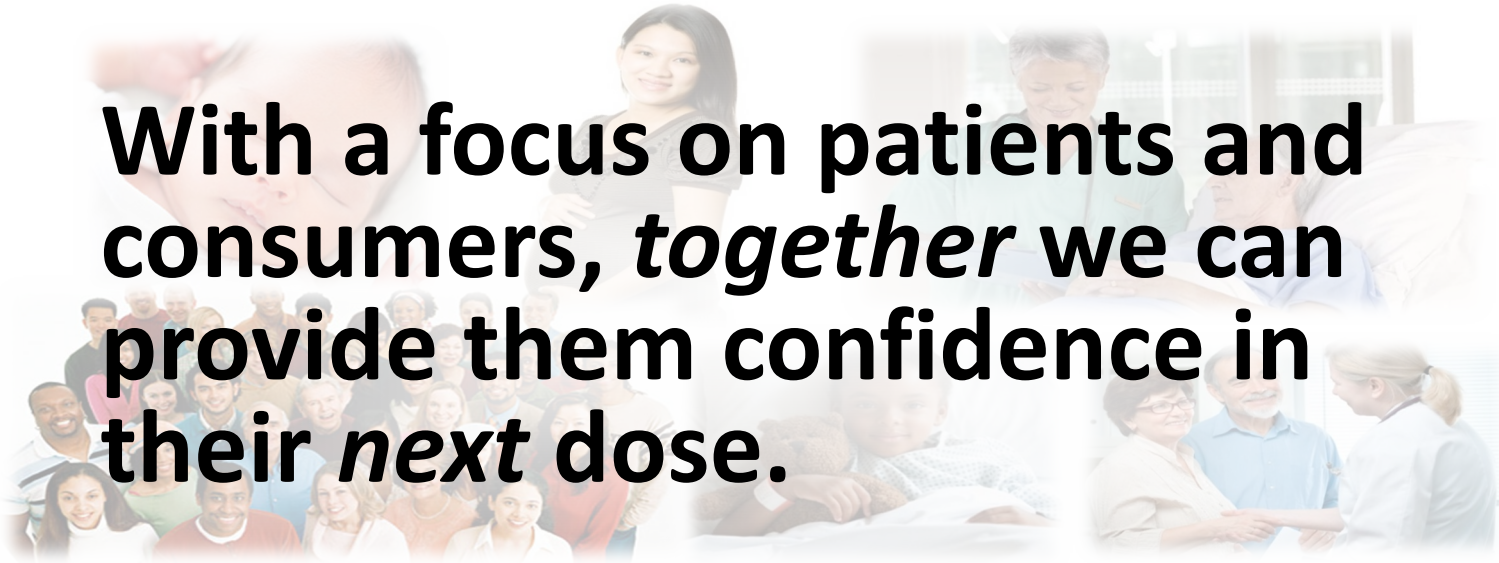
YOU



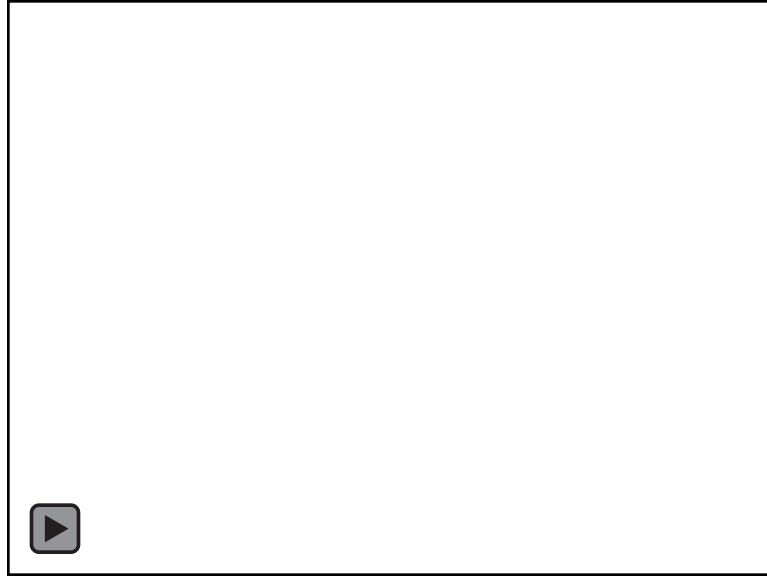
PAYORS
PURCHASERS
PROVIDERS
STUDENTS
COMPOUNDERS
REGULATORS

PATIENTS
CONSUMERS
TEACHERS
MANUFACTURERS
PHARMACISTS
HOSPITALS

A Shared Responsibility

A collage of various images related to healthcare and patients, including a close-up of a person's face, a woman holding a child, a doctor examining a patient, a group of people, and a doctor talking to a patient.

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





U.S. FOOD & DRUG
ADMINISTRATION