U.S. FOOD & DRUG ADMINISTRATION

# Compliance Trends

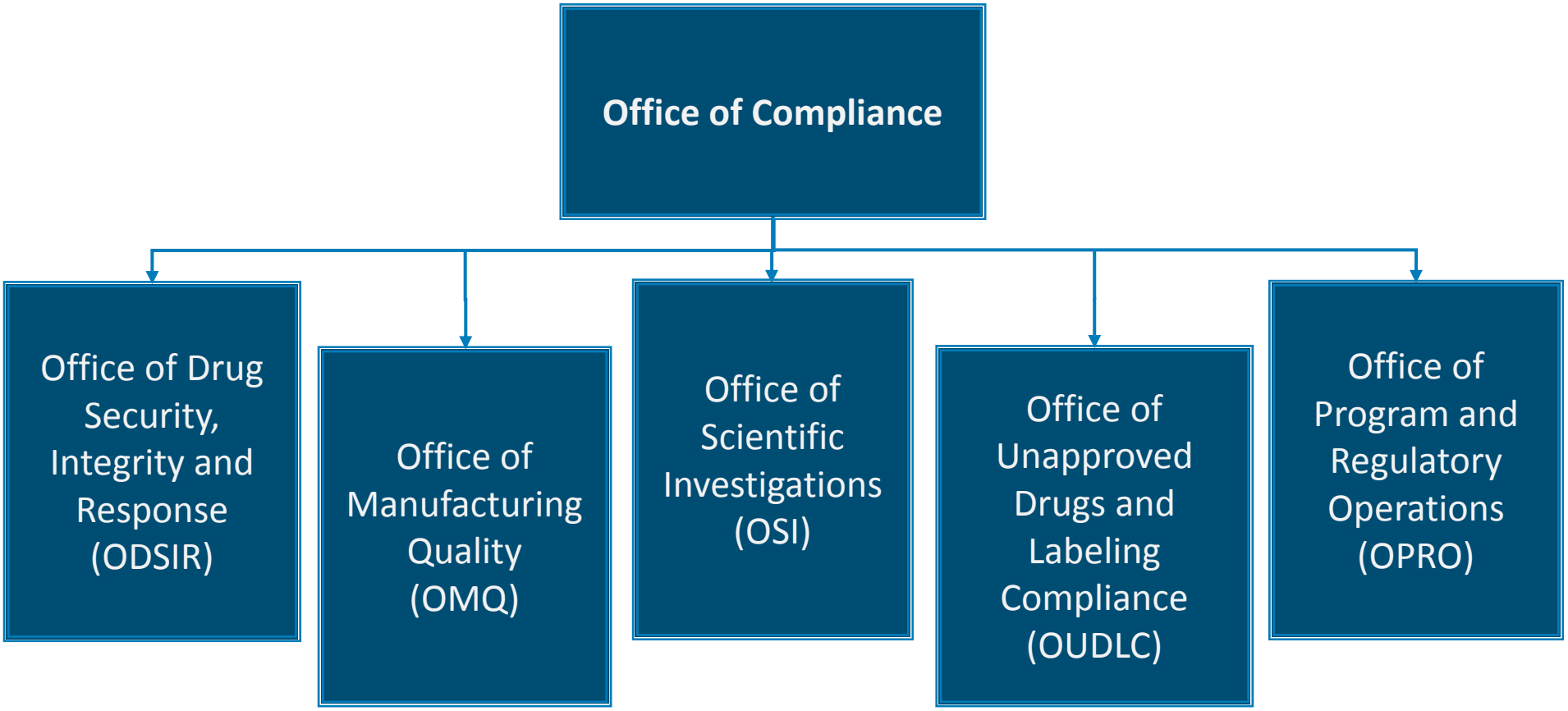
**Paula Katz**
Director, Manufacturing Quality Guidance and Policy Staff
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

*India Pharmaceutical FORUM 2017 – Towards Excellence in Quality*
Indian Pharmaceutical Alliance
Mumbai, India
Feb. 24, 2017

# Agenda

- OMQ: Who We Are and What We Do
- Understanding CGMP Requirements
- Enforcement and Trends
- Policy Issues and Initiatives
- Questions

# Office of Compliance Structure



# OMQ's Mission

- CDER Office of Compliance mission:

  **Promote and protect the public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.**

- OMQ supports this mission by developing and implementing compliance and enforcement actions focused on drug manufacturing.

# What OMQ Does

- Evaluate compliance with Current Good Manufacturing Practice (CGMP) for drugs.
- Evaluate inspection reports and evidence gathered by FDA investigators in ORA, collaborating with other offices.
- Review information from other FDA offices including Office of Process and Facilities and Office of Surveillance.
- Take steps to achieve voluntary compliance and/or recommend legal action

# Primary Considerations CGMP Enforcement

**Is the drug "adulterated"?**

- Food, Drug & Cosmetic Act (FD&C Act)
- FDA regulations at 21 CFR 210 & 211
- For API, standards are set forth in ICH Q7

**Most important – patient risk**

- High risk ➡ FDA takes quick action
- Sub- or super-potent
- Contamination
- Sterility concerns
- Other defects

# Legal Basis for CGMP

**Section 501(a)(2)(B):**

"A *drug*... shall be *deemed* to be *adulterated* if the *methods* used in, or the *facilities* or *controls* used for, its *manufacture*, *processing*, *packing*, or *holding* do not conform to or are not operated or administered in conformity with *current good manufacturing practice* to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented* to *possess*."

# Legal Basis for CGMP

## Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)
### Amendment to section 501

CGMP "includes the implementation of *oversight* and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the *safety of raw materials*, materials used in the manufacturing of drugs, and finished drug products."

# CGMP for *Finished Pharmaceuticals*
# 21 CFR Part 211

Subpart A - General Provisions

Subpart B - Organization and Personnel

Subpart C - Buildings and Facilities

Subpart D - Equipment

Subpart E - Control of Components and Drug Product Containers and Closures

Subpart F - Production and Process Controls

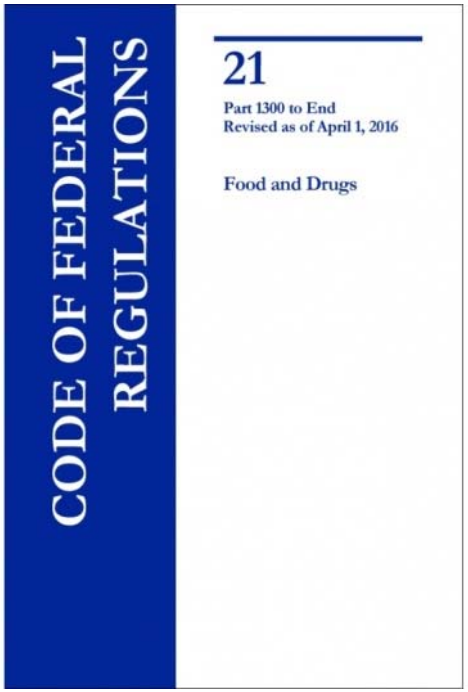
Subpart G - Packaging and Labeling Controls

Subpart H - Holding and Distribution

Subpart I - Laboratory Controls

Subpart J - Records and Reports

Subpart K - Returned and Salvaged Drug Products



# ICH Q7 and Active Pharmaceutical Ingredients

- ICH Q7 represents FDA's current thinking on CGMP for API.
- No CGMP *regulations* for API, so FDA generally considers API manufacturing and testing facilities that follow ICH Q7 to comply with statutory CGMP.
  - Alternate approaches may be used.
  - 501(a)(2)(B) requirements can be met if approach ensures API purported or represented purity, identity, and quality.

**ICH - International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use**

# ICH Q7 and Active Pharmaceutical Ingredients

**Find ICH Q7 and other ICH guidance online:**
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm.

Highly recommended:

- ICH Q9 *Quality Risk Management*
  *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf*
- Q10 *Quality Systems*
  *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf*

Also recommended:

- ICH Q8 *Quality Pharmaceutical Development*
  *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf*
- ICH Q11 *Development and Manufacture of Drug Substances*
  *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf*

Note: You might hear “drug substance” instead of “API” when dealing with FDA reviewers or people who have review-related questions.

# Delaying, Denying, Limiting, or Refusing Inspection

- July 9, 2012: FDASIA signed into law.
- Adds 501(j) to the FD&C Act to deem adulterated a drug that *"has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection."*

# Import Alert 99-32
## Delaying, Denying, Limiting, or Refusing Inspection

- Detention without physical examination of products from firms refusing FDA foreign establishment inspection
- If the article is a drug that has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or ***agent*** of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection):
  "The article of drug is subject to refusal of admission pursuant to Section 801(a)(3) in that the article of drug appears to be adulterated under section 501(j) of the FD&C Act."
- See www.accessdata.fda.gov/cms_ia/importalert_521.html

# Our Toolbox

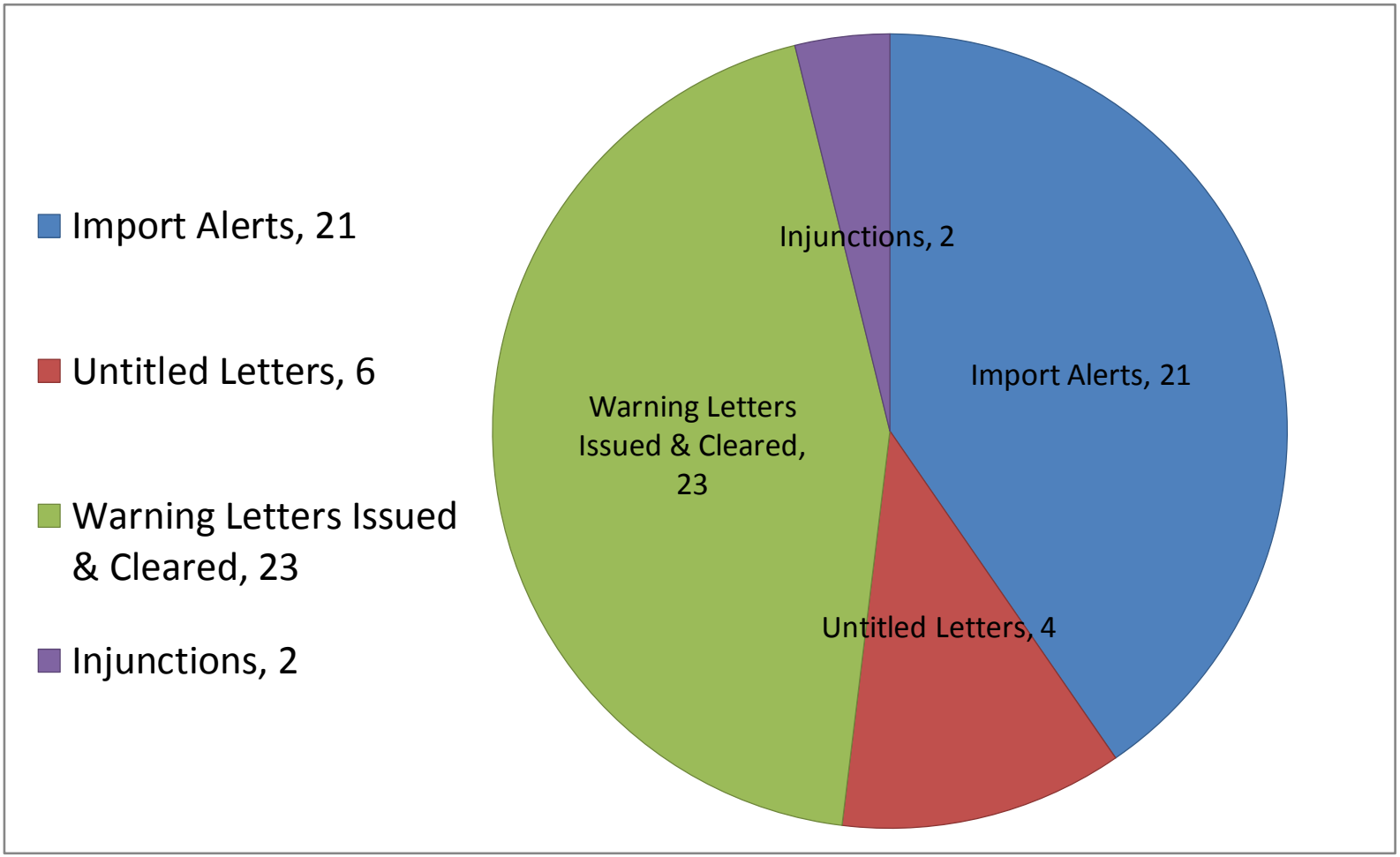
- Regulatory meetings
- Injunction
- Consent decrees
- Import alerts
- Seizures
- Warning letters
- Untitled letters
- And more

# Will FDA Issue an Import Alert?

**IA 66-40 or 99-32 if**:

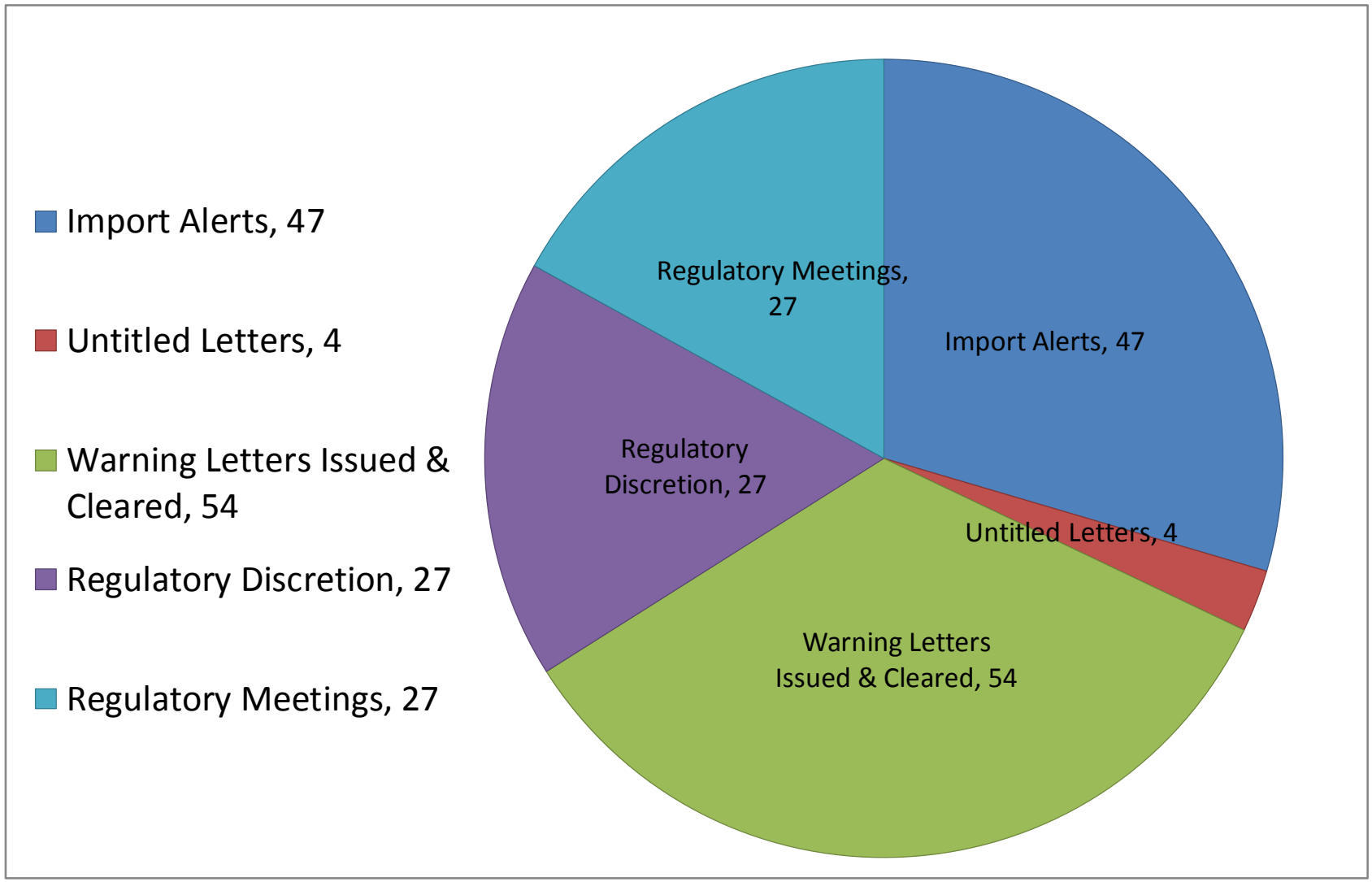
- CGMP violation could cause drug quality defect with potential adverse patient health consequences
- Repeat violations
- Significant data integrity violations
- Delay, denial, refusal or limitation of inspection

# OMQ Enforcement Actions* in 2015



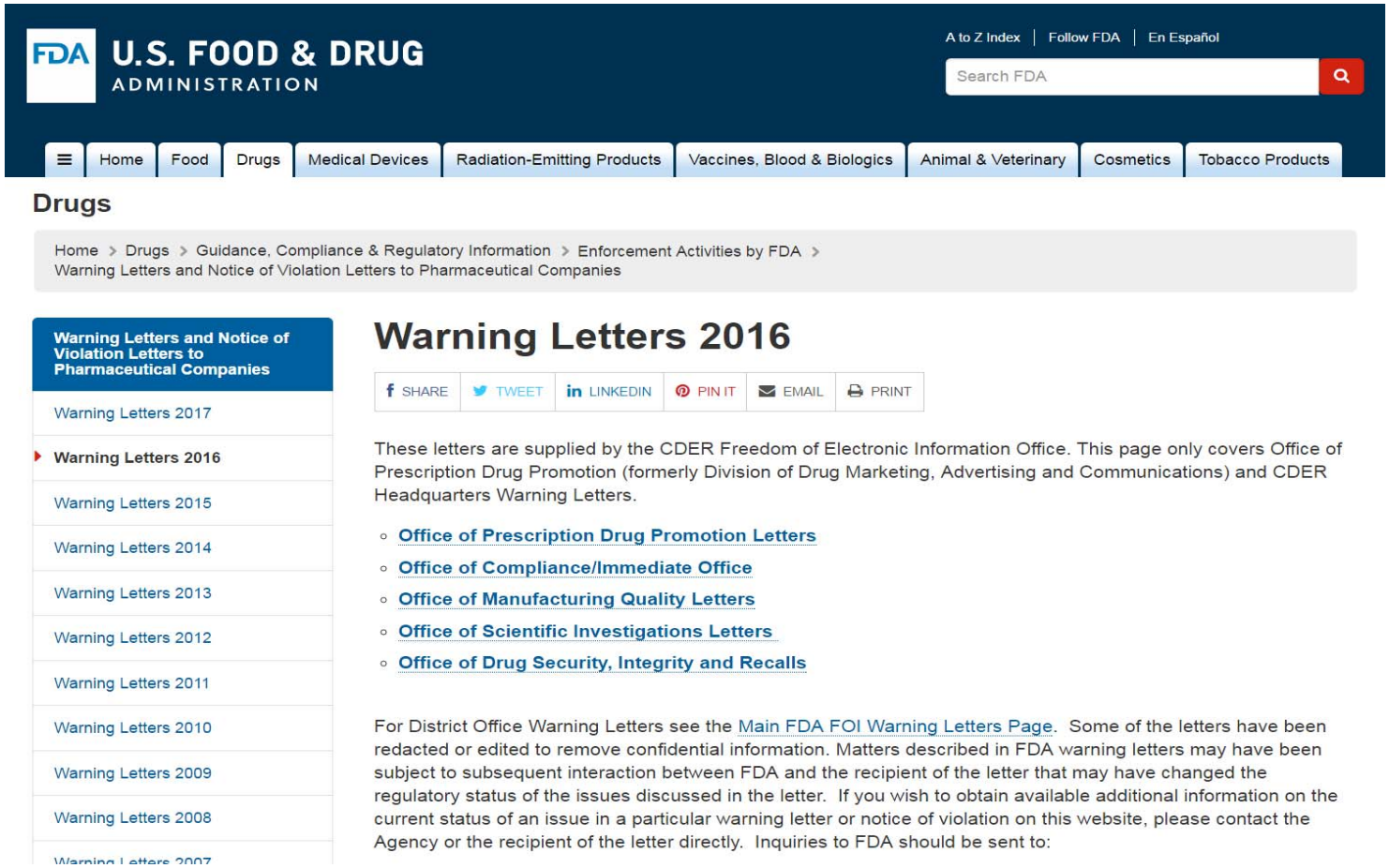

*Excludes compounding-related actions

# OMQ Enforcement Actions* in 2016




*Excludes compounding-related actions

# Recent Warning Letter Trends



FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Guidance, Compliance & Regulatory Information > Enforcement Activities by FDA > Warning Letters and Notice of Violation Letters to Pharmaceutical Companies

**Warning Letters and Notice of Violation Letters to Pharmaceutical Companies**

- Warning Letters 2017
- **Warning Letters 2016**
- Warning Letters 2015
- Warning Letters 2014
- Warning Letters 2013
- Warning Letters 2012
- Warning Letters 2011
- Warning Letters 2010
- Warning Letters 2009
- Warning Letters 2008
- Warning Letters 2007

## Warning Letters 2016

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

These letters are supplied by the CDER Freedom of Electronic Information Office. This page only covers Office of Prescription Drug Promotion (formerly Division of Drug Marketing, Advertising and Communications) and CDER Headquarters Warning Letters.

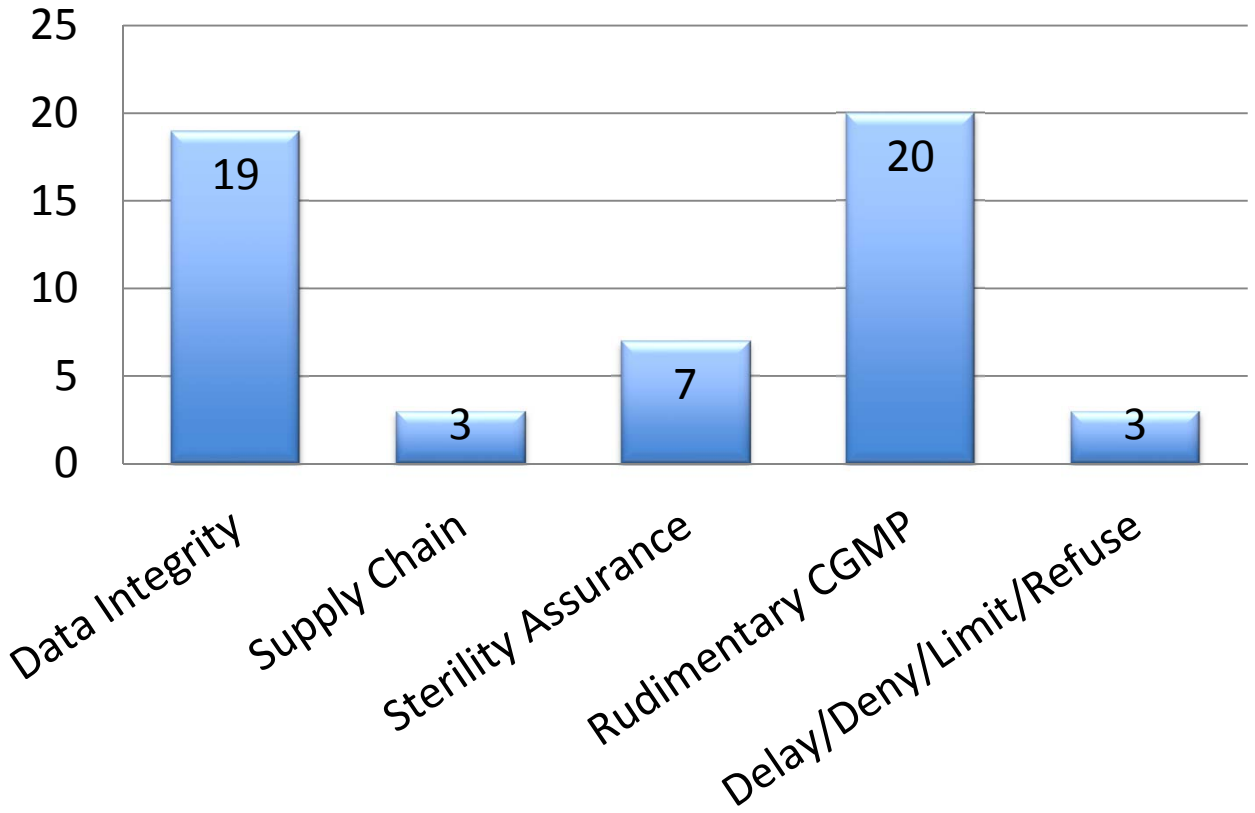
- Office of Prescription Drug Promotion Letters
- Office of Compliance/Immediate Office
- Office of Manufacturing Quality Letters
- Office of Scientific Investigations Letters
- Office of Drug Security, Integrity and Recalls

For District Office Warning Letters see the Main FDA FOI Warning Letters Page. Some of the letters have been redacted or edited to remove confidential information. Matters described in FDA warning letters may have been subject to subsequent interaction between FDA and the recipient of the letter that may have changed the regulatory status of the issues discussed in the letter. If you wish to obtain available additional information on the current status of an issue in a particular warning letter or notice of violation on this website, please contact the Agency or the recipient of the letter directly. Inquiries to FDA should be sent to:

# Recent Warning Letter Trends

- Data integrity
  - Lack of control over access to computerized systems
  - Non-contemporaneous record-keeping
  - Deletion, falsification, alteration, or other manipulation
- Supply chain
  - API Repackers/Relabelers
  - Contract Manufacturers
  - Heparin supply chain
- Sterility assurance
  - Compounding and conventional
  - Aseptic technique, EM, design
- Rudimentary CGMP
  - Release testing
  - Cleaning, equipment maintenance, basic sanitation
  - Cross-contamination risks
  - More often for non-application/OTC monograph drugs
- Delay/Deny/Limit/Refuse

# Recent Warning Letter Trends



# GDUFA II

- FDA commitment to improve OAI-related timeframes
- OMQ is modifying our processes to accelerate OAI decisions and take action faster (Import Alerts, regulatory meetings, advisory notices)

# Recent CGMP Guidances

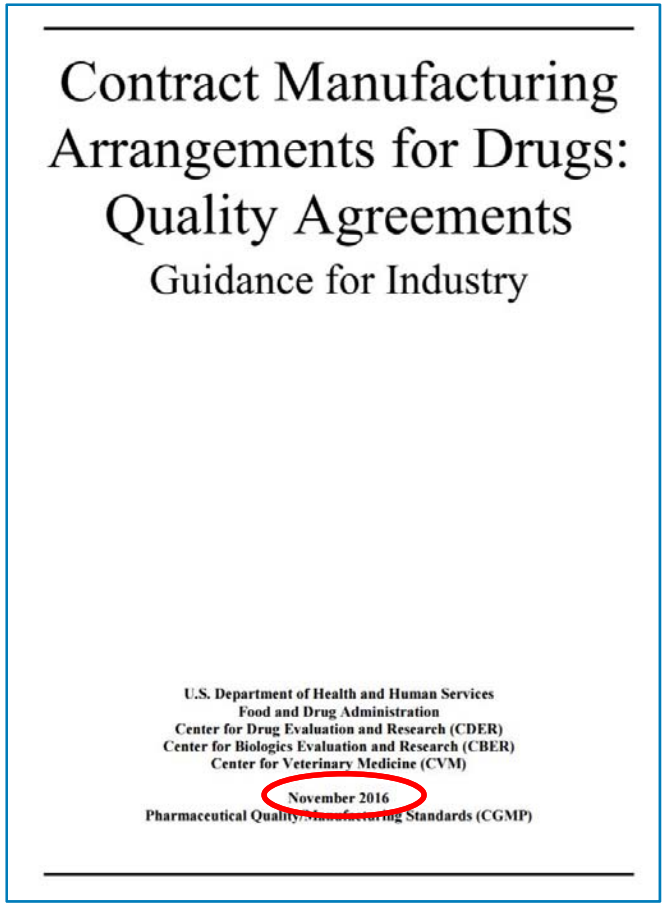
- CGMP Requirements for Combination Products (January 2017) http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm429304.pdf
- Contract Manufacturing Arrangements for Drugs: Quality Agreements (November 2016) http://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf
- Data Integrity and Compliance with CGMP (Draft, April 2016) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf
- Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection (October 2014) http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

# Other Guidance for Industry

**See FDA Guidance for Industry (Drugs) web page**:
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality (6/25/13)
- Non-Penicillin Beta-Lactam Drugs: A CGMP Framework (4/17/13)
- Process Validation: General Principles and Practices (1/2011)
- Testing of Glycerin for Diethylene Glycol (5/1/07)
- Investigating Out-of-Specification Test Results for Pharmaceutical Production (10/11/06)
- Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (9/27/06)
- PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (9/29/04)
- Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (9/29/04)

# Now Final: FDA Guidance on Quality Agreements


Contract Manufacturing Arrangements for Drugs: Quality Agreements

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)
Center for Veterinary Medicine (CVM)

November 2016

Pharmaceutical Quality/Manufacturing Standards (CGMP)


**Quality agreements define expectations and responsibilities in a contract manufacturing arrangement up front.**

# FDA Guidance on Quality Agreements

## What is a "Quality Agreement"?

- a comprehensive written agreement that defines responsibilities of the Quality Units of each party in contract manufacturing of drugs subject to CGMP.

## Why?

- to explain how quality agreements can be used to define, establish, and document the responsibilities of parties involved in the contract manufacturing of drugs subject to CGMP.

**Clarifying roles and responsibilities improves efficiency and oversight of outsourced manufacturing operations and relationships between parties…*Ultimately improves the quality of drugs that patients consume.***

# FDA Guidance on Quality Agreements

**Applies to manufacturers of:**

- Active pharmaceutical ingredients
- Finished drug products
- Biological drug products

**Builds on quality risk management principles in:**

- ICH Q7 (Good Manufacturing Practice Guidance for API)
- ICH Q9 (Quality Risk Management)
- ICH Q10 (Pharmaceutical Quality System)

**Addresses key elements in quality agreements:**

- clear definitions of CGMP-related roles
- manufacturing operations and activities of each party

**Benefits**

- Owners who use contract facilities
- Contract facilities who provide services
- Patients

# Draft Guidance on Data Integrity

**What is "Data Integrity"?**

- requirements for complete, consistent, and accurate data

**Why?**

- to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required in 21 CFR parts 210, 211, and 212

**Available online:**

- www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf

# Paper requirements = electronic requirements

Requirements for record retention and review do not differ by data format.

Paper-based and electronic data record-keeping systems are subject to the same requirements.

# Guidance on Delaying, Denying, Limiting, Refusing Inspection

***Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*** (October 2014)
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

- More cases involving delaying, denying, limiting, refusing inspection.
- Guidance on examples of statements or physical actions intended to avoid inspection or to mislead, deceive, or impede the investigator.

# FDA Guidance on Out-of-Specification Test Results

- FDA regulations require an investigation be conducted whenever an OOS test result is obtained (211.192)
- The purpose of the investigation is to determine the cause of the OOS result
- Even if a batch is rejected based, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products
- The investigation should be thorough, timely, unbiased, well-documented, and scientifically sound
- FDA recommends a phased investigation, starting with the laboratory before expanding to manufacturing

FDA Guidance

www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf

# Guidance on CGMP for Sterile Drug Products Produced by Aseptic Processing

- Guidance on CGMP when manufacturing sterile drug and biological products using aseptic processing.
- Assists sterile drug manufacturing facilities to meet CGMP requirements relating to facility design, equipment suitability, process validation, and quality control.
- Includes coverage on Isolators and Blow-Fill-Seal Technology.
- Online at www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf

# *Questions?*