

# Compliance Trends and Guidance While Engaging Manufacturers

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# Learning Objectives

- Describe CDER's Office of Compliance and Office of Manufacturing Quality
- Identify current trends in CGMP enforcement program
- Discuss the importance of contract manufacturer and supplier selection and different tools to use during selection and throughout commercial manufacturing

Office of Manufacturing Quality

# What We Do



# CDER/OC Mission

To shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and ***risk-based*** enforcement action.

# What OMQ Does

- We evaluate compliance with **C**urrent **G**ood **M**anufacturing **P**ractice (**CGMP**) for drugs based on inspection reports and evidence gathered by FDA investigators.
- We develop and implement compliance policy and take regulatory actions to protect the public from ***adulterated*** drugs in the U.S. market.



Source: FDA

# Drug Adulteration Provisions

## U.S. Federal Food, Drug, & Cosmetic Act

- 501(a)(2)(A): Insanitary conditions
- 501(a)(2)(B): Failure to conform with CGMP
- 501(b): Strength, quality, or purity differing from official compendium
- 501(c): Misrepresentation of strength, etc., where drug is unrecognized in compendium
- 501(d): Mixture with or substitution of another substance
- 501(j): Deemed adulterated if owner/operator delays, denies, refuses, or limits inspection

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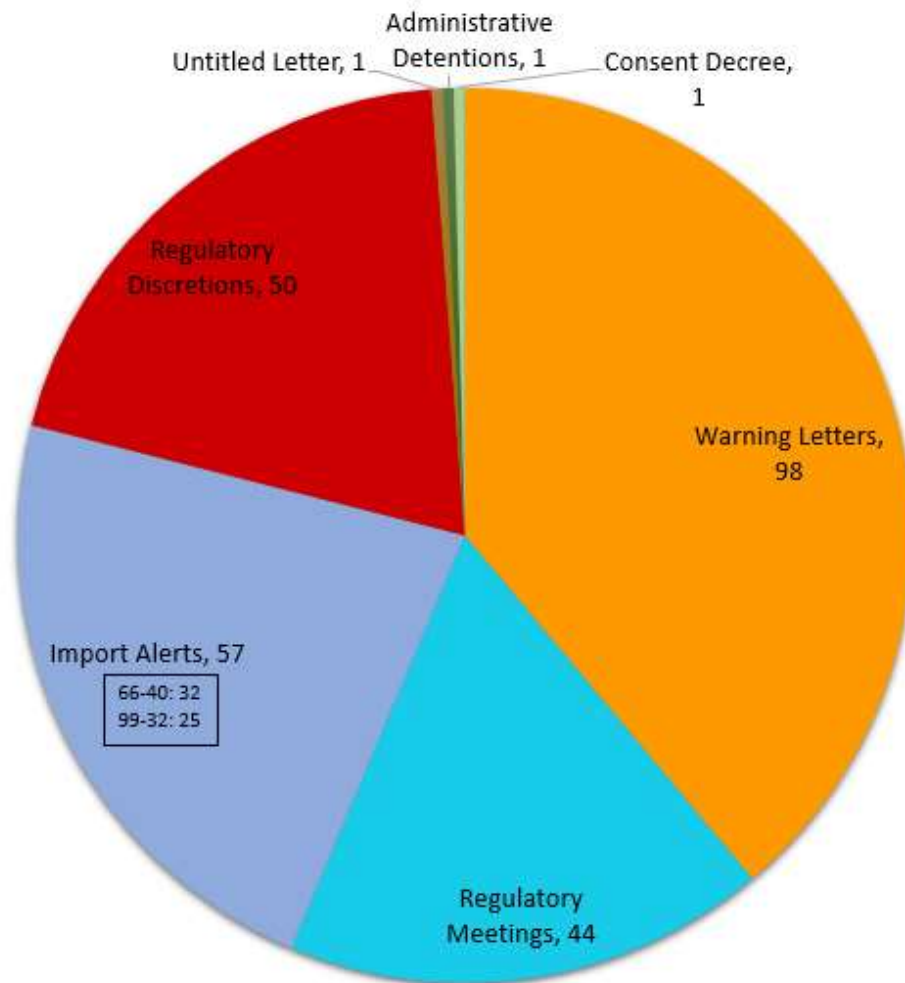
# FY 2019 Actions and ConOps Update

# Enforcement and Advisory Tools



## FY2019 Regulatory Actions

Regulatory Meetings	Injunctions
Consent Decrees	Import Alerts
Seizures	Warning Letters
Untitled Letters	Administrative Detention



Excludes compounding-related actions

Actions dated October 1, 2018 to September 30, 2019



# OMQ Warning Letters by Region FY15 to FY19



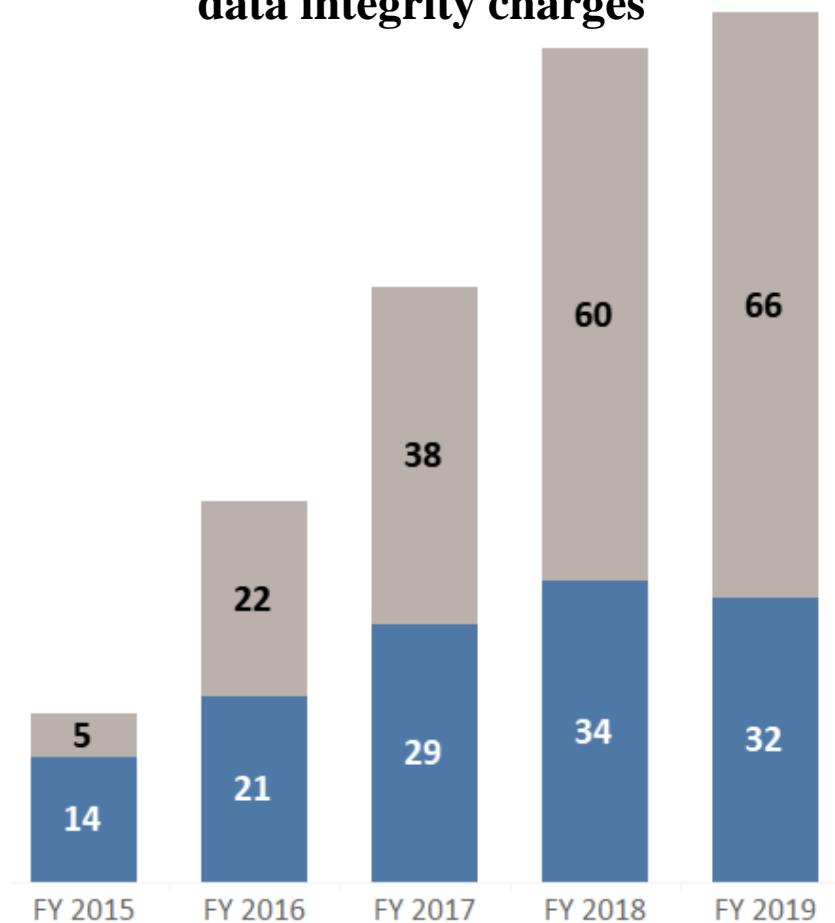
Compounding Warning Letters not included.

# *Recent Warning Letter Trends*

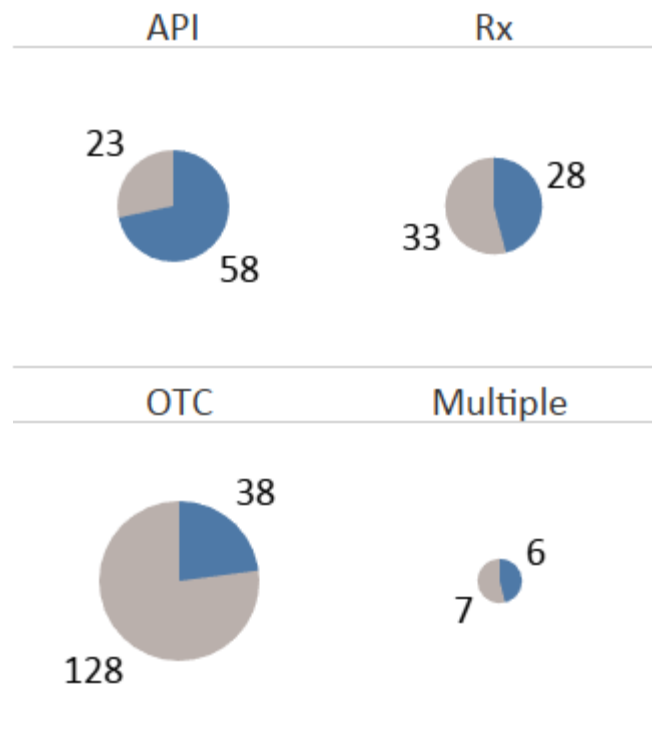
- Rudimentary CGMP
  - Release testing
  - Cleaning, equipment maintenance, basic sanitation
  - Cross-contamination risks
  - More often for non-application/OTC monograph drugs
- Data Integrity
  - Lack of control over access, non-contemporaneous, deletion/falsification/alteration
- Supply Chain
  - API Repackers/Relabelers
  - Contract Manufacturers
- Sterility Assurance
  - Compounding and conventional
  - Aseptic technique, environmental monitoring, design
- Delay/Deny/Limit/Refuse

# Data Integrity

**Warning letters issued containing data integrity charges**



**Distribution of data integrity charges by drug type**



Office of Manufacturing Quality

# Selection of Manufacturers and Suppliers

# ***Food Drug and Cosmetic Act (Section 501 (2012))***

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- ...“current good manufacturing practice” 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
  - finished drug products

CGMP requires effective quality management

# ***ICH Q10: Oversight of Outsourced Activities (Section 2: Management Responsibility) (2008)***

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- The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials.



## ***ICH Q10: Oversight of Outsourced Activities (Section 2: Management Responsibility) (2008)***

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- Assess prior to outsourcing operations or selection of raw material suppliers
- Establish a written agreement with outsourcer
- Monitor and review the performance and quality of the material, and identify/implement any needed improvements
- Ensure use of approved sources

# ***FDA GFI, Contract Manufacturing Arrangements for Drugs: Quality Agreements***



- Outlines critical roles played by both product owners and contracted facilities
- Explains how manufacturers should use quality agreements to define, establish, and document their responsibilities
- Emphasizes that Quality Agreements should:
  - define parties' responsibilities
  - assure full CGMP conformance, and
  - facilitate consistent delivery of safe and effective medicines



# Tools for the Initial Selection and Ongoing Risk Management for Contract Manufacturing/Supplier Qualification (as appropriate)



Risk Management Strategy

Understanding of inherent characteristics of the product/component

Process Understanding / Process Validation

Contract Manufacturer or Supplier Quality Questionnaire

Communication Infrastructure (incl. Change Mgmt. Plan)

Audit Program and Evaluation of Findings

Quality Agreements

Metrics/Analytics Programs

Report Cards

# ***‘Two-fers:’ WL to Both***

- Contracted Facility: “As a contract laboratory that tests drugs, **your firm is responsible for complying with CGMP**. In addition, it is also essential that your firm provide test results for evaluation and consideration by the owner of the product to consider in its final disposition decision.”
- Owner: Failure to properly evaluate contract laboratory to ensure CGMP compliance of operations occurring at the contract site. Did not audit the CTL; after FDA inspected, Owner audited and found critical and major deficiencies.
  - “Although you have agreements with other firms that may delineate specific responsibilities for each party, **you are ultimately responsible for the quality of your products and the reliability of test results**. Regardless of who tests your products or the agreements in place, you are required to manufacture these products in accordance with the Act to assure their identity, strength, quality, purity, and safety.”

# ***3 Warning Letters – Jan 2018***

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- You do not have a supplier qualification program. While you source components from various suppliers, you have not performed any testing to validate the reliability of each supplier's certificate of analysis"
- Your firm neglected to qualify suppliers before relying on their certificates of analysis.
- You failed to test incoming active pharmaceutical ingredients (API) you use in manufacturing drug products to determine their identity, purity, strength, or other appropriate specifications. Instead, your firm released API based on certificates of analysis from your supplier without establishing the reliability of the supplier's analysis through appropriate validation."

# ***Additional References***

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- 21 CFR 210-211
- FDA GFI, Q7, Current Good Manufacturing Practices for Active Pharmaceutical Ingredients
- FDA GFI, Q9, Quality Risk Management
- FDA GFI, Quality Systems Approach to Pharmaceutical CGMP Regulations

# Challenge Question #1

**Which of the following is an enforcement and advisory tool used by OMQ to regulate CGMP manufacturers:**

- A. Warning Letter
- B. Import Alert
- C. Injunctions
- D. All of the Above

## Challenge Question #2

**Oversight of manufacturing of raw materials, in-process materials, and finished drugs is part of current good manufacturing practice.**

- A. True
- B. False
- C. Maybe True, Maybe False

# Key Messages



Initial selection of contract manufacturers and suppliers is the a critical decision



Quality Risk Management can be used as a systematic approach to management of contract manufacturing and supplier qualification



Owners and Contracted/Supplier Facilities should work together proactively to characterize and control risks to product quality and patient safety

Information is not knowledge. Let's not confuse the two.

- *W. Edwards Deming*



# Questions?

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