U.S. FOOD & DRUG ADMINISTRATION

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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Director, Office of Compliance

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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.
Director, Office of Compliance

Join Us in a Commitment to Quality

Michael Kopcha, Ph.D., R.Ph.
Director, Office of Pharmaceutical Quality

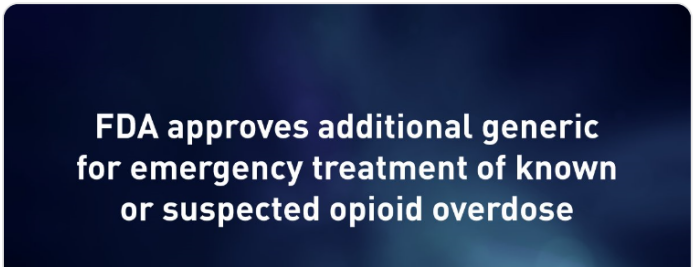
The Generic Drug Program: Collaborating for Success

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



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

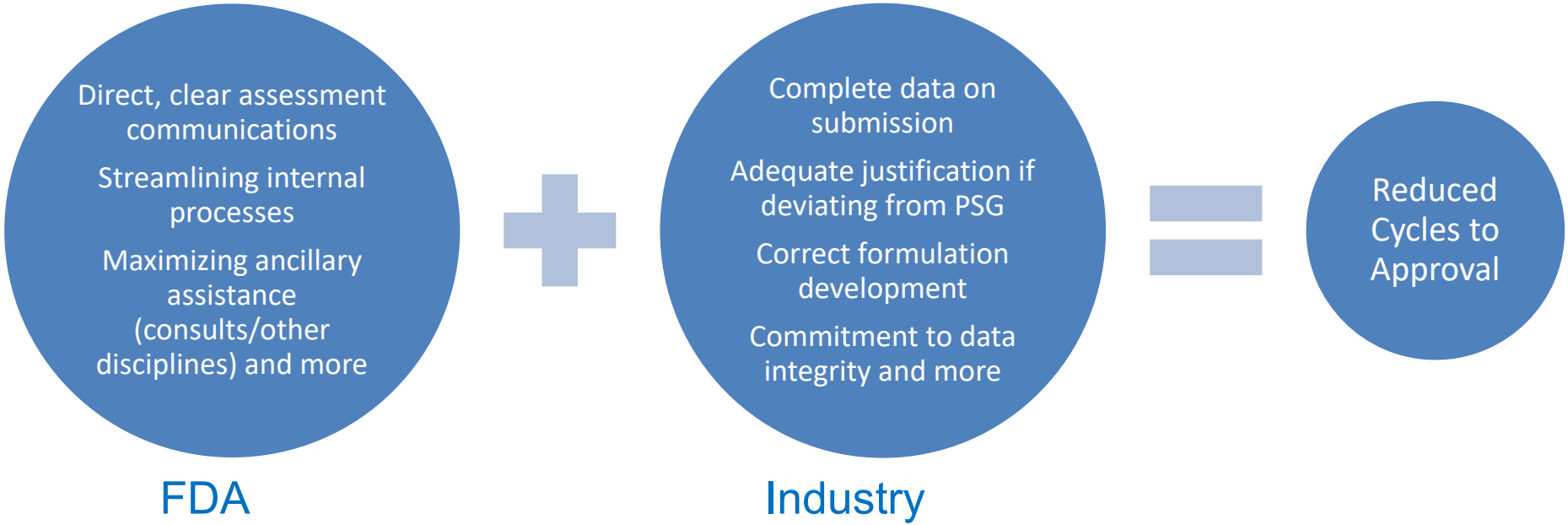
Maximizing GDUFA II mechanisms is critical

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!

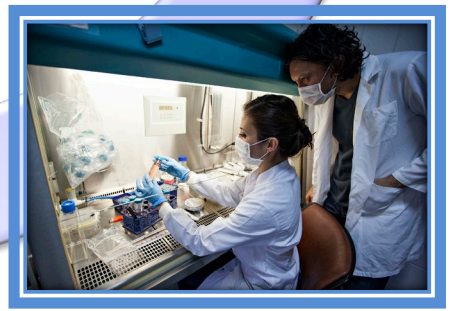
Example: Mutual Commitment to Maximizing Best Practices for First-Cycle Approval



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

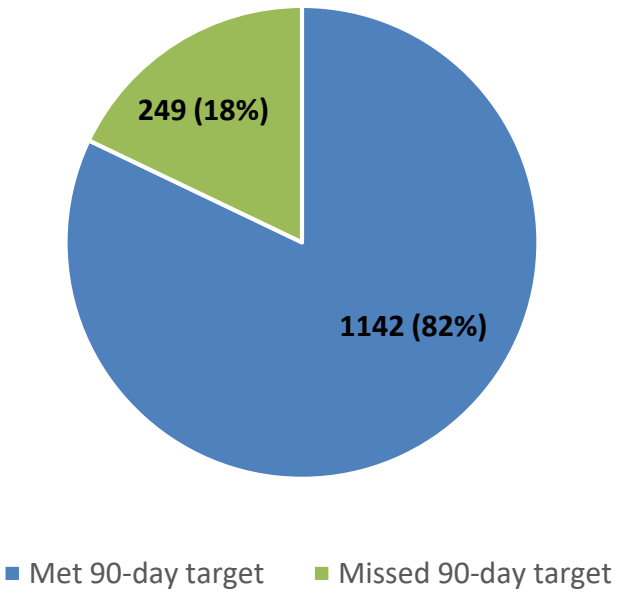
OAI Regulatory Actions

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

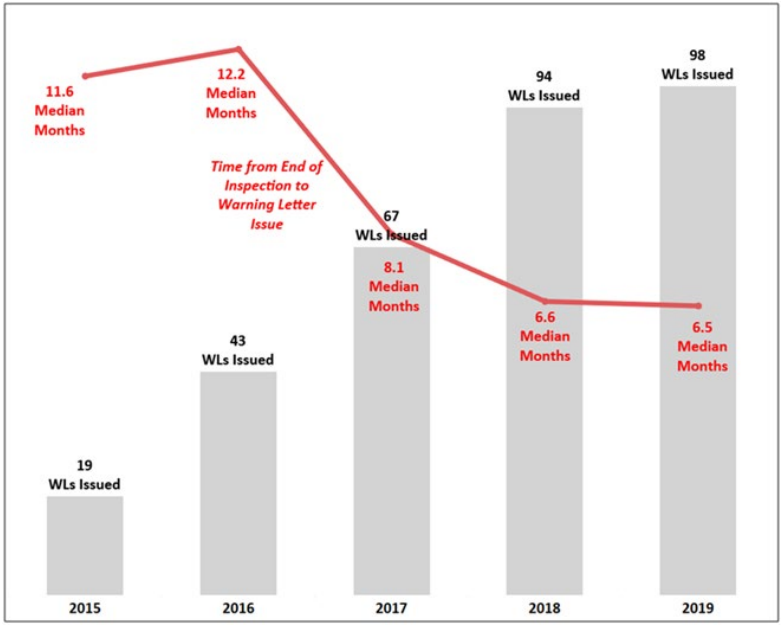
Key Performance Indicators

90-day Classification Letters in FY 2018

1,391 classification letters issued in FY18



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

Total CGMP Warning Letters by Region: FY 2019

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

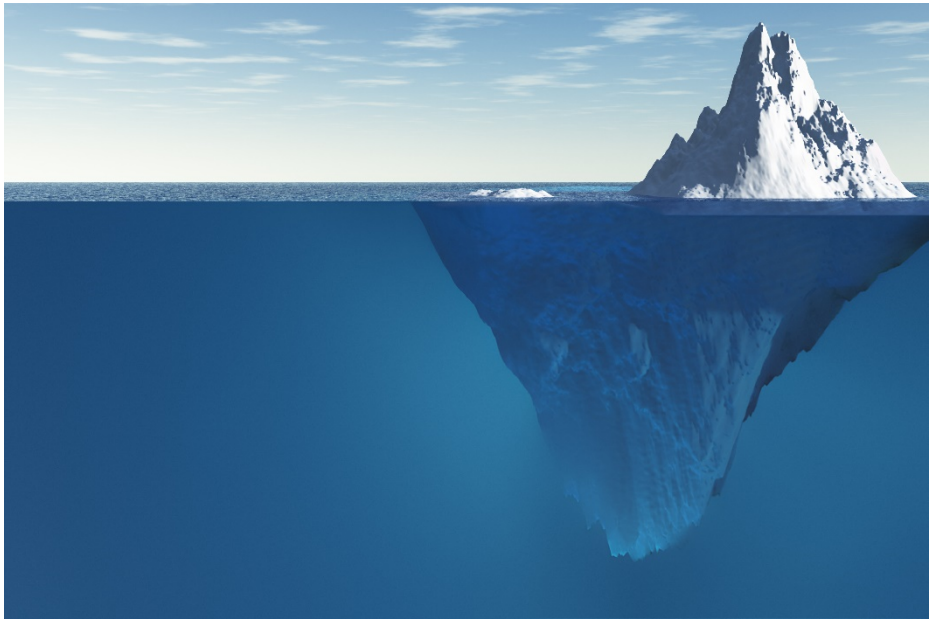
Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer. (17.60)

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

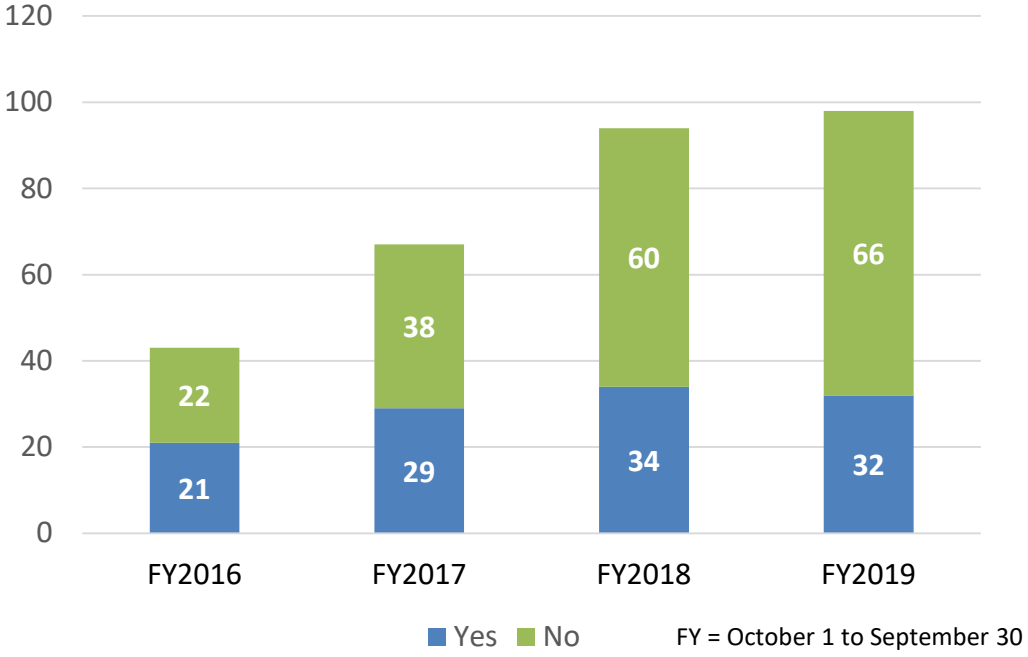
- Data integrity is evidence that data are complete, consistent, and accurate
- CGMP is the minimum requirement
- Data integrity underpins CGMP
- Lapses obscure other problems



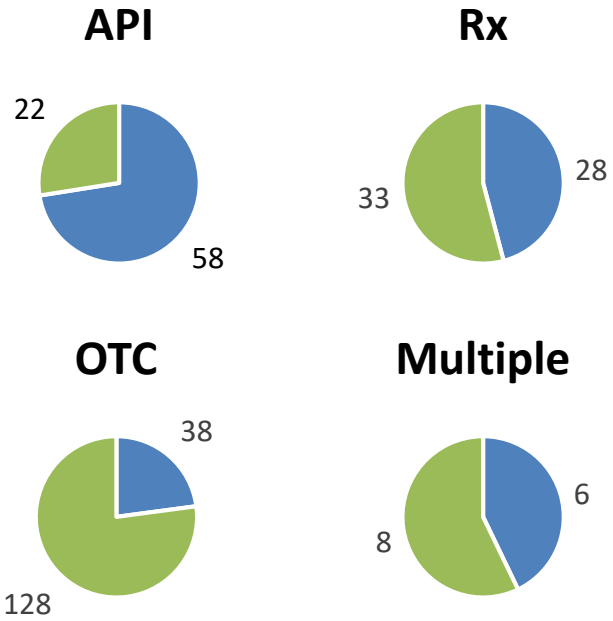
Data integrity problems you can see are the tip of the iceberg.

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."

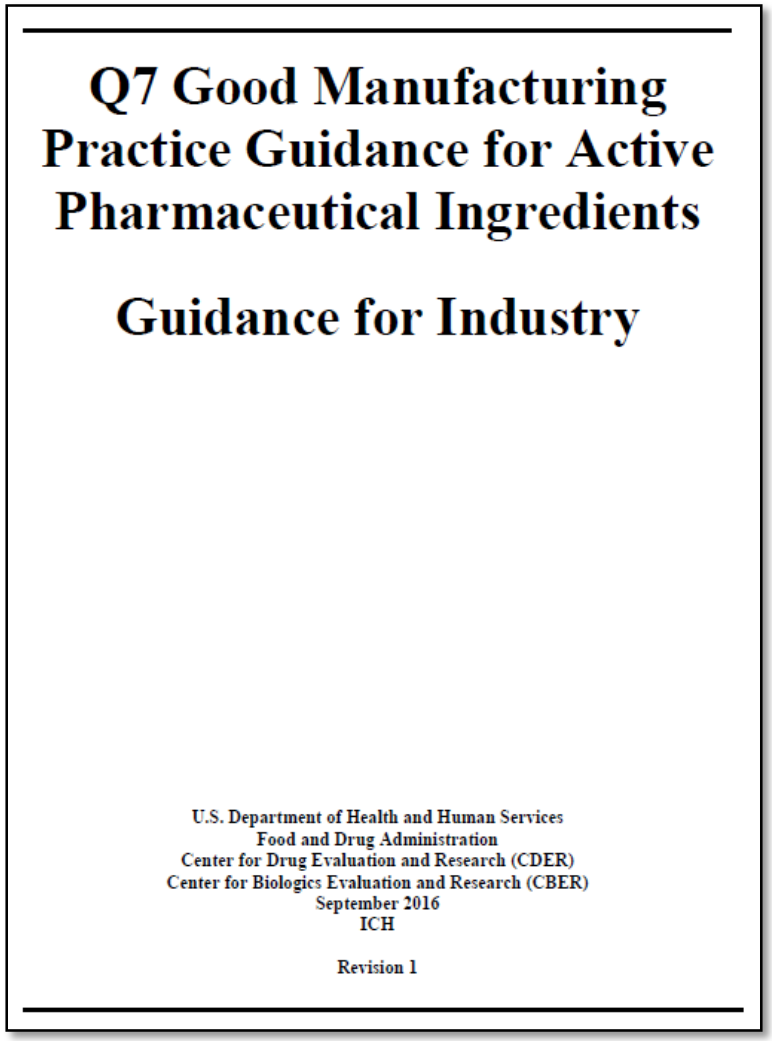
Statement on new testing results, including low levels of impurities in ranitidine drugs

"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

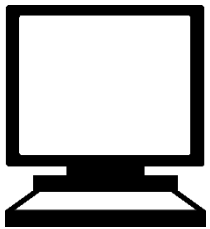


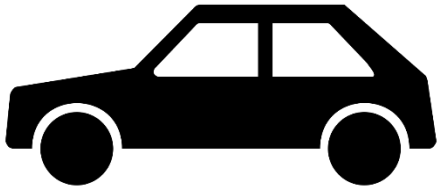
- Provides guidance regarding CGMP for the manufacturing of APIs under an appropriate system for managing quality
- Intended to help ensure APIs meet the quality and purity characteristics that they purport, or are represented, to possess

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.


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.


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

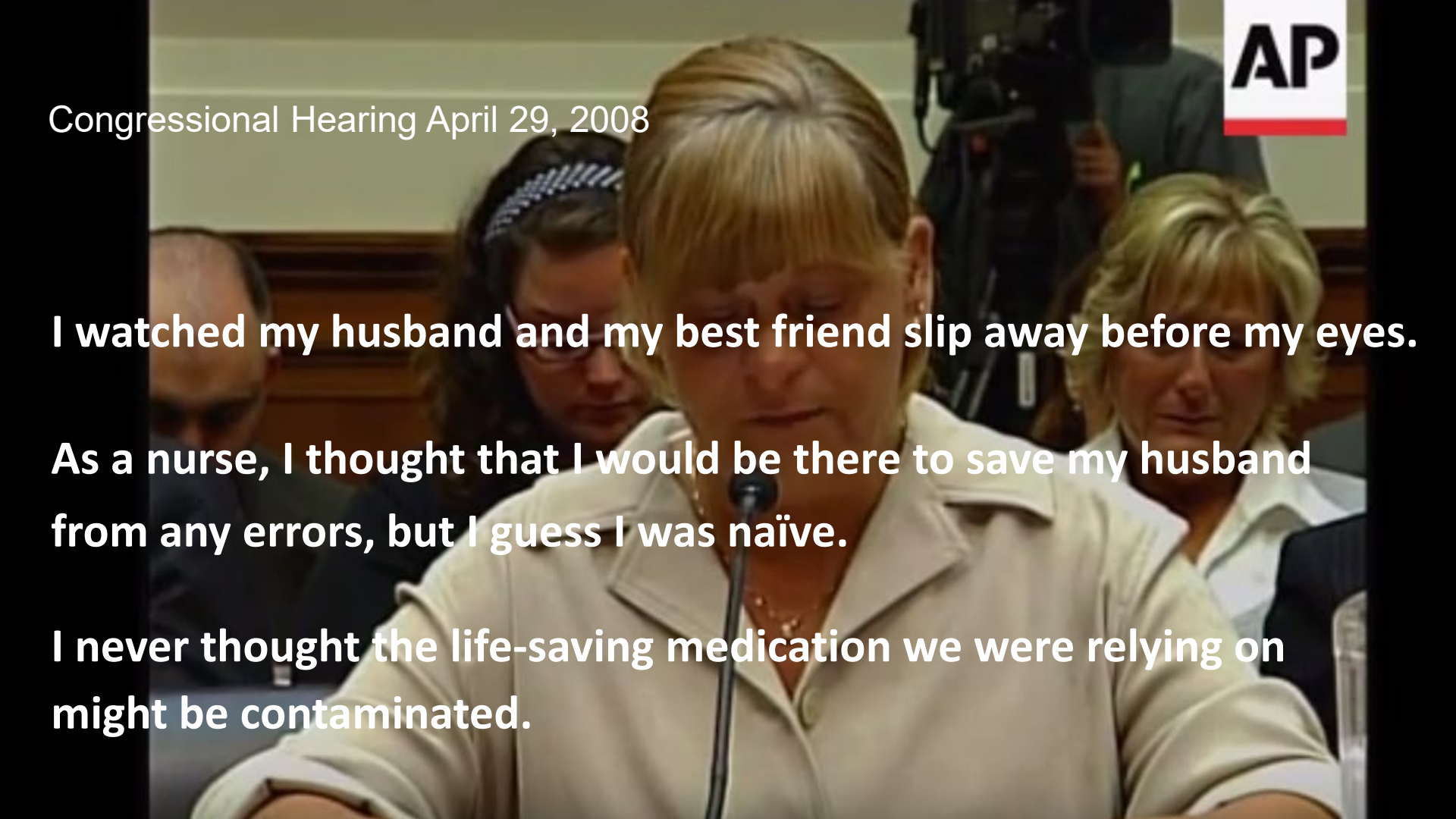
Need to prove that drugs are safe and effective

2015

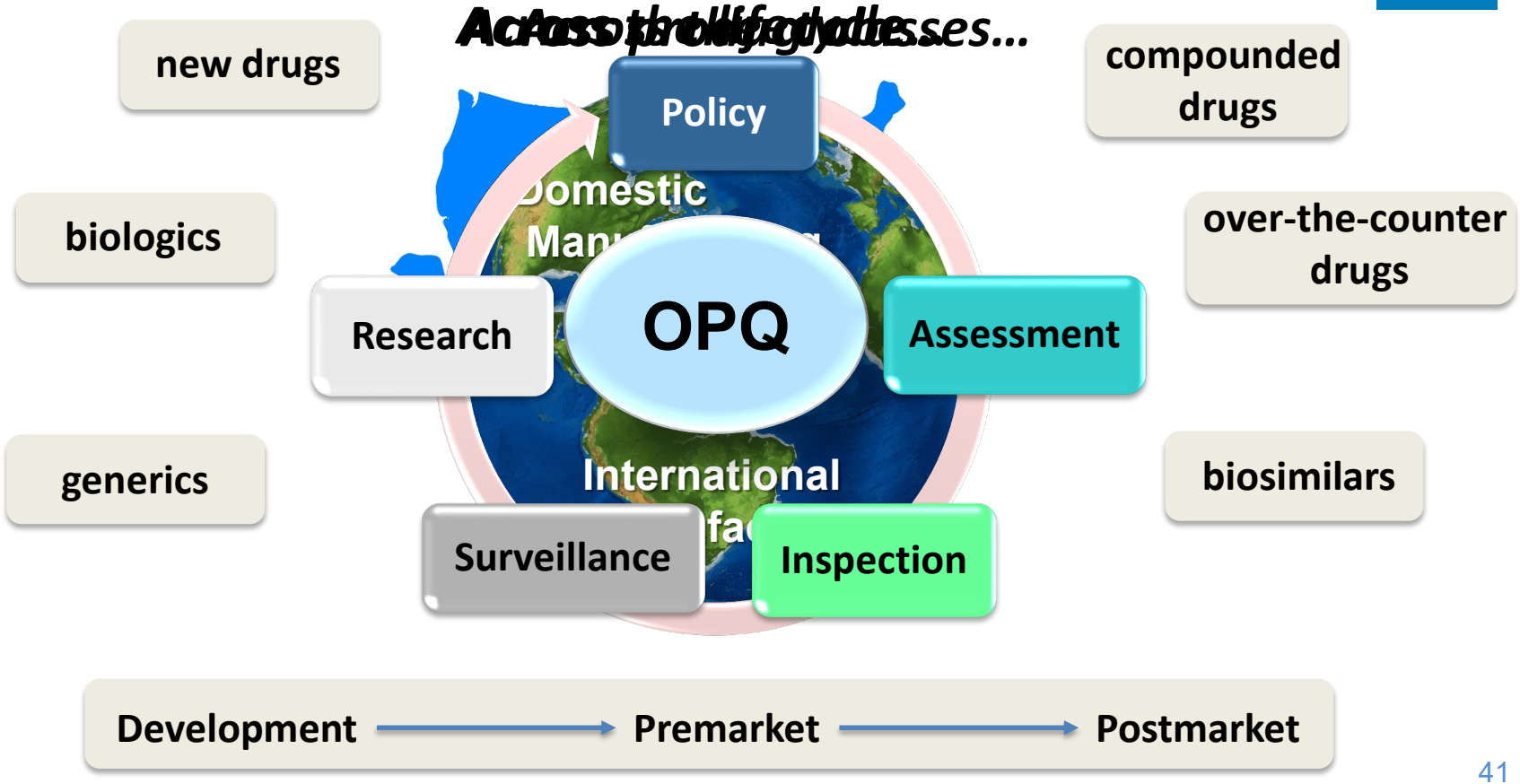
Serious injuries and deaths from global heparin crisis

FDA establishes Office of Pharmaceutical Quality

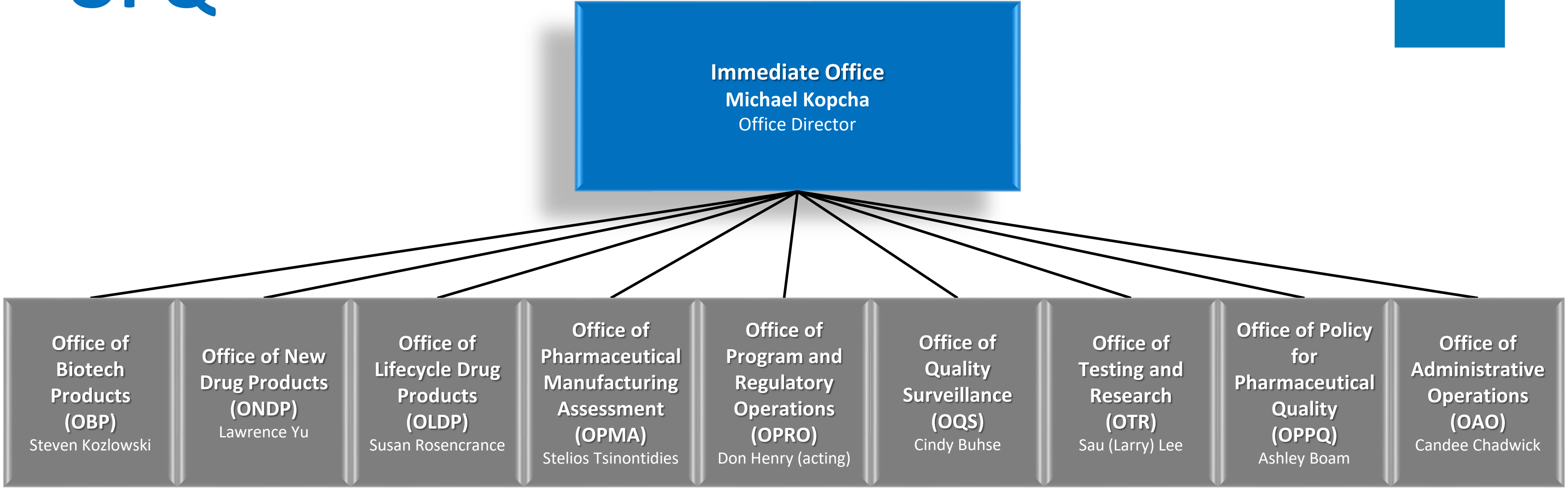
Integrates functions and elevates FDA's commitment to quality


Congressional Hearing April 29, 2008
AP
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



OPQ



Performs all administrative operations

[illegible]

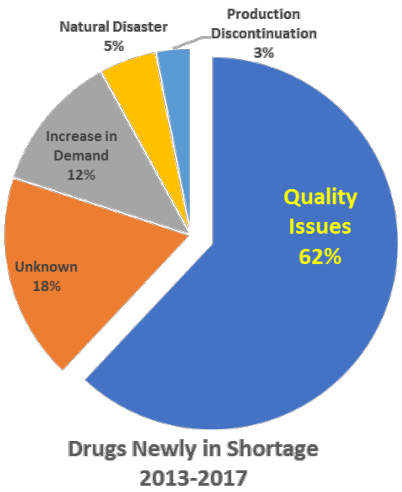
The State of Pharmaceutical Quality

Key findings from FY 2018:

- **More regulated sites** manufacture products[1] 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



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.

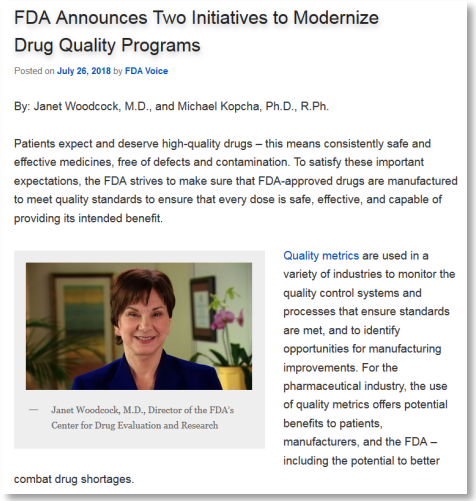
Drugs *should be* no different.

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.

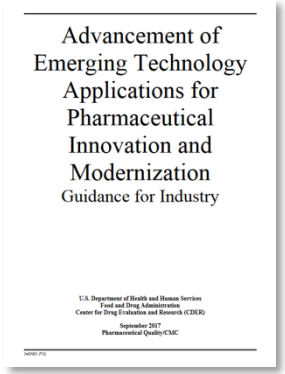
— Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research

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



Emerging Technologies

Small 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

Biological Molecules

- 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**

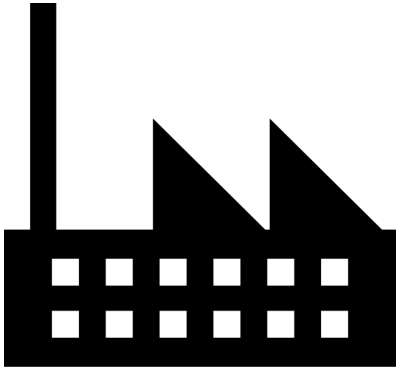
138 complex generic drugs were approved in FY 19

  - Mid-Review Cycle Meetings

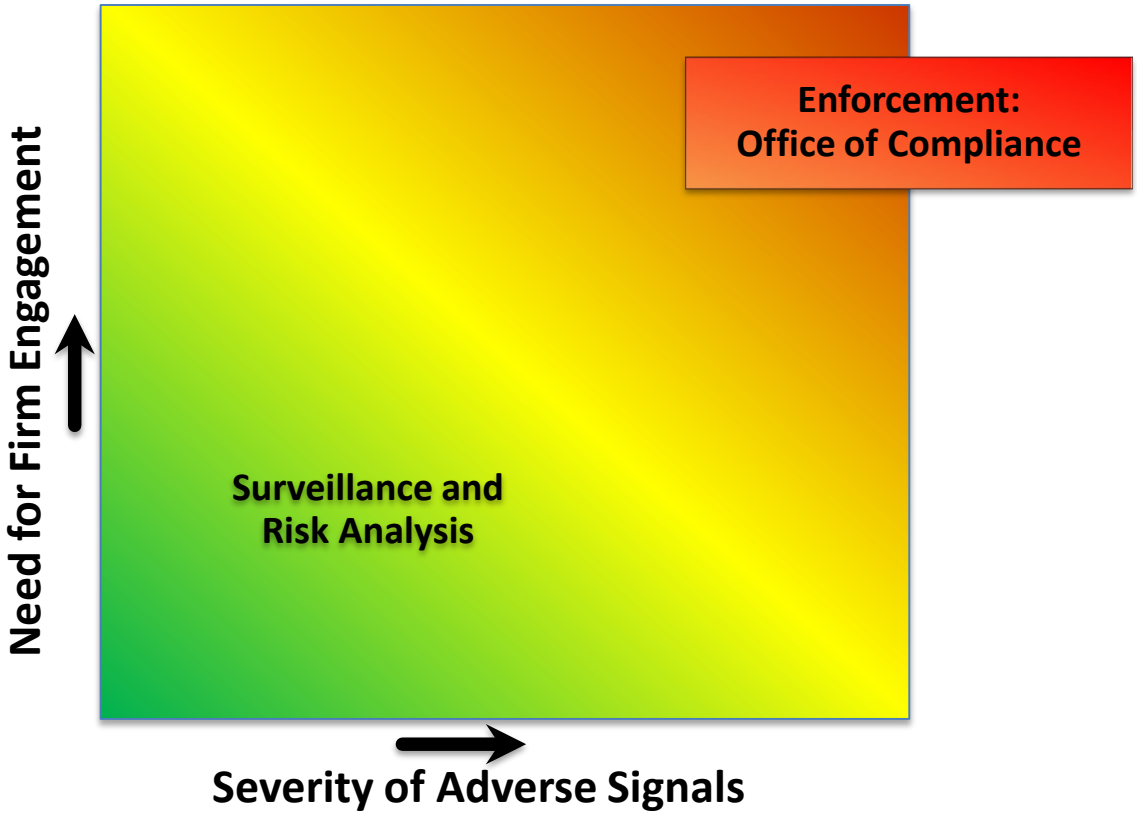
Site Engagement Program

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


We can’t do this alone
Join us in a commitment to pharmaceutical quality

YOU

PAYORS

PURCHASERS

PROVIDERS

STUDENTS

COMPOUNDERS

REGULATORS

PATIENTS

CONSUMERS

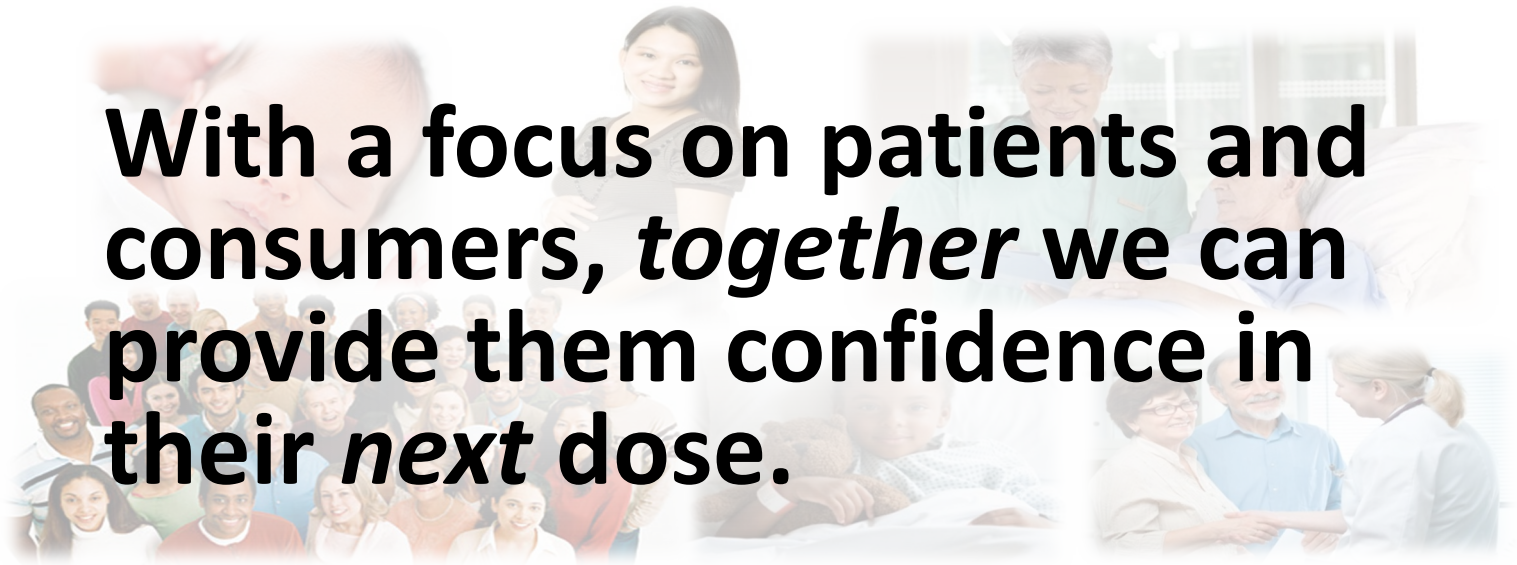
TEACHERS

MANUFACTURERS

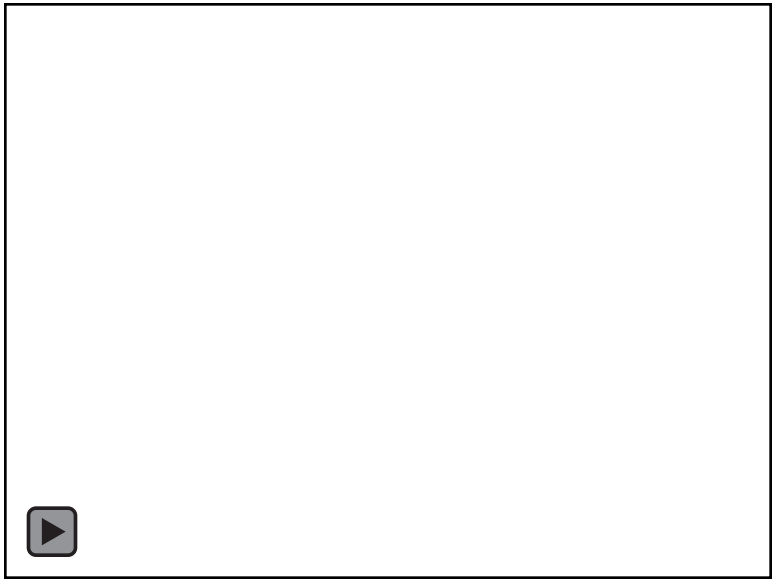
PHARMACISTS

HOSPITALS

A Shared Responsibility



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

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