U.S. FOOD & DRUG ADMINISTRATION

Quality-Related Compliance Actions and Trends

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Learning Objectives

- Update on implementation of ConOps
- Recent Trends in FDA inspections of Over-the-Counter (OTC) drug manufacturers
- Recent Compliance Actions for Active Pharmaceutical Ingredient (API) repackagers

Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A 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

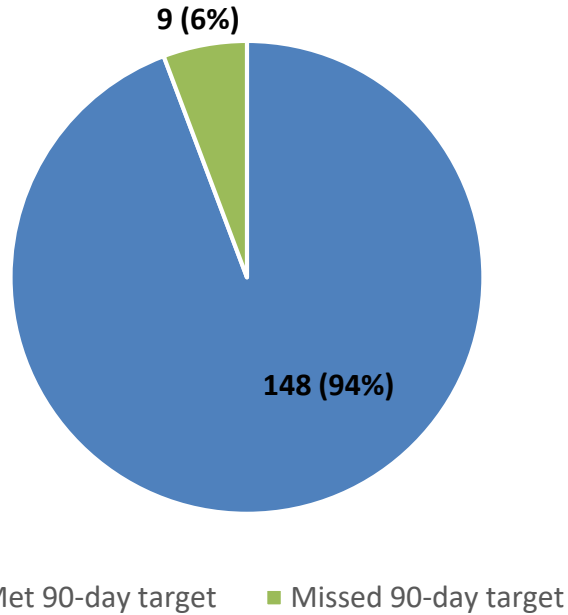
OAI Regulatory Actions

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

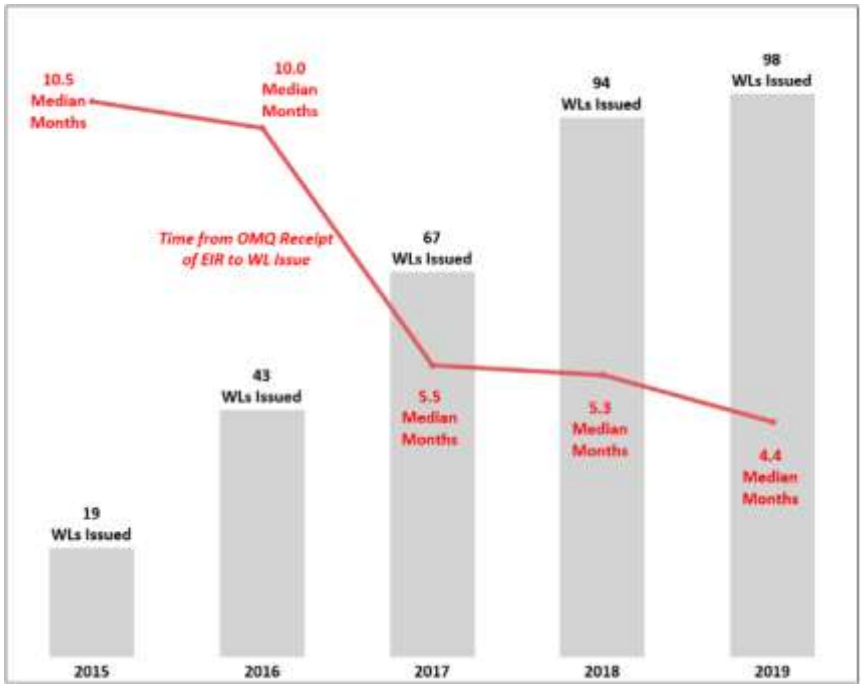
Key Performance Indicators

90-day OAI Classification Letter

157 classification letters from October 1, 2018 to June 30, 2019



From FY2015 to FY2019*, there has been an overall median *58% improvement* while increasing Warning Letter issuance



*CGMP Warning Letters Issued from October 1, 2014 to September 30, 2019

Challenge Question 1

Do OTC and non-application drug manufacturers have to meet the same manufacturing standards as application drugs?

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FDA Surveillance Inspections

FDA NEWS RELEASE

Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's global efforts to help assure product quality and transparency at foreign drug manufacturing facilities

- In 2018, the FDA published a document outlining the policies and procedures for the Site Selection Model used by the FDA to prioritize manufacturing sites for routine quality-related (CGMP) surveillance inspections.

History

- Before 2012, the Food, Drug, and Cosmetic Act required the FDA to inspect domestic drug manufacturing sites every two years.
  - No timeframe outlined for inspecting foreign drug manufacturing sites.
- The shift to overseas production of U.S. goods, including some drugs and their components, predominantly occurred in the early 2000s.
  - Resulting in a large imbalance in which facilities were inspected.

Addressing the Imbalance

- Congress passes the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012.

- FDASIA changed the requirement for the FDA to inspect domestic and foreign drug manufacturing sites “in accordance with a ***risk-based*** schedule.”

FDA's Effort to Implement the Risk-Based Schedule

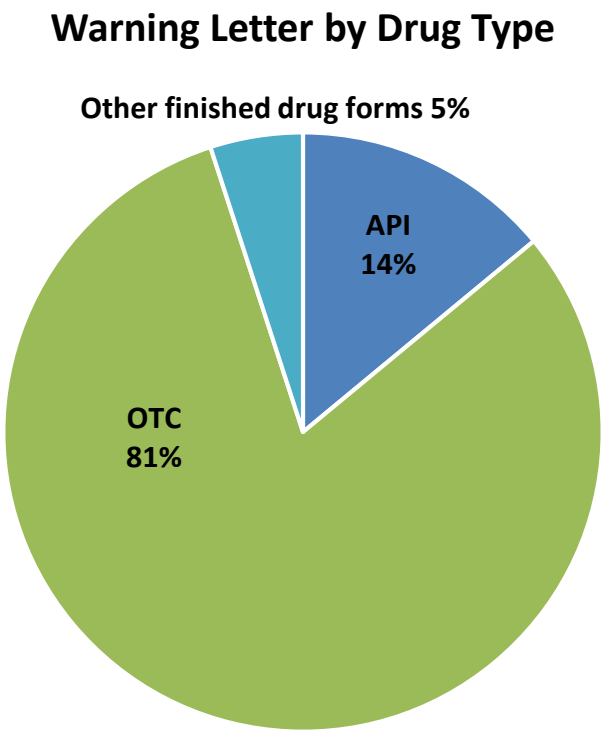
- In 2016, the FDA determines that there are nearly 1000 foreign drug manufacturing sites that have never been inspected.
- The FDA commits to conducting inspections of these foreign drug manufacturing sites in three years.

What did these inspections reveal?

Results

- **75%** of the foreign drug manufacturing sites that had never been inspected were found to be ***compliant*** with CGMP.
  - Inspections were classified as no action indicated (NAI) or voluntary action indicated (VAI).
- **25%** of the foreign drug manufacturing sites that had never been inspected were found to be ***non-compliant*** with CGMP.
  - Inspections were classified as official action indicated (OAI).

Regulatory and Enforcement Actions for "Never Inspected" Sites



- Increase in OAI classification causes an increase in regulatory and enforcement actions
  - more warning letters
  - more import alerts
    - for CGMP issues
    - for refusing an FDA inspection
- Majority are OTC sites

warning letter data from June 21, 2016, to June 30, 2019

Total CGMP Warning Letters by Country FY2015 to FY2019

Europe WLs and China/Hong Kong WLs Grouped into one dot respectively,

Non-compliance Trends for OTCs

1. Data integrity
2. Facility and/or equipment concerns
3. Lack of raw material and finished drug testing
4. Concerns with glycerin
5. Contract manufacturers

Lack of Raw Material and Finished Drug Testing

Recent warning letter:

"Your firm released your finished over-the-counter (OTC) drug product, [redacted], ***without testing for the identity and strength of the active ingredient***, [redacted]. Without this testing, you do not have scientific evidence that your drug product conformed to specifications prior to release."

Lack of Raw Material and Finished Drug Testing

Recent warning letter:

"Your firm ***failed to test incoming active pharmaceutical ingredients and other components*** you use in manufacturing your [redacted] OTC drug product to ensure that each component met specifications, including identity. You also 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."

Concerns with Glycerin

There have been multiple warning letters related to glycerin testing over the past few years.

Warning letter:

> "You ***failed to test incoming components*** you use in manufacturing drug products to determine their conformance to identity, purity, strength, and other appropriate specifications…"
>
> "For example, your firm ***did not test each lot of glycerin used as a component of your drugs*** to determine whether diethylene glycol (DEG) or ethylene glycol was present…"

DEG contamination in pharmaceuticals has resulted in various lethal poisoning incidents in humans worldwide.

FDA takes glycerin supply chain controls seriously

Guidance for Industry: Testing of Glycerin for Diethylene Glycol

"The origin of the glycerin was not easily apparent from the [certificate of analysis] (COA). The COA obtained by the pharmaceutical manufacturers of the syrups was often a copy of a COA on the letterhead of the distributor and not the COA provided by the manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known because the glycerin may be been sold several times between when it was made and its use in medicinal syrup or other drug product."

"As a result of these practices, diethylene glycol contaminated glycerin entered the pharmaceutical raw material supply chain."

FDA Guidance for Industry: Testing of Glycerin for Diethylene Glycol

Guidance for Industry: Testing of Glycerin for Diethylene Glycol

"Drug product manufacturers perform a specific identity test that includes a limit test for DEG on all containers of all lots of glycerin before the glycerin is used in the manufacture or preparation of drug products because of the serious hazard associated with DEG contamination."

Challenge Question 1

Do OTC and non-application drug manufacturers have to meet the same manufacturing standards as application drugs?

Challenge Answer 1

Yes, the Current Good Manufacturing Practice (CGMP) requirements are the same, irrespective of whether a drug is named in an application or not.

Active Pharmaceutical Ingredient (API) Repackagers

Challenge Question 2

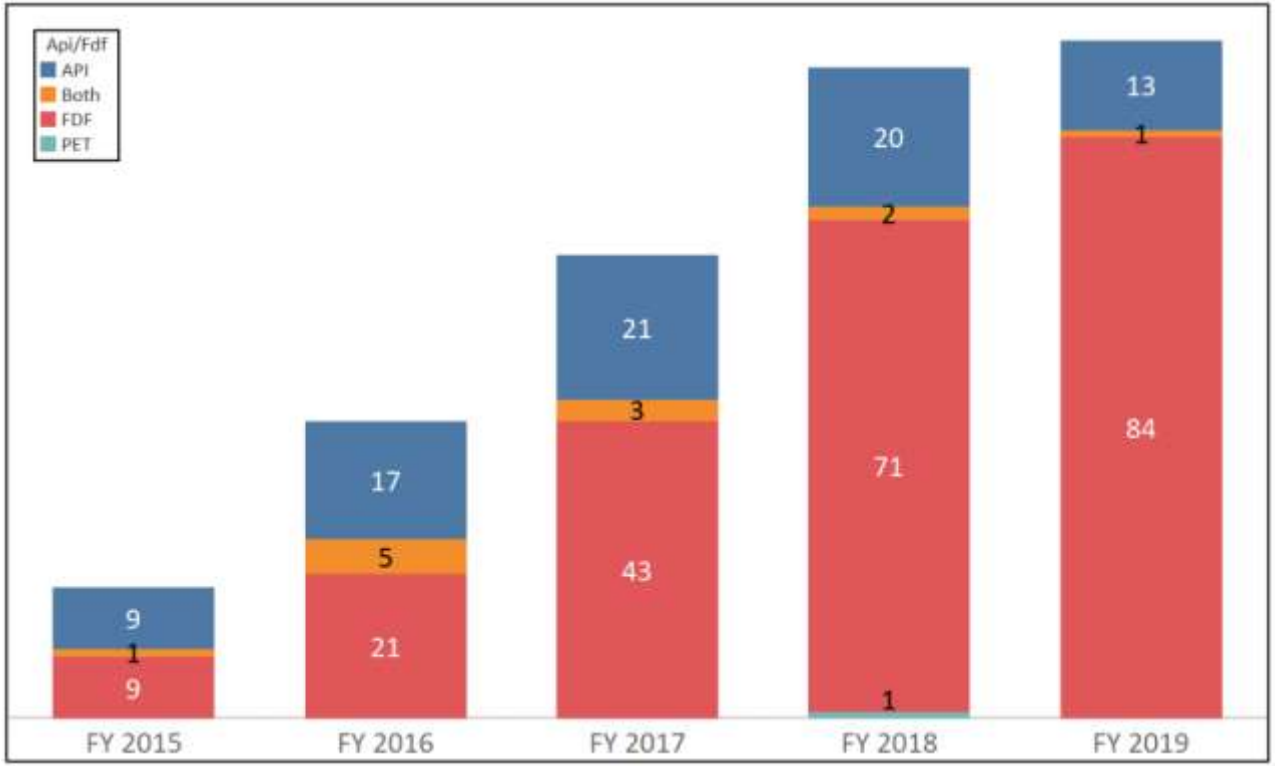
Do API repackers/brokers/traders have to tell their customers the name of the original API manufacturer?

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 API are manufactured in conformance with CGMP

CGMP Warning Letters by API/FDF Type Over Fiscal Year



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Obfuscation of API Supply Chain Information

FDA NEWS RELEASE

FDA warns repackers distributing pharmaceutical ingredients, including opioids, for putting consumers at risk with significant violations of manufacturing quality standards

"For patient safety and supply chain transparency, repackers must follow all quality standards pertaining to them – including clearly identifying the original manufacturer of the drugs, such as opioids, to their customers who use them to make the finished drugs patients take every day. This information is vitally important to ensure the drugs patients take meet high quality standards that patients deserve."

Janet Woodcock, MD

Director of FDA's Center for Drug Evaluation and Research

Observations for API Repackers

- Failures to conform to CGMPs including failure to thoroughly investigate complaints regarding sub-potent API
- Failure to provide adequate certificates of analysis for API
- Failure to conduct cleaning validation studies to demonstrate that their cleaning procedures are adequate to prevent potential cross-contamination

Observations for API Repackers

- Failure to maintain traceability of the 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)

Challenge Question 2

Do API repackers/brokers/traders have to tell their customers the name of the original API manufacturer?

Challenge Answer 2

Yes.

Under CGMP API repackers are required to tell their customers the name of the original manufacturer.


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