U.S. FOOD & DRUG ADMINISTRATION

CDER/OC/OMQ Update And Recent Cross Contamination Case Studies

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- DISCLAIMER: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Food and Drug Administration

Outline

- What OMQ Does
- FY 2019 Actions and ConOps Update
- Inspecting the Uninspected
- How Does India Fit In?
- India Warning Letter Trends
- Recent Cross Contamination Cases

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

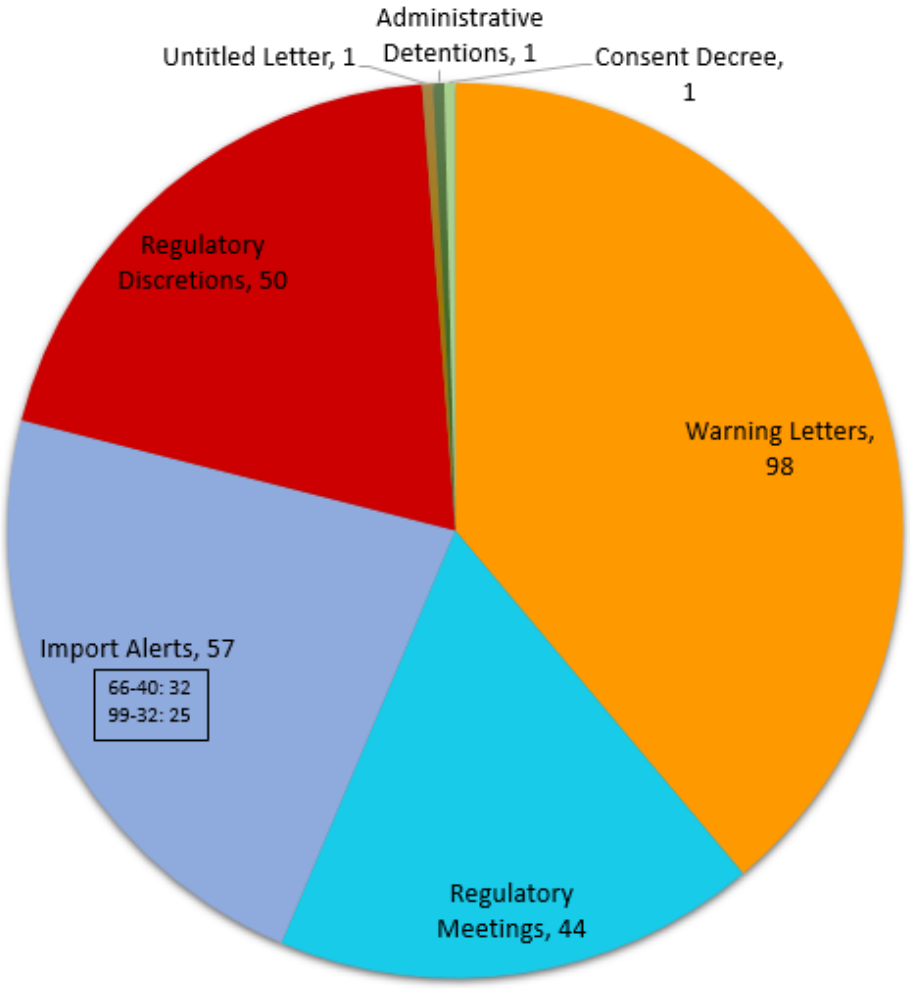
Office of Manufacturing Quality

FY 2019 Actions and ConOps Update

Enforcement and Advisory Tools

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

FY2019 Regulatory Actions



Excludes compounding-related actions

Actions dated October 1, 2018 to September 30, 2019

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

Two Examples of FDA Key Performance Indicators

90-day Classification Letter

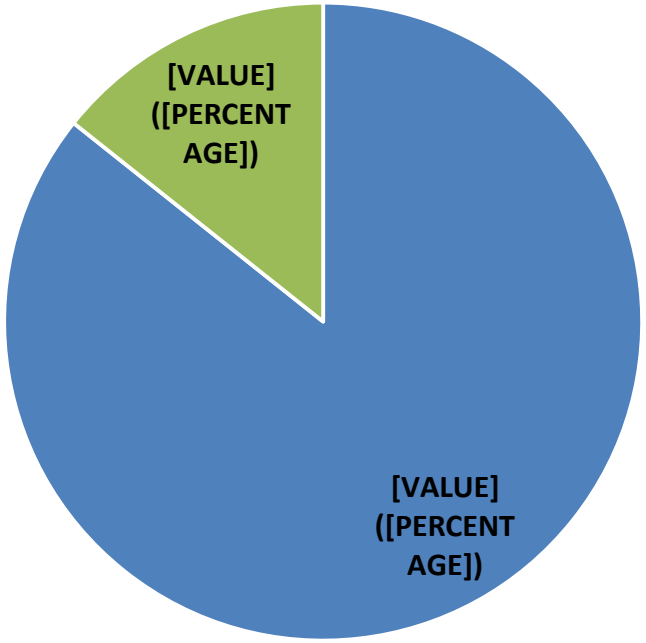
- Rate of classification letters issued by FDA in *90 days* from close of inspection
- GDUFA II Commitment

OAI Regulatory Actions

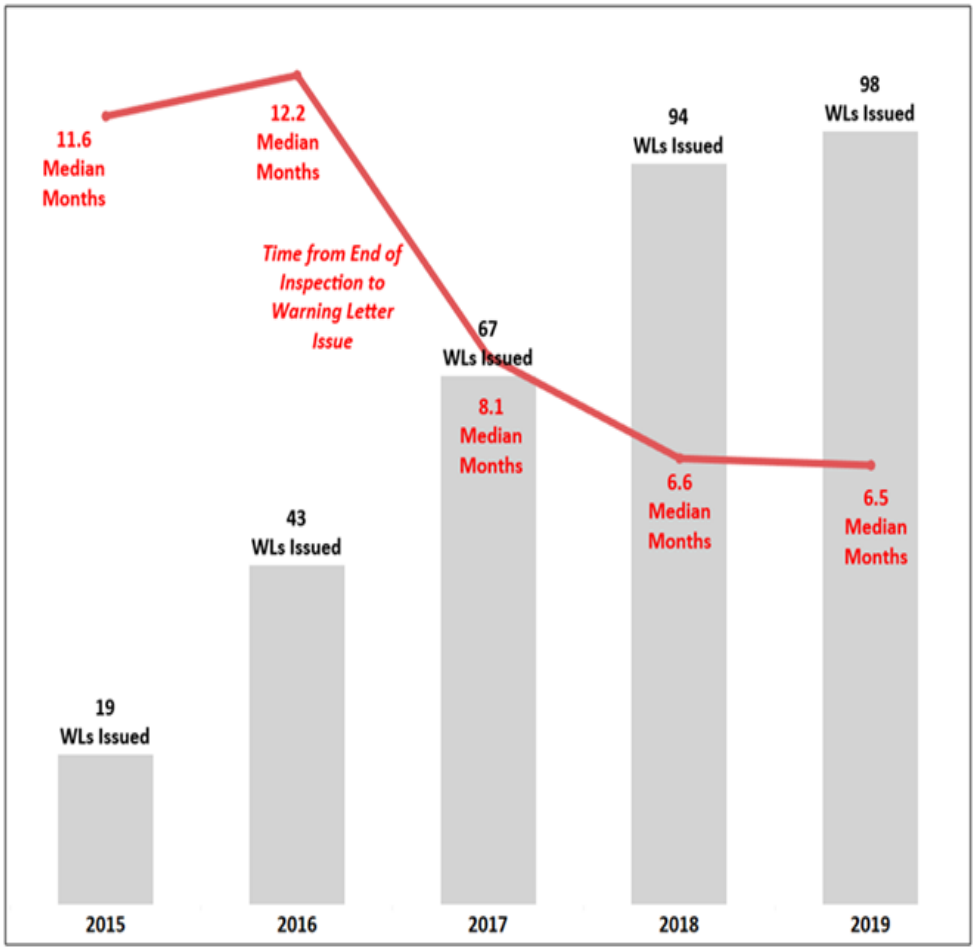
- Rate of OAI regulatory actions completed in *6 months* from the closing of the inspection

ConOps Key Performance Indicators

90-day Classification Letters in FY 19



FY 2015-2019: Overall median 46% improvement in time to issue warning letters from the end of inspection



Inspecting The Uninspected

A Brief Recent History Lesson

- Before 2012, the FD&C Act required inspections of domestic drug manufacturers every 2 years.
  - But the law was silent on foreign sites…
- At the same time, globalization of drug manufacturing occurs.
  - Resulted in a large imbalance in which facilities were inspected.

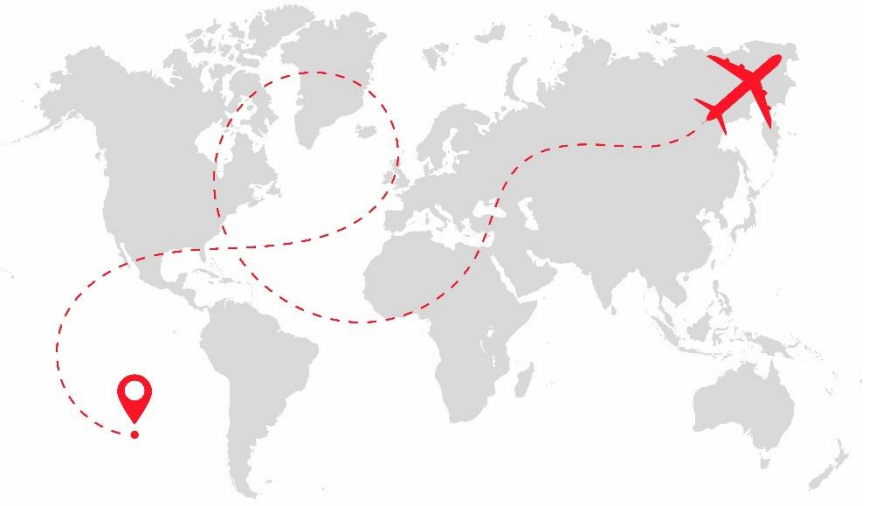
To Address the Imbalance

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

- FDASIA changed the requirement for FDA to inspect domestic and foreign drug establishments "in accordance with a risk-based schedule."

FDA's Effort to Implement

- The GAO works with FDA and finds almost 1000 drug facilities with no inspection history.
- FDA commits to inspecting "the never inspected" within 3 years.
- FDA has almost completed the herculean task of inspecting these firms.



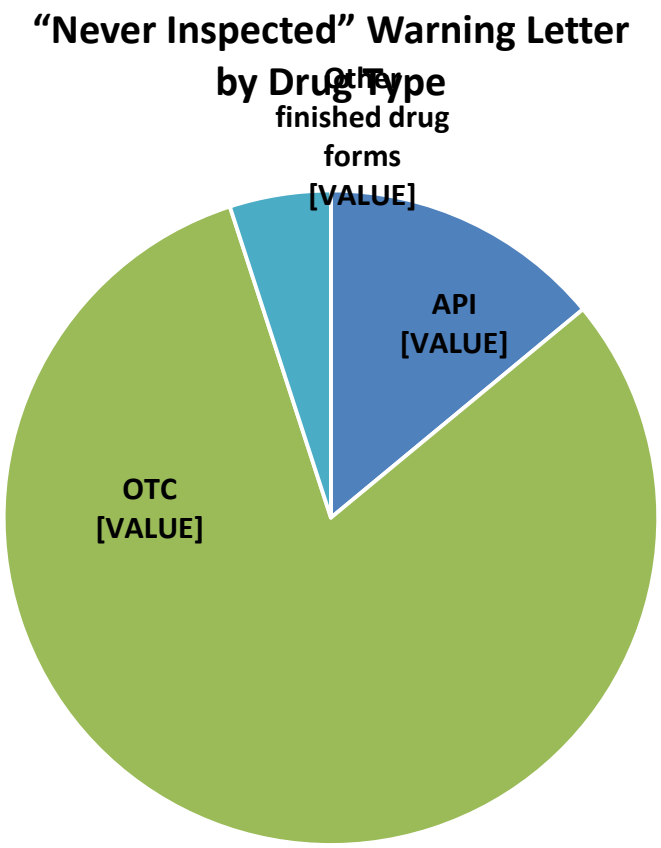
- What did we find?

Outcomes from Inspections of "Never Inspected" Firms

The majority of sites (75%) were found to be compliant with CGMP.

The noncompliance rate (also known as the OAI rate) was markedly higher than in previously inspected firms.

Regulatory Actions for "Never Inspected" Sites

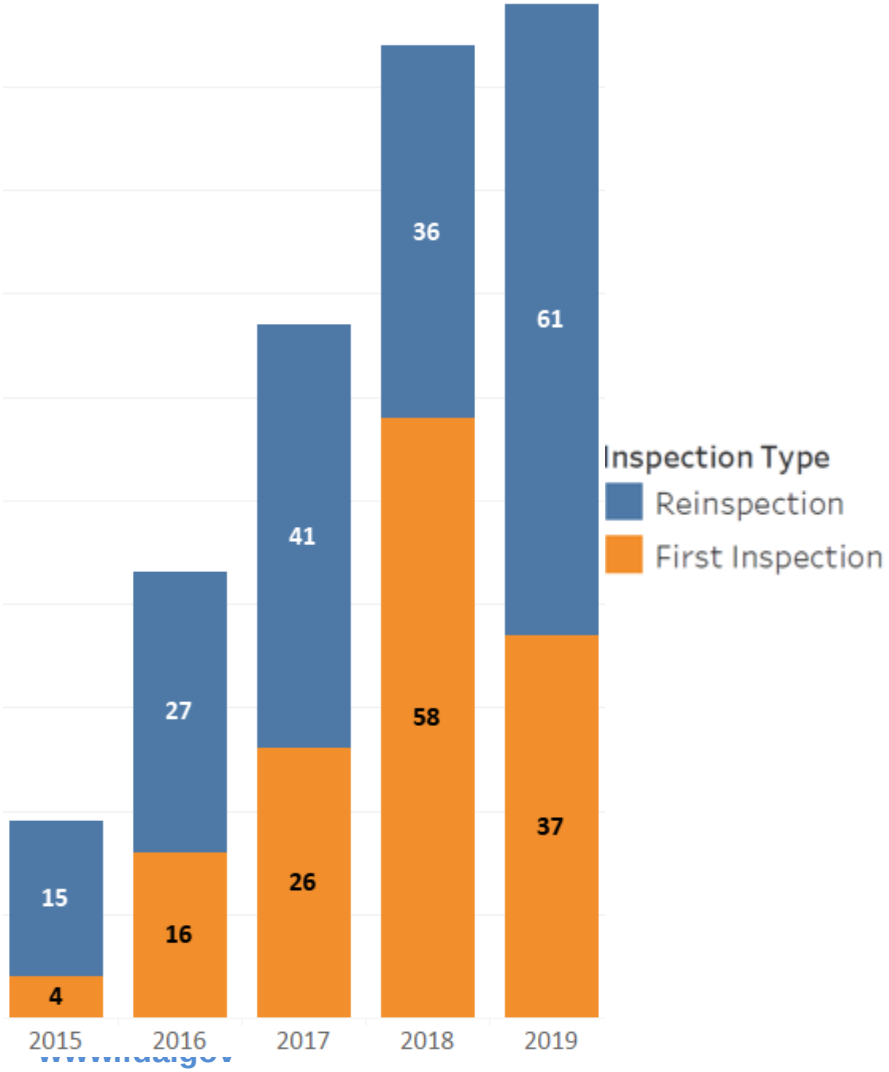


Warning Letter data from June 21, 2016, to June 30, 2019

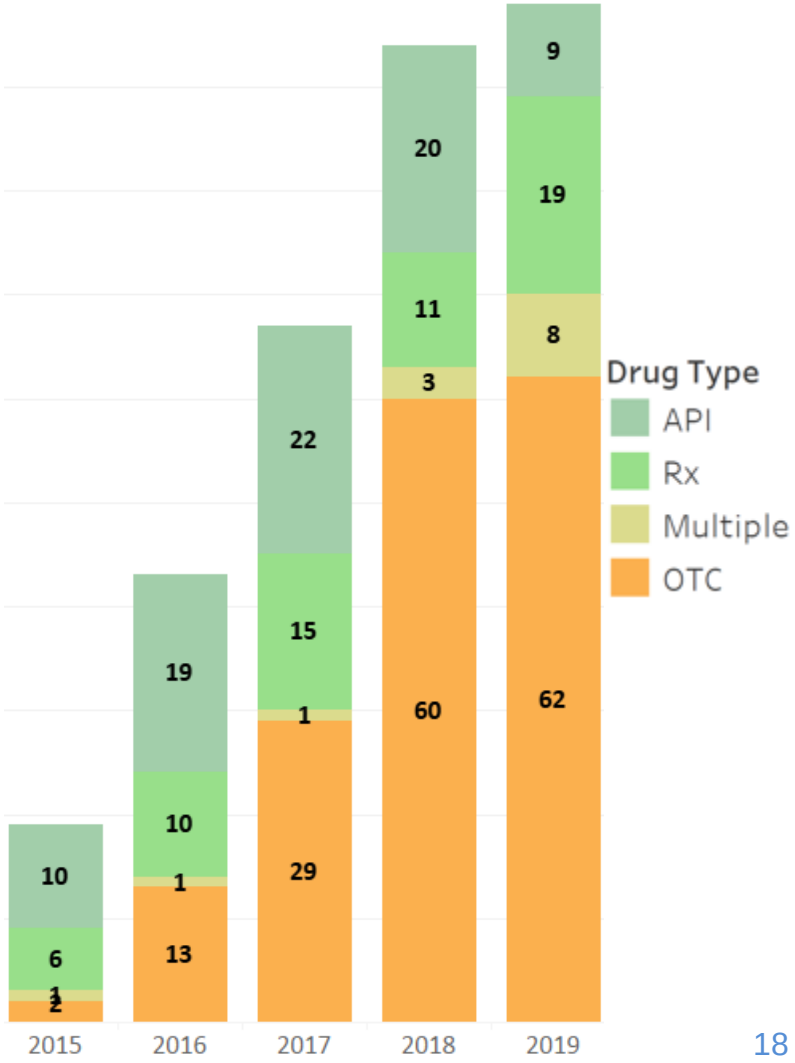
- Increase in OAI classification causes an increase in regulatory and enforcement actions
  - more Warning Letters
  - more Import Alerts
    - for CGMP issues
    - for refusing an FDA inspection
- Majority are OTC sites

Trends in CGMP Warning Letters

Warning Letters Issued
after Initial vs Reinspections by FY



Warning Letters Issued
by Drug Type Manufactured by FY



Common Themes in Warning Letters for OTC Manufacturers (FY19 and FY20)

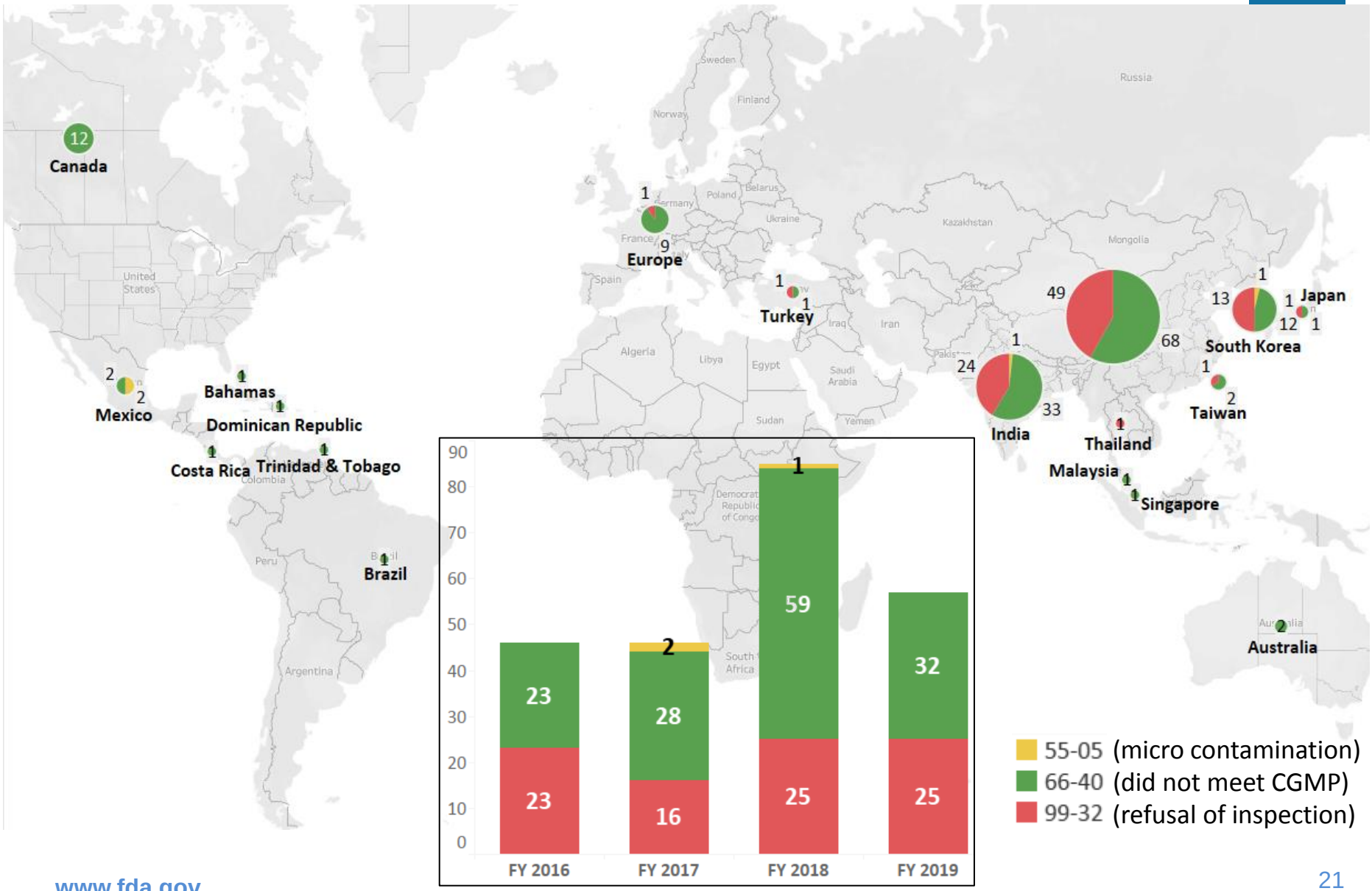
1. Lack of Raw Material and Finished Drug Testing
2. Facility/Equipment Concerns
3. Lack of Data Integrity
4. Potential contamination (e.g., Glycerin)
5. Problems related to contract manufacturers

Many OTC manufacturers received a Warning Letter and were placed on Import Alert

Examples of Import Alerts OMQ Utilizes

- Import alert 99-32
  - Detention without physical examination of products from firms refusing FDA foreign inspection
- Import alert 66-40
  - Detention without physical examination of drugs from firms which have not met drug CGMPs
- Import alert 55-03
  - Detention without physical examination or different forms of heparin and heparin-products
- Import alert 55-05
  - Detention without physical examination of finished dosage drug products, active pharmaceutical ingredients and inactive ingredients for potentially hazardous microbiological contamination

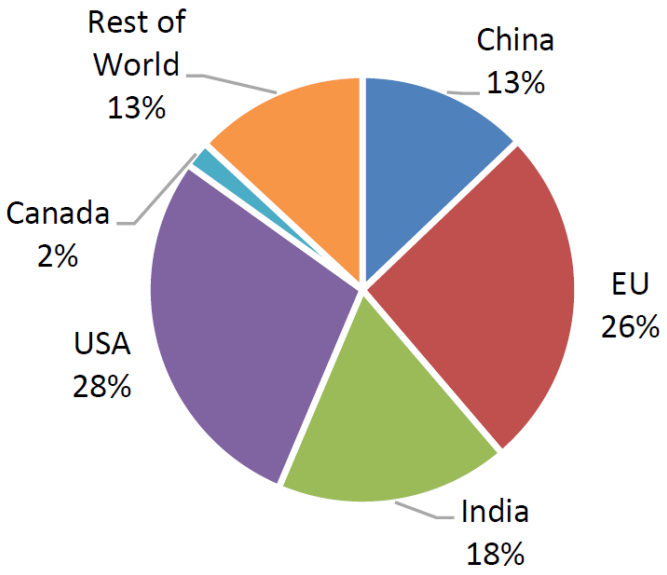
Import Alerts by Type



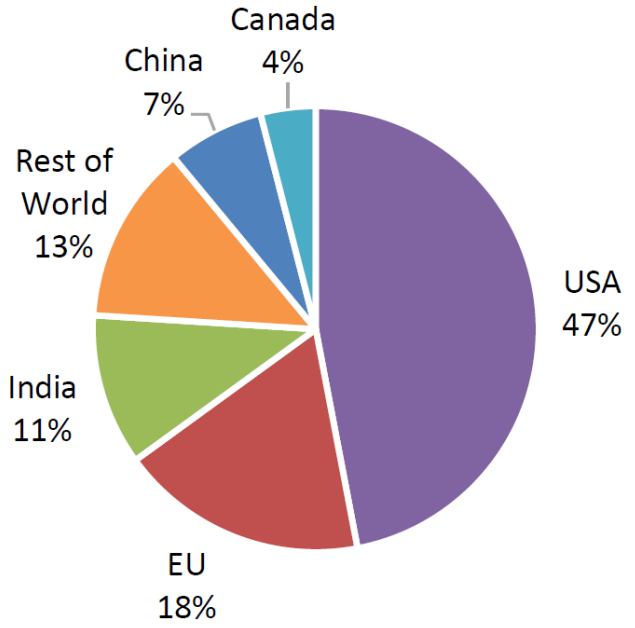
How Does India Fit In?

Inventory Snapshot

Percentage of Active Pharmacetical Ingredient Manufacturing Facilities for All Drugs by Country or Region, August 2019



Percentage of Finished Dosage Form Manufacturing Facilities for All Drugs by Country or Region, August 2019



https://docs.house.gov/meetings/IF/IF02/20191210/110317/HHRG-116-IF02-Wstate-WoodcockMDM-20191210.pdf

CGMP/Adulteration Warning Letters by Region FY15 to FY19

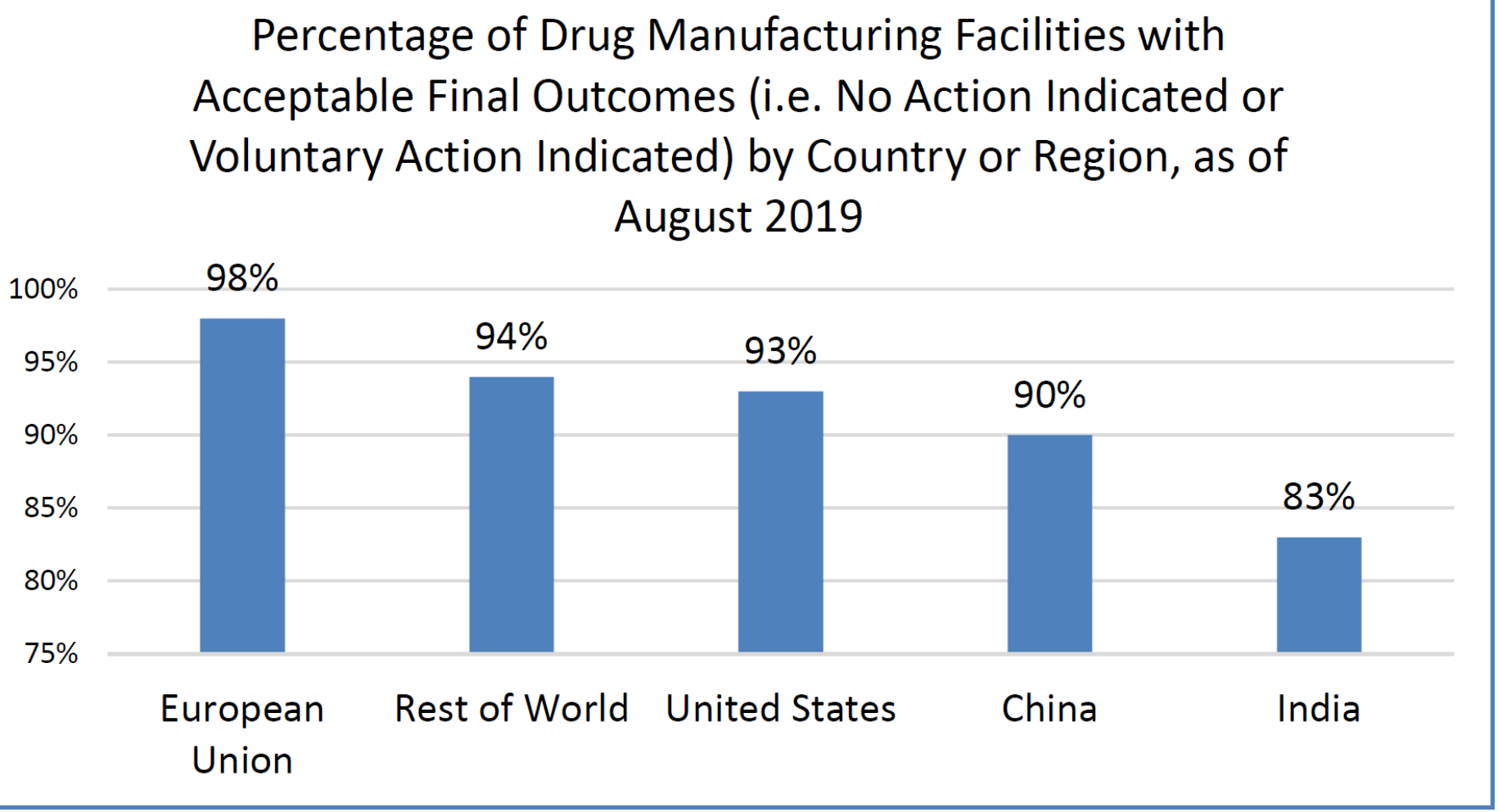
*European Countries grouped into one region
**Compounding Warning Letters not included

How Does India Fit Into This

The majority of sites in India (83%) were found to be compliant with CGMP.

The compliance rate in India is markedly lower than the compliance rate worldwide

Compliance Rate by Country/Region



https://docs.house.gov/meetings/IF/IF02/20191210/110317/HHRG-116-IF02-Wstate-WoodcockMDM-20191210.pdf

India Warning Letter Trends

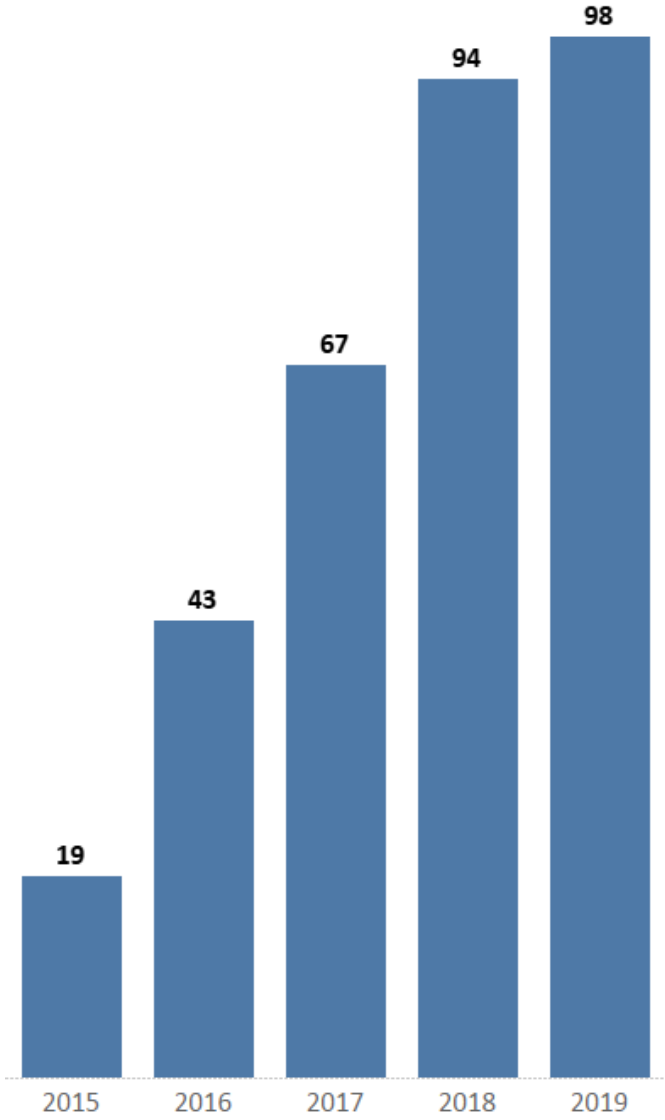
CGMP Warning Letters FY15-19

Warning Letters by Country

State	2015	2016	2017	2018	2019
United States	2	7	15	19	54
China	2	14	19	24	14
India	9	11	14	15	17
Europe	3	5	8	8	2
South Korea			2	9	5
Canada	1		3	7	1
Japan		1	3	3	
Taiwan		3		2	1
Mexico				3	
Brazil		2	1		
Australia				3	
Singapore			1		1
Turkey					1
Thailand	1				
Philippines			1		
New Zealand	1				
Malaysia					1
Dominican Republic				1	
Costa Rica					1
Grand Total	19	43	67	94	98

Compounding Warning Letters not included.

Warning Letters by Fiscal Year



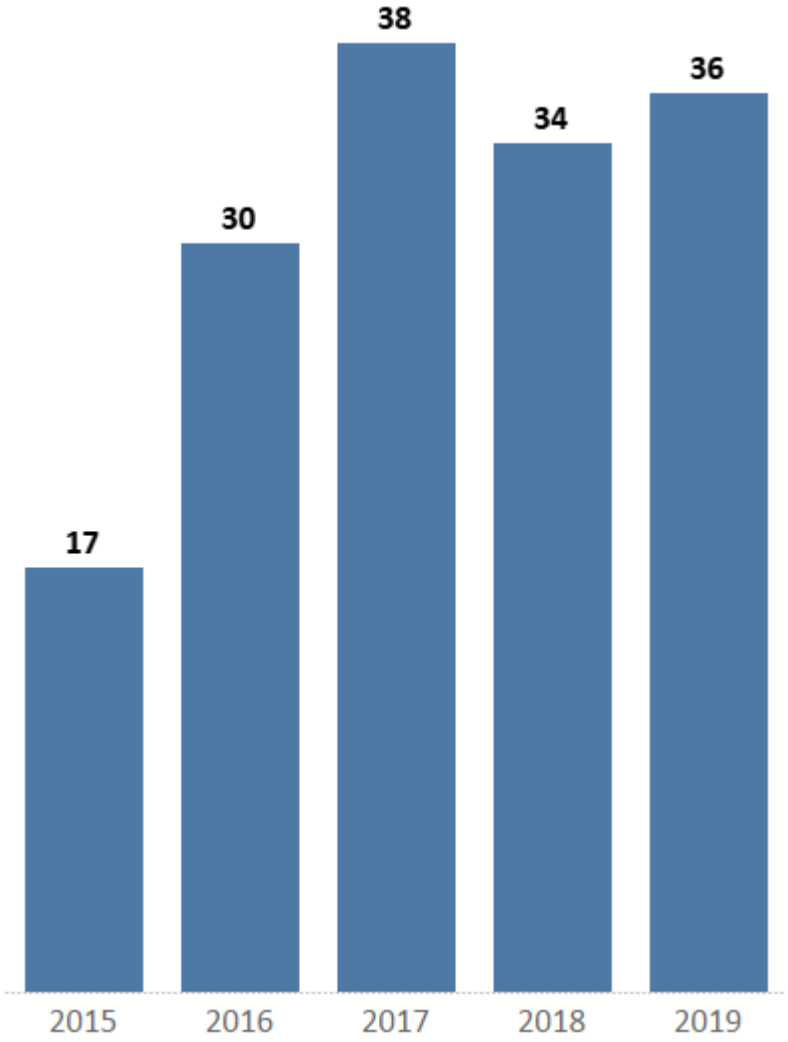
Non-OTC CGMP Warning Letters FY15-19

Non OTC Warning Letters by Country

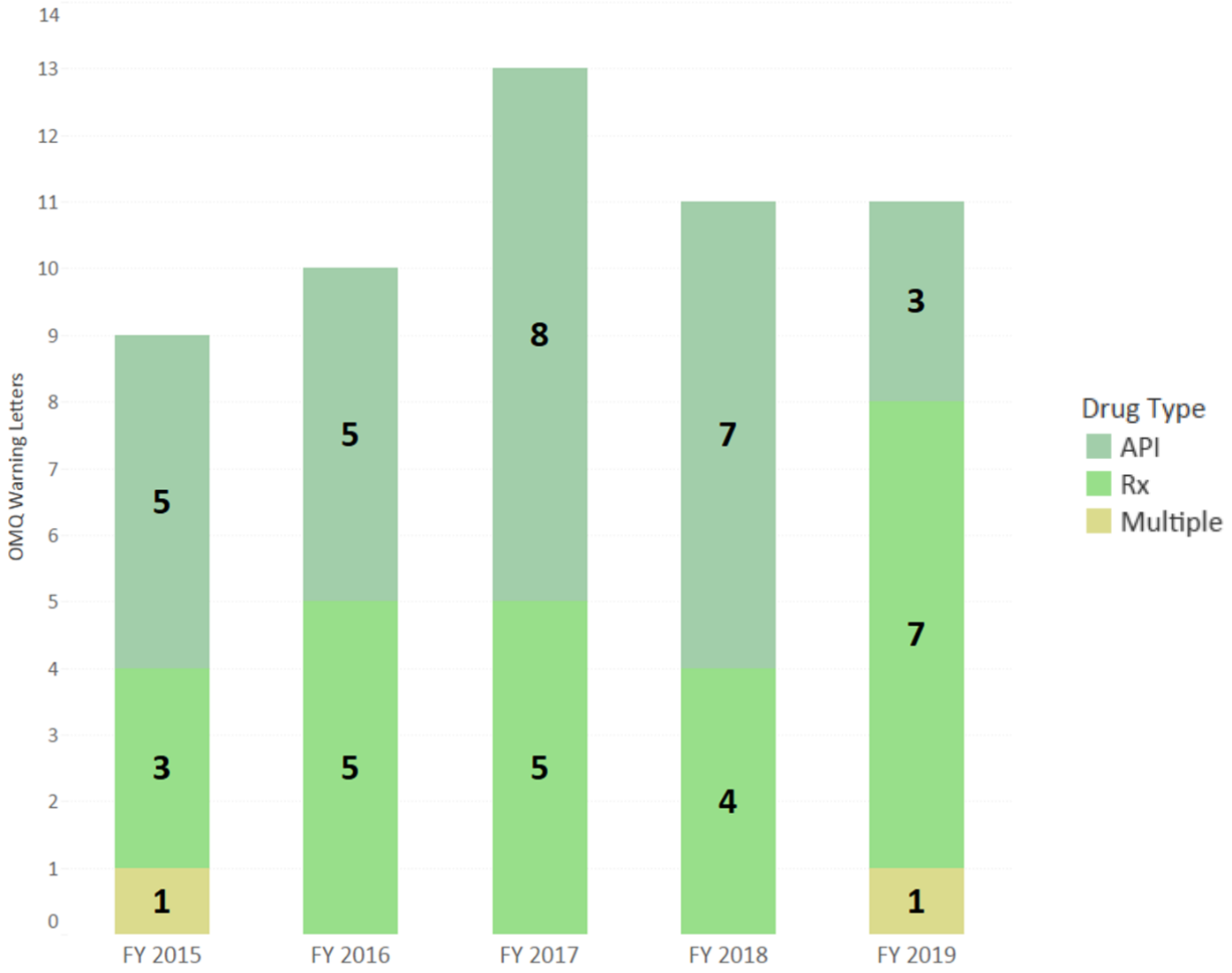
State	2015	2016	2017	2018	2019
India	9	10	13	11	11
United States	1	6	5	5	20
China	2	9	10	9	4
Europe	3	3	6	2	
Japan		1	3	3	
Canada	1			2	
Turkey					1
Thailand	1				
Taiwan		1			
South Korea				1	
Brazil			1		
Australia				1	
Grand Total	17	30	38	34	36

Compounding Warning Letters not included.

Warning Letters by Fiscal Year



Non-OTC India Warning Letters by Drug Type FY15 to FY19



Top 20 Citations/Observations Non-OTC Warning Letters to Firms in India FY2015-2019

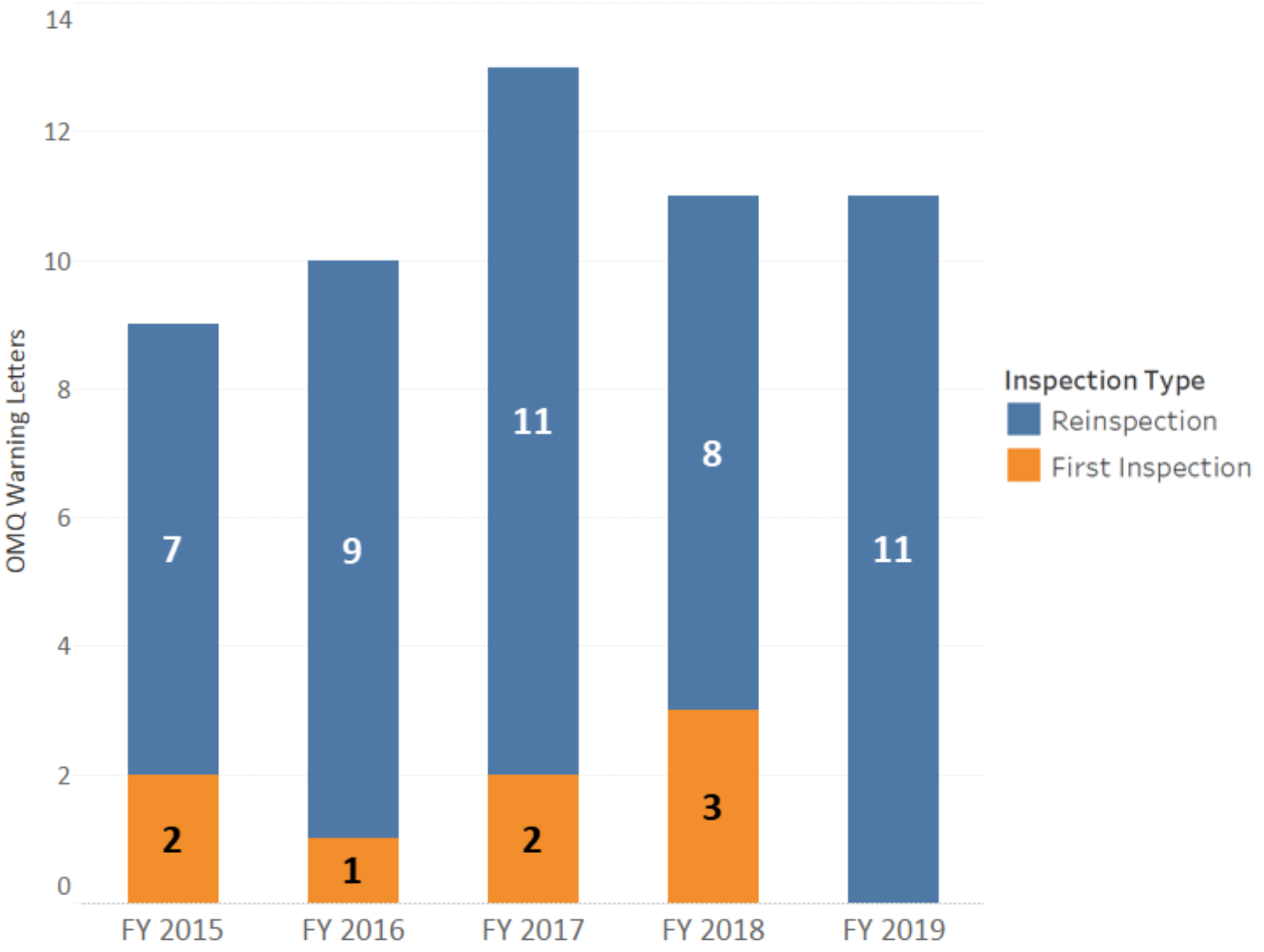
Charge	2015	2016	2017	2018	2019	Gra..
211.192 - Investigations of discrepancies and OOS results.	3	3	3	5	7	21
ICH Q7 5.43 - Unauthorized access.	4	6	1	1	1	13
211.194(a) - Laboratory records include complete data.	2	3	2		2	9
ICH Q7 11.15 - Failure to investigate OOS results.		3		4	1	8
ICH Q7 11.12 - Test procedures not appropriate/scientifically sound.	1	2	3	1		7
211.113(b) - Control of microbiological contamination (sterile).	1	3	2		1	7
211.68(b) - Controls to prevent unauthorized access of systems.	2	2	2			6
ICH Q7 6.60 - Complete data.	2	1	1	1		5
ICH Q7 4.70 - Building maintenance and cleanliness.	2	1		1		4
211.67(a) - Equipment cleaning and maintenance.		1	2		1	4
211.160(b) - Lack of established lab controls.	1	2	1			4
ICH Q7 2.3(4) - Failure to report and evaluate all production deviations.		1	1	1		3
ICH Q7 2.22 - Quality unit not exercising responsibility.	1		2			3
ICH Q7 2.15 - Contemporaneous records.	1	2				3
211.22(d) - Written procedures for responsibilities of quality unit.	1		2			3
211.22(a) - Responsibilities of quality unit.		1	1		1	3
ICH Q7 8.30 - Written procedures for control of processing steps.		2				2
ICH Q7 6.14 - Contemporaneous records, data destroyed.	1		1			2
ICH Q7 6.11 - Control of documents with maintenance of revision histories.	1		1			2
ICH Q7 5.15 - Minimize contamination with open equipment.	1			1		2

54 Non-OTC India Warning Letters Issued FY2015 to FY2019

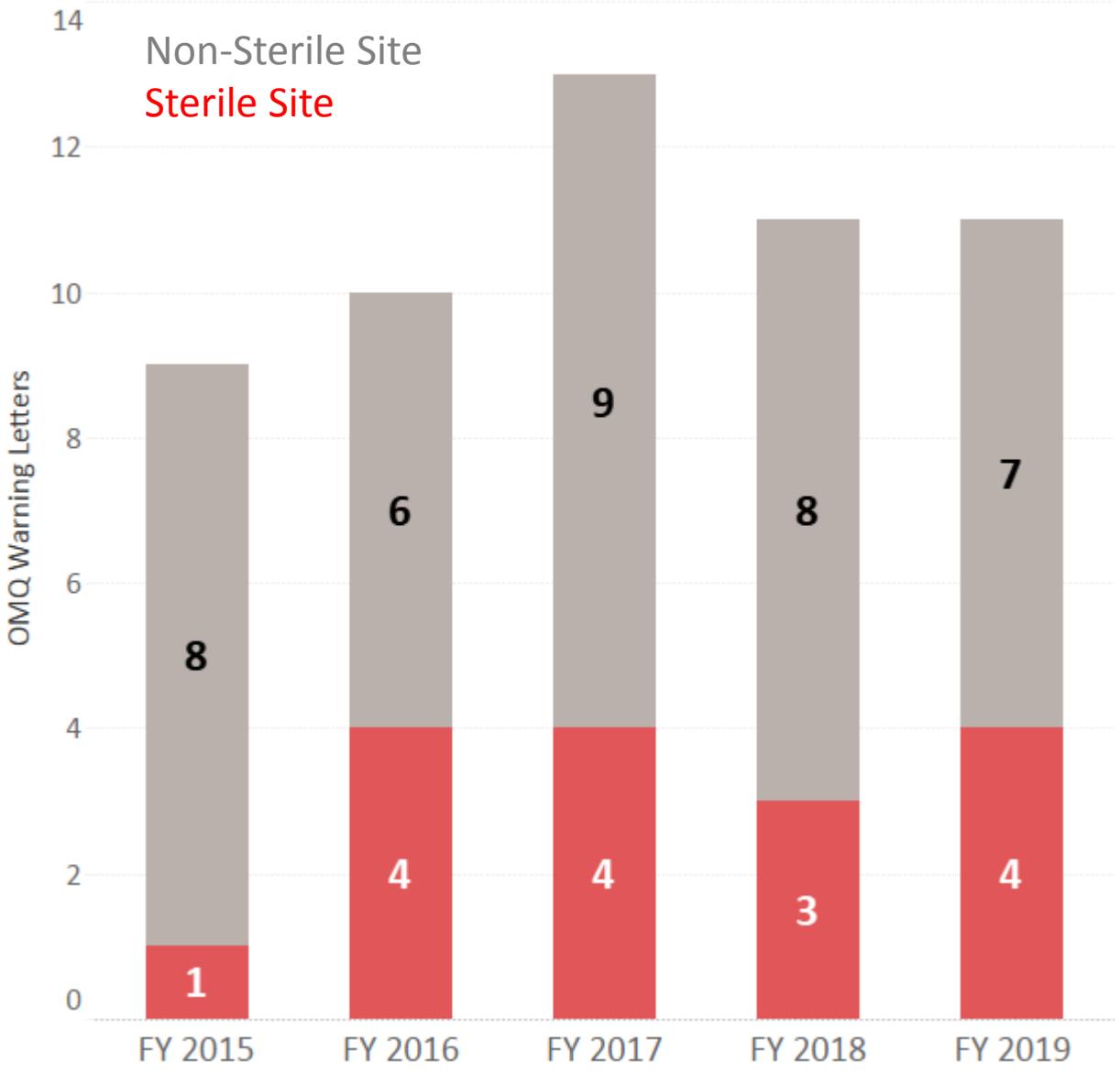
Some Key Findings From the Data

- Most Warning Letters issued to drug manufacturers in India are not for initial inspections.
- Topics of Warning Letters include:
  - Inadequate controls for sterile drug manufacturing
  - Lack of Data Integrity/Inadequate OOS investigations
  - Poor cross contamination controls

Non-OTC India Warning Letters by Initial vs Re Inspection FY15 to FY19



Non-OTC India Warning Letters
Sterile vs Non Sterile Site FY15 to FY19



Aseptic Processing Guidance

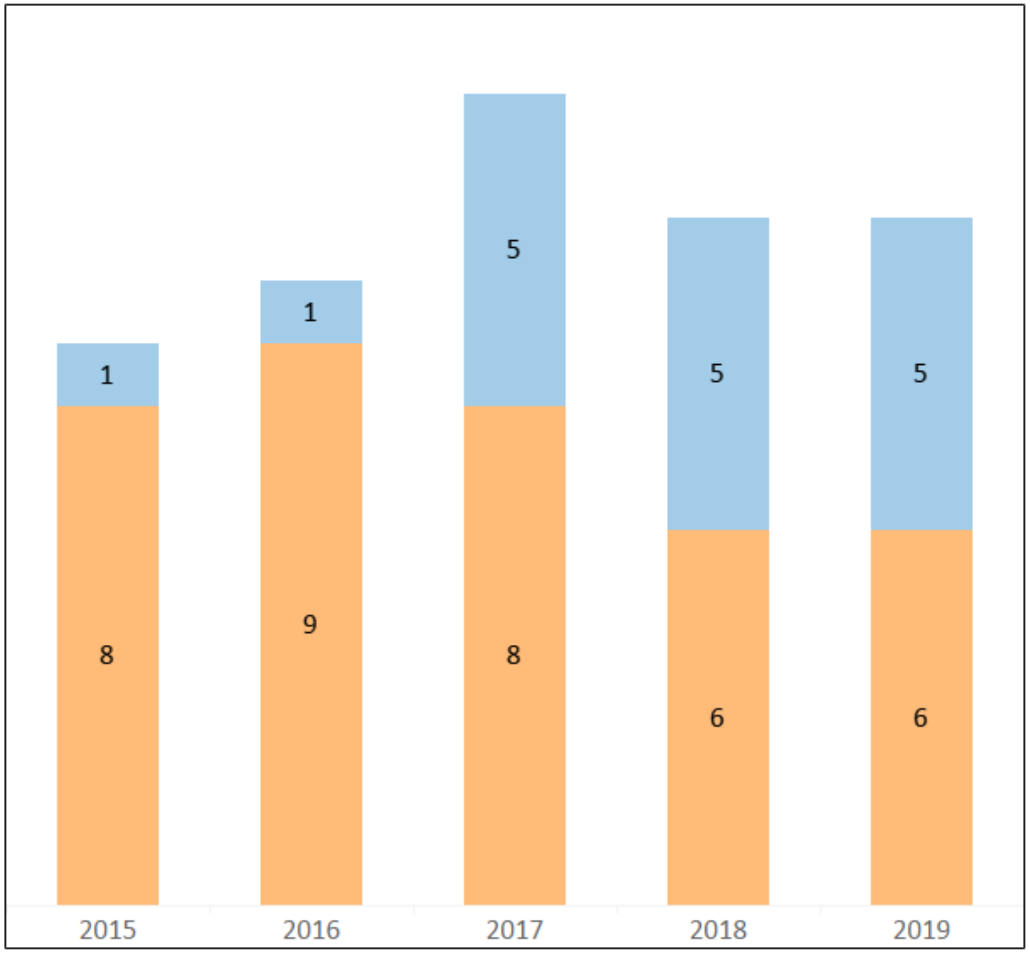
Sterility Assurance is Paramount from a Patient Risk Perspective

- FDA Guidance, ***Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.***
- Assists sterile drug manufacturers with CGMP expectations for facility design, equipment suitability, process validation, and quality control.
- Covers multiple technologies in this space.

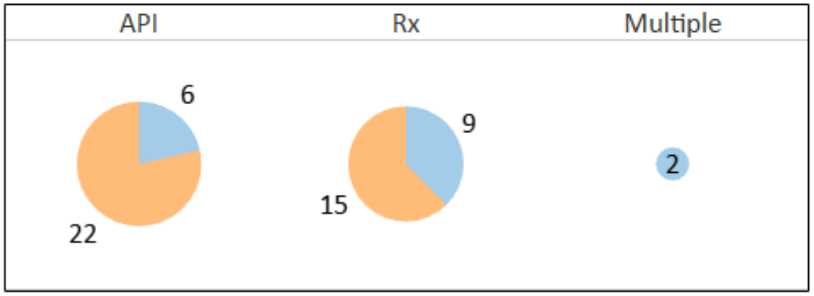
Link: https://www.fda.gov/media/71026/download

Non-OTC India Warning Letters with Data Integrity Concerns

Warning Letters Issued Containing Data Integrity Charges by Fiscal Year



Distribution of Data Integrity Charges by Drug Type



Importance of Data Integrity

- Data integrity – evidence that data are complete, consistent, and accurate.
- Applies to CGMP via the FD&C Act, CFR 210, 211, 212.
- FDA Guidance document: ***Data Integrity and Compliance with CGMP,*** published December 2018, clarified the role of data integrity in CGMP for drugs
  - https://www.fda.gov/media/119267/download
- **CGMP Lab Control Q&A**, including some Data Integrity topics:
  - https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-laboratory-controls

FDA Guidance on OOS Test Results

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

- Regulations require investigation for OOS test results (211.192).
- Purpose is to determine the cause of the OOS result and conduct appropriate follow up.
- Even if a batch is rejected, manufacturer must determine whether the result could effect other batches or products.
- The investigation should be thorough, timely, unbiased, well-documented, and scientifically sound.
- FDA recommends a phased investigation, starting with understanding the laboratory result before expanding to manufacturing.
- Identifying the root cause of a laboratory or manufacturing problem enables a manufacturer to correct and prevent recurrence

Link: https://www.fda.gov/media/71001/download

Recent Cross Contamination Cases

Recent Warning Letter Trends: Cross Contamination

- Many Warning Letters and Import Alerts are for manufacturers with risks for dangerous cross contamination.
- Applies to domestic and foreign facilities.
- Risks ranging from pharmaceutical to industrial chemical cross contamination.

Recent Warning Letter Trends: Cross Contamination

Industrial chemical cases

- *It is unacceptable as a matter of CGMP to continue manufacturing topical drugs using the same equipment that you use to manufacture industrial-grade products, including those that contain known skin irritants.*

- *Records we reviewed during our inspection and information you submitted in your response confirmed that two of the human drugs you manufactured contained the pesticide [redacted]. You manufactured the pesticide and the human drugs using shared equipment.*

– Two Warning Letters (non India)

Recent Warning Letter Trends: Cross Contamination

Import Alerts/Warning Letters for potent drugs

- **Hormones:**
  An API firm makes multiple potent drugs (including hormones) on shared equipment, but didn't validate cleaning.

- **Beta Lactams:**
  A finished-dosage firm makes OTC drugs for the US market, but uses the same facility to make beta lactam drugs.

– Two recent cases (non India)

Emerging Trend in India: Cross Contamination via Ductwork

This is not a new technical issue:

- **In 2012**
  - FDA conducted an inspection of a US Generic drug manufacturer based on field alert reports (FARs) submitted to FDA regarding an issue discovered by the firm during maintenance.

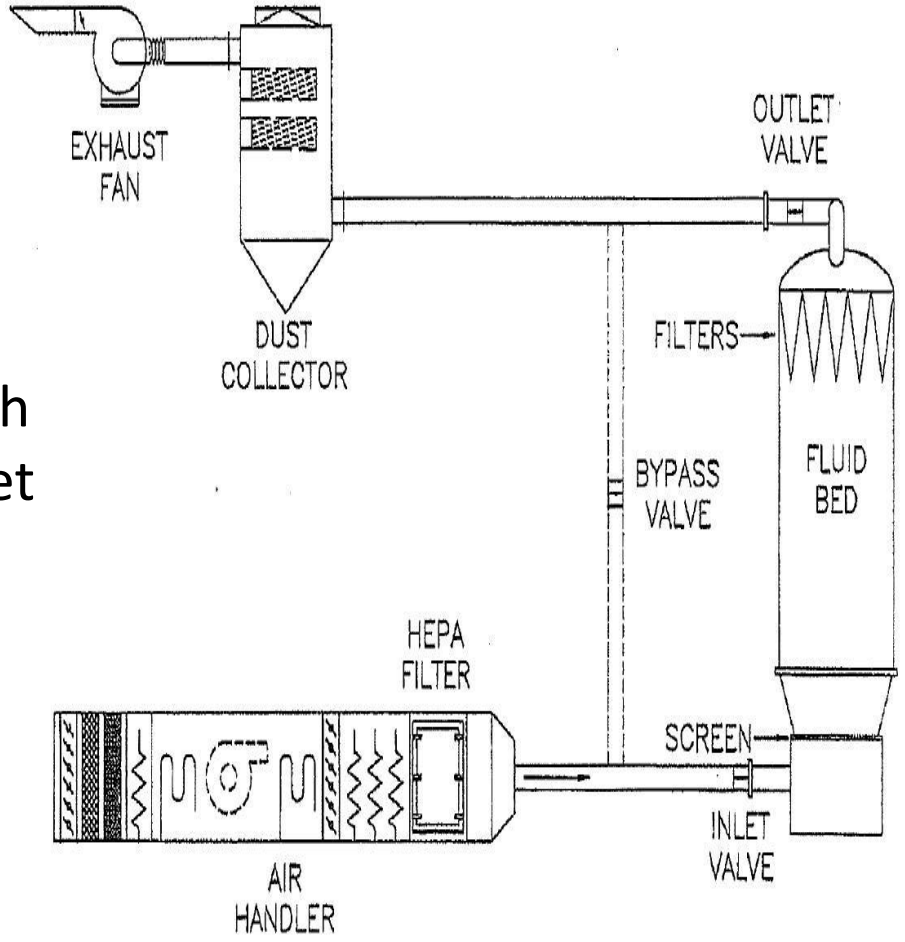
- **Firm makes a multitude of drugs on fluid bed dryers (including hormones)**
  - Cross contamination from one drug to another occurring via fluid bed ductwork.

Emerging Trend in India: Cross Contamination via Ductwork

Emerging Trend in India: Cross Contamination via Ductwork

Failure Modes from the 2012 US Case:

- Drug fines passed through filter bags at the top of the fluid bed
- Vertical drop in duct bypass allowed material passing through filter bags to re-enter the air inlet while processing the next batch
- Material also dropped through the fluid bed screen and remained in the inlet/went into next batch.

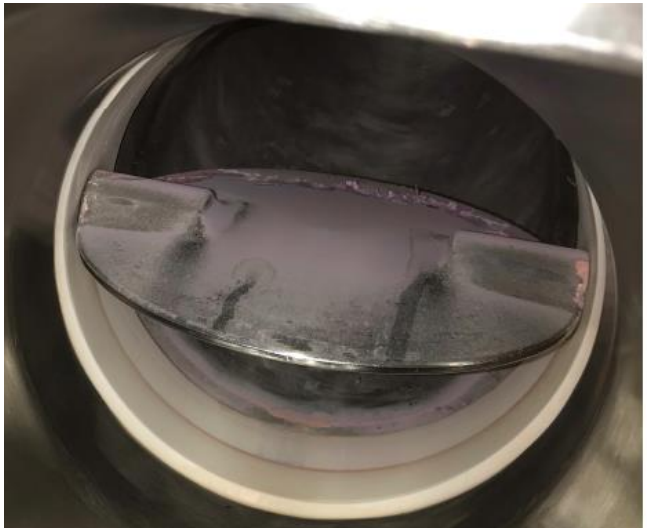


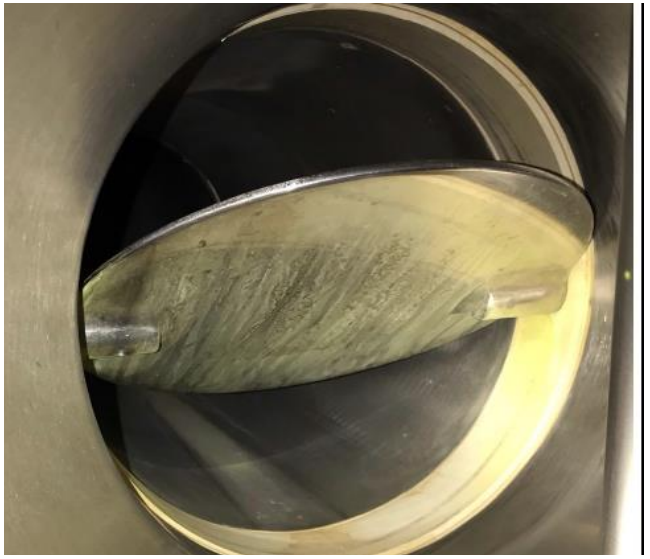
Emerging Trend in India: Cross Contamination via Ductwork

History Repeats Itself…

- **In 2019**

  FDA conducted an inspection of a Indian generic drug product manufacturer making a multitude of drugs (include potent compounds) on non dedicated fluid bed dryers





Emerging Trend in India: Cross Contamination via Ductwork

History Repeats itself…

- **Analytical testing confirms severity of the issue**
  - Analysis of residues and swab samples confirm drug carryover in ductwork
  - Retain sample analyses confirm resulting cross contamination in finished drug products

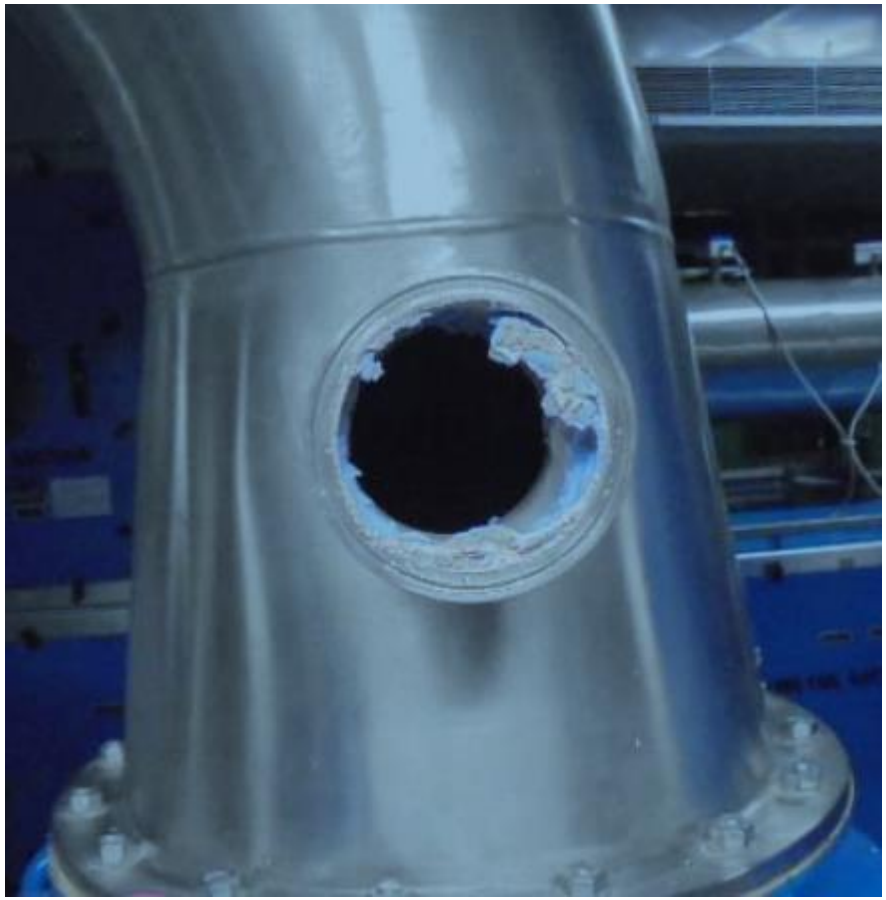
- **Recall of numerous batches ensues**

- **Warning Letter issued**

Emerging Trend in India: Cross Contamination via Ductwork

History repeating, but not just Fluid Beds….

- Another 2019 inspection of a generic manufacturer in India found material carryover in duct work of non dedicated fluid bed dryer and tablet coater ductwork



Emerging Trend in India: Cross Contamination via Ductwork

History repeating, but not just Fluid Beds….

- Sample analysis also confirmed cross contamination between drug products
  - For drugs made on non-dedicated fluid beds
  - For drugs made on non-dedicated tablet coaters

- Note, while levels may vary, cross contamination cannot be assumed to be uniformly distributed
  - Positive test results, even below calculated permissible daily exposure (PDE) levels, are of concern

- Warning Letter Issued

In Summary

In Summary

- CGMP Regulatory Actions have increased as FDA inspected the “uninspected,” typically OTC sites.
- The majority of Indian manufacturers have acceptable inspection outcomes.
- However CGMP problems related to sterile manufacturing, data integrity, and OOS result investigations persist.
- A recent trend of cross contamination associated with duct work for non dedicated equipment has emerged.

In Summary

- OMQ works to minimize consumer exposure to unsafe, ineffective, and poor quality drugs.
- We take actions against firms with poor CGMP or when other information calls into question the quality of drugs for U.S. patients.

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION