# Active Pharmaceutical Ingredient (API) Manufacturing Facility Inspections

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Drug Master File and Drug Substance Workshop
CDER Small Business and Industry Assistance
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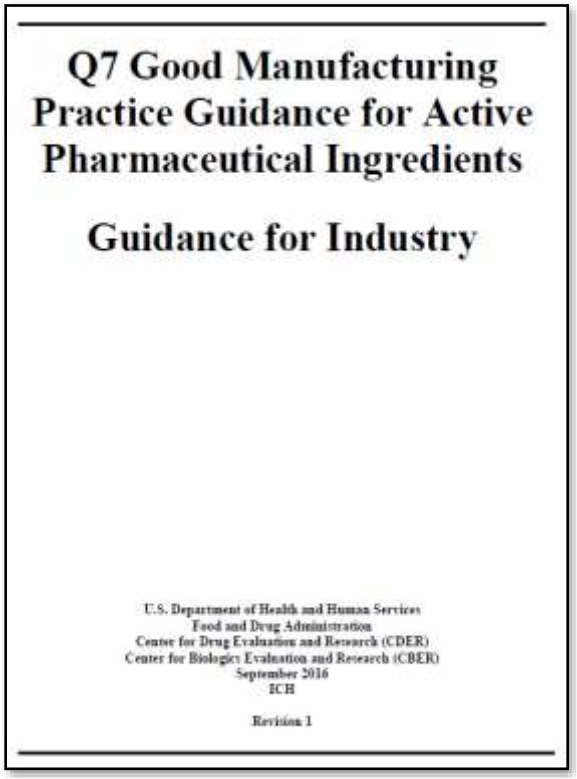
# Agenda

1. Regulatory Authority for API Manufacturers
2. Site Selection and Inspection Types
3. Responding to FDA Form 483
4. API Manufacturers Deviation Themes

# Regulatory Authority for API Manufacturing


Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Guidance for Industry

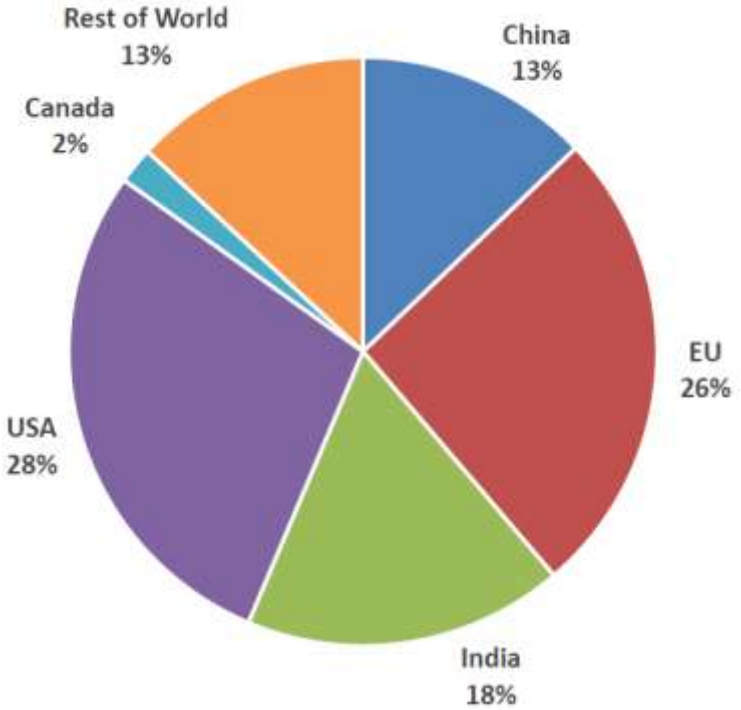
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 2016
ICH

Revision 1

- Statutory authority for API Current Good Manufacturing Practices (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

# API Manufacturing Facilities Supplying the U.S. Market*



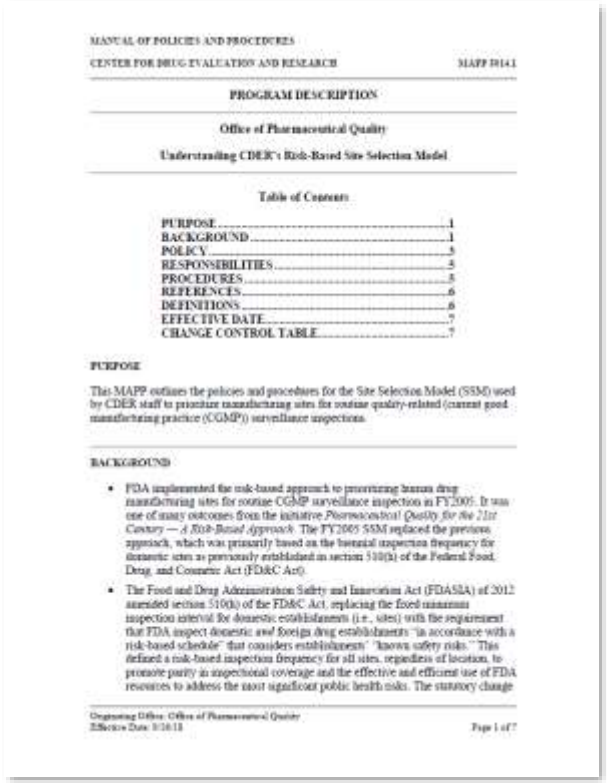

More than 70% of API manufacturing facilities supplying the United States market are located overseas

* as of December 2019



https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Updated%20Testimony%20-%20Woodcock%20%28FDA%29%2020191210.pdf

# CDER's Surveillance Site Selection Model (SSM)



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5014.1

PROGRAM DESCRIPTION

Office of Pharmaceutical Quality

Understanding CDER's Risk-Based Site Selection Model

Table of Contents



PURPOSE

This MAPP outlines the policies and procedures for the Site Selection Model (SSM) used by CDER staff to prioritize manufacturing sites for routine quality-related (current good manufacturing practice (CGMP)) surveillance inspections.

BACKGROUND

- FDA implemented the risk-based approach to prioritizing human drug manufacturing sites for routine CGMP surveillance inspection in FY2005. It was one of many outcomes from the initiative *Pharmaceutical Quality for the 21st Century — A Risk-Based Approach*. The FY2005 SSM replaced the previous approach, which was primarily based on the biennial inspection frequency for domestic sites as previously established in section 510(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
- The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended section 510(h) of the FD&C Act, replacing the fixed minimum inspection interval for domestic establishments (i.e., sites) with the requirement that FDA inspect domestic *and* foreign drug establishments "in accordance with a risk-based schedule" that considers establishments' "known safety risks." This defined a risk-based inspection frequency for all sites, regardless of location, to promote parity in inspectional coverage and the effective and efficient use of FDA resources to address the most significant public health risks. The statutory change

Originating Office: Office of Pharmaceutical Quality
Effective Date: 9/16/13 Page 1 of 7

- Inherent Product Risk
- Facility Type
- Patient Exposure

*Fairly* Static

- Inspection History
- Time Since Last Inspection
- Hazard Signals

Dynamic

# Types of Inspections

- Pre-approval Inspections
- Surveillance Inspections
- For-cause Inspections

# FDA Form 483

- The FDA Form 483, provided at the conclusion of an inspection, notifies the company's management of objectionable conditions

- Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and implement corrections expeditiously

Photo: FDA

# Responding to an FDA 483 Gives a Firm an Opportunity to Provide

- An assessment of distributed products' quality based on the observational findings
- Details on how the firm has addressed the observations and/or plans to address the observations
- The conditions or systemic issues that led to the observations occurring
- Additional information such as information on the scope of the issues, impact to other drugs, and whether the observations are isolated incidents or global in nature

# Tips for Responding to FDA Form 483

- If an observation is not clear, ask during the closeout meeting
- Recommend responding to verbal observations in the response*
- If we receive a response more than 15 business days after issuance, we do not plan to routinely include a response on the apparent adequacy of the corrective actions in a subsequent action
  - For actions that cannot be completed within 15 business days, recommend including a plan addressing the observations, including timelines and deliverables

*See Investigations Operations Manual 5.11.4.3.15

# Advice for Response Content

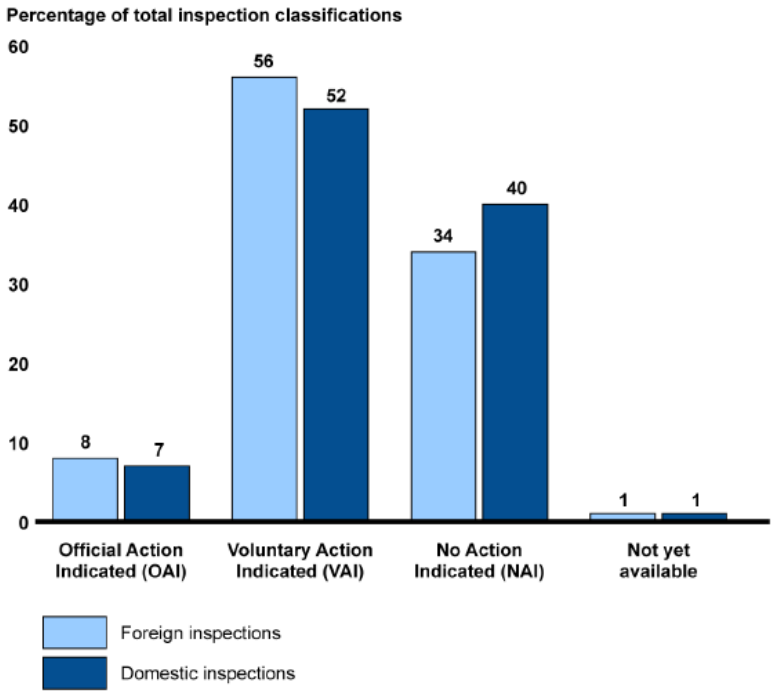
- A patient- and product-focused risk assessment of the observations, including an assessment of distributed products.
- A detailed response to each observation, including the comprehensive investigation plan; the CAPA plan; a summary of completed actions, including interim actions; and a planned effectiveness check, with any results.
- A communication plan, including timelines, to update FDA on any incomplete items.
- A copy of the FDA 483 issued at the close of the inspection.

# Inspection Outcomes

- *No Action Indicated (NAI)* means that no objectionable conditions or practices (e.g., quality problems) were found during the inspection (or they were minor problems that do not justify further regulatory action)

- *Voluntary Action Indicated (VAI)* means objectionable conditions or practices were found but the Agency is not prepared to take or recommend any administrative or regulatory action.

- *Official Action Indicated (OAI)* means regulatory and/or administrative actions will be recommended




**FDA Inspection Classifications for Foreign and Domestic Drug Establishments by Type of Classification, Fiscal Year 2012 through 2018**

Source: GAO Analysis of FDA data | GAO-20-626T

# Alternative Approaches to Inspections During COVID-19 Pandemic

# COVID-19's Impact on Inspections

- Protecting safety and security of drug supply chain is one of FDA's highest priorities
- Mission-critical inspections continue, including pre-approval and for-cause inspections deemed mission-critical
- ORA using COVID-19 Advisory Rating system to determine when other inspections may be conducted
- Visit fda.gov webpage for all current information
(https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19#inspections)

## Manufacturing, Supply Chain, and Drug Inspections | COVID-19

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**On this page**

- Developing and Manufacturing Drugs Including Biologics
- Inspections Q&A
- Records Requests in Support of Application Assessment
- Contact Us
- References

FDA has guidance on how to implement manufacturing process and facility changes, and the process for reporting these types of changes to the application in the references below.

### Developing and Manufacturing Drugs, Including Biologics, for Treating or Preventing COVID-19

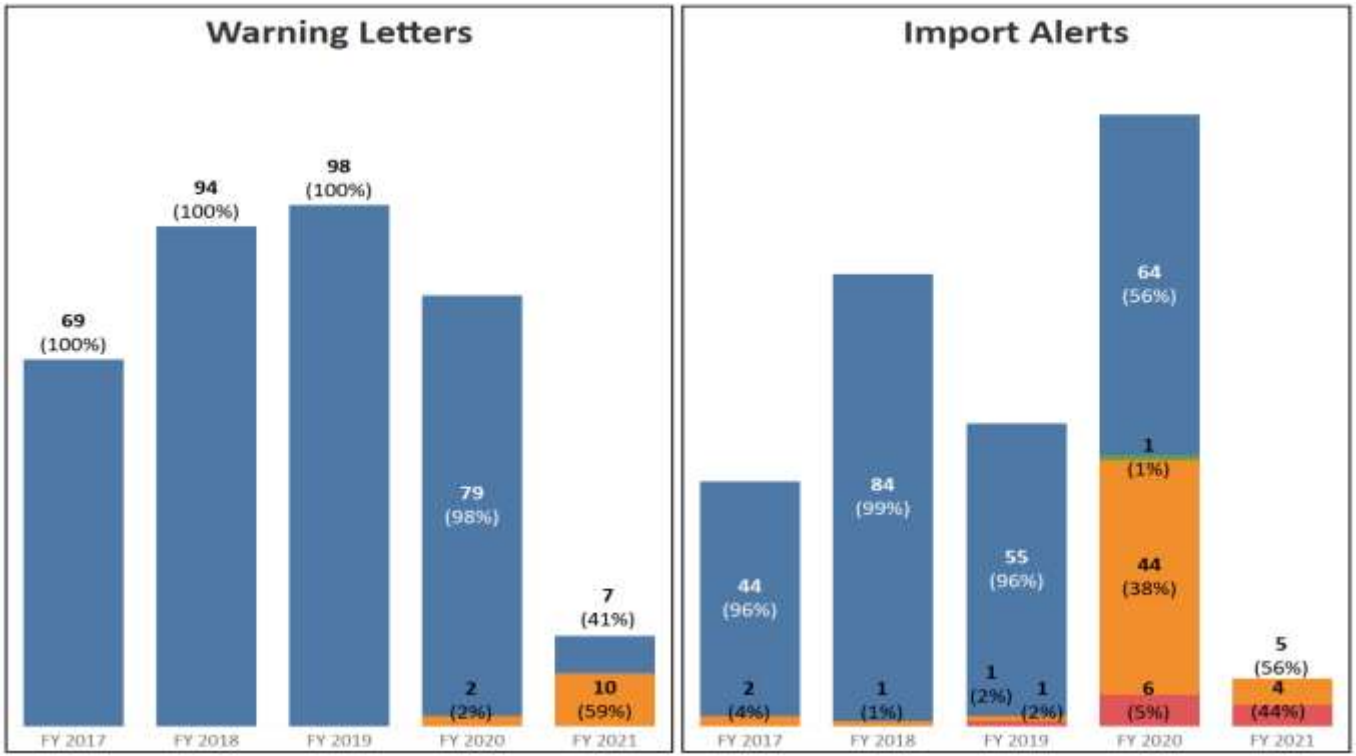
FDA is committed to helping get medical products to market quickly and to helping ensure that these products are safe, effective and high quality. Manufacturers, applicants and sponsors, including those working under U.S. government contracts, must comply with the applicable laws and regulations that govern drug development and manufacturing to protect the public health, including during the COVID-19 outbreak.

As part of this commitment, FDA provides information to stakeholders concerning drug and biologics development and manufacturing, including for products to diagnose, cure, mitigate, treat or prevent COVID-19 and for other critically needed products to treat symptoms of COVID-19 or to provide supportive care to those with COVID-19.

# Use of Alternative Tools

- FDA utilizing alternative approaches to provide oversight and take regulatory actions, including:
  - Sampling
  - Using information shared by foreign regulatory partners
  - Requesting records and information

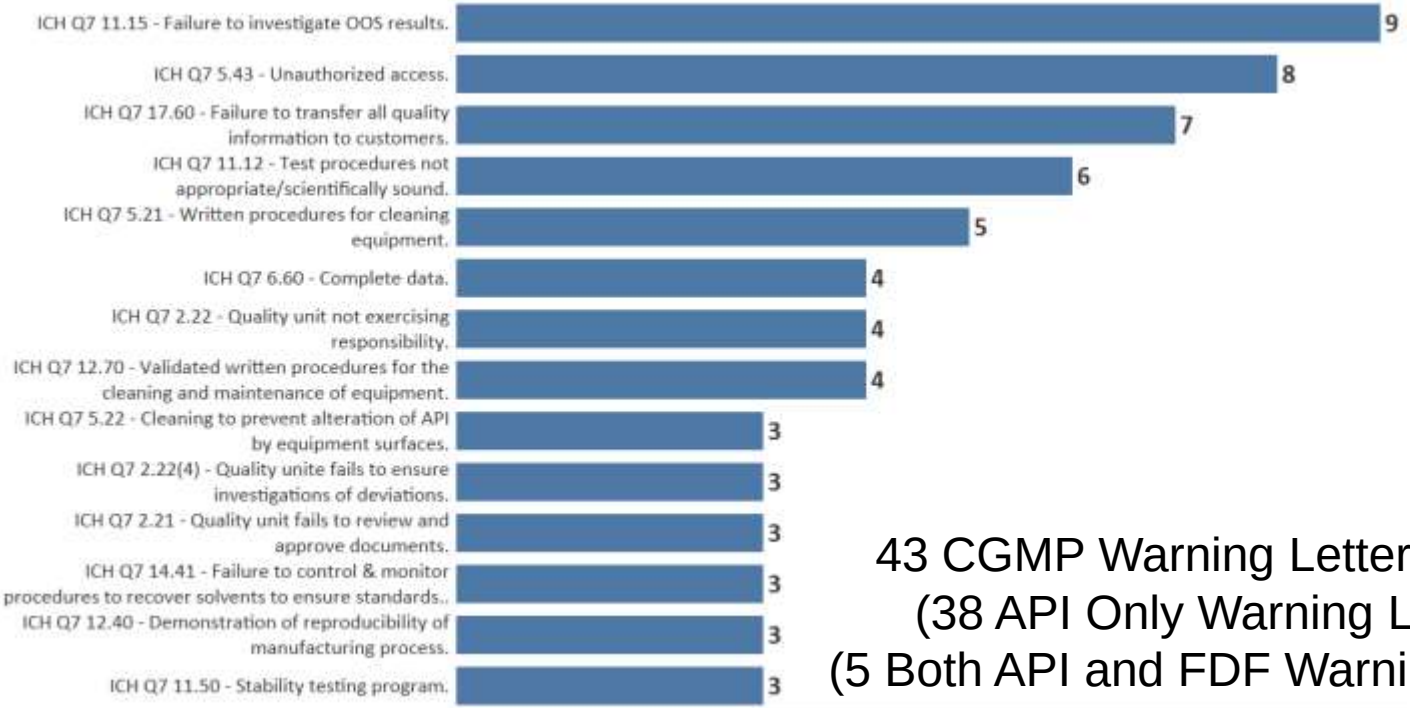
# Shift in Source for Drug Adulteration Regulatory Actions*




*as of 11/30/2020

# API Manufacturers
# CGMP Deviation Themes

# Most Common CGMP Deviations* for API Manufacturers on Warning Letters FY2018-FY2020




43 CGMP Warning Letters Issued
(38 API Only Warning Letters)
(5 Both API and FDF Warning Letters)

*Q7 references for categorization only

U.S. FOOD & DRUG ADMINISTRATION

# Investigations

# Production and Laboratory Investigations – Key Themes

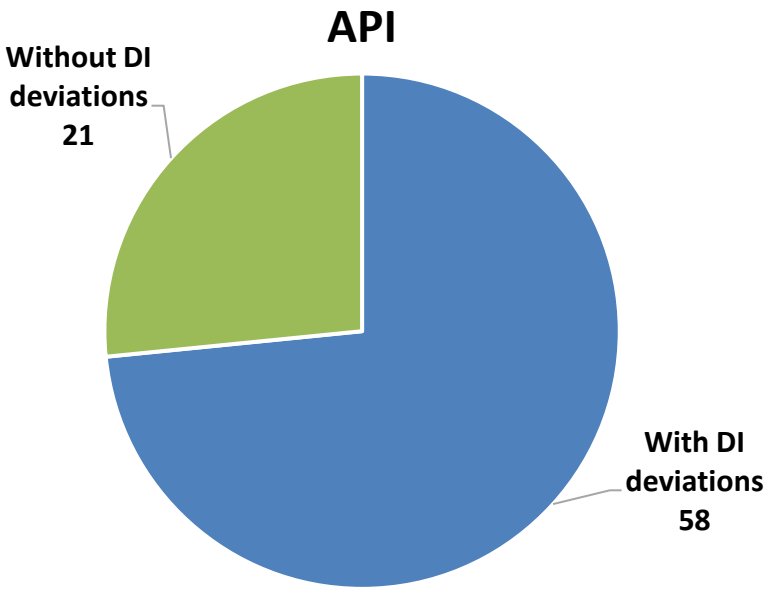
- Investigation and corrective actions that do not address deviations in a systemic way
- Conclusions not supported by evidence
- No product impact assumed based on analytical testing
- Analytical method variability blamed for the OOS without adequate justification
- Failure to investigate atypical peaks
- Not extending investigation to manufacturing (Phase II) if root cause is not conclusively identified and justified during Phase I
- Human error is frequently cited as a root cause in failure investigations
- Re-training is too often the corrective action for events deemed to be caused by human error

Out-of-Specification Guidance – https://www.fda.gov/media/71001/download
Quality Systems Guidance - https://www.fda.gov/media/71023/download


# Data Integrity

# Data Integrity

**Warning Letters Issued to API Manufacturing Facilities Containing Data Integrity Deviations (FY16-FY19*)**




73% of Warning Letters issued, between FY16 and FY19*, to API manufacturing facilities contained Data Integrity deviations

FY = October 1 to September 30
FY19* = October 1 to August 16, 2019

# Data Integrity – Key Themes

- Unreported OOS results or failures with no justification or explanation
- Deleting data
- Discarding or deleting results without justification and re-running/retesting samples
- Backdating and fabricating data
- Altering time clock to misrepresent testing date/time
- Activities not recorded contemporaneously
- Changing name of a sample to a standard
- Running sample from different lot
- Aborting run based
- Trial injections on stand alone equipment
- Copying existing data as new data
- Uncontrolled access to computer systems
- Disabling or deleting audit trails
- Manipulating integration parameters, sample weights, etc.
- Pre-filling batch records
- Duplicate batch records
- Disconnecting system during run

# Data Integrity – Remediation Tips

- Scope: Systems involved in DI and other related systems that could have similar problems
  - Production and process records (validation batches, biobatches, etc.)
  - Testing equipment, records and associated meta data
  - Investigations
  - Equipment (deleted, altered, missing records; aborted sequences)
- Causes of DI breaches:
  - Procedural, documentation-related, personnel, system related, quality culture, or other
- Risk assessment to evaluate impact on product and patient
- Identify gaps that allowed DI issues to occur without detection
- Impact on approved and pending applications
- Time frame and products

Data Integrity Guidance – https://www.fda.gov/media/119267/download

# Key Messages

- For patient safety and supply chain transparency, API manufactures must follow all quality standards – including clearly identifying the expectations from their suppliers and service providers
- 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

# Thank You!

- Send questions regarding this presentation to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar April 9, 2021.
- Please refer to the following presentations on March 3rd and 4th for additional information: *API Manufacturing Facility Inspections.*