Overview of Drug Manufacturing Inspections

Understanding FDA Inspections and Data Webinar
September 6, 2023

Overview

- Applicable Manufacturing Standards
- Understanding CGMP Inspections and 483s
- How FDA Reviews Inspectional Findings
- FDA Regulatory Actions
- Where to find inspection and other compliance documents

Applicable Manufacturing Standards

Jennifer Maguire
Director, Office of Quality Surveillance
Office of Pharmaceutical Quality
CDER | US FDA

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Drug Manufacturing Standards

- All drugs must be manufactured under Current Good Manufacturing Practice per section 501(a)(2)(B) of the FD&C act
  - Applies to prescription and non-prescription drugs (e.g., drugs approved under section 505(c) or 505(j) of the FD&C Act, OTC monograph drugs, certain compounded drugs)

- CGMP standards are further specified based on drug type, e.g.:
  - CGMP Regulations for finished pharmaceuticals (21 CFR 210, 211) and Positron Emission Tomography drugs (21 CFR 212)
  - CGMP Guidance for Active Pharmaceutical Ingredient manufacture (ICH Q7)

- For application products, inspections of manufacturing facilities may be conducted prior to approval to assess CGMP compliance, ability to meet application commitments, and data integrity.

Facilities That Are Inspected

- Facilities are required to register with FDA and list their products.
- After a facility starts manufacturing, they are subject to routine CGMP surveillance inspections based on risk-based site selection model.
- If warranted by information, facilities may be subject to “For Cause” inspections.

CDER's Risk-Based Site Selection Model (SSM)

Purpose

To prioritize manufacturing sites (aka facilities) for routine CGMP surveillance inspections.* These inspections ensure that sites consistently manufacture drug products of acceptable quality and minimize patient and consumer exposure to adulterated drug products.

Background

The SSM was originally developed for FY2005 and updated several times to meet statutory requirements. It uses multiple risk factors that relate to drug product quality and the sites that manufacture them.

Statutory Foundations

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 sites with a risk-based schedule.

Additional Information

The SSM Work Group reviews the SSM annually and changes are approved by the SSM Steering Committee. Additional SSM information is available in CDER MAPP 5014.1.

*Excludes human drug compounding outsourcing facilities registered under section 503B of the FD&C Act (21 U.S.C. 353b), medical gas sites, inactive ingredients (excipients), and drugs intended for use only in clinical trials

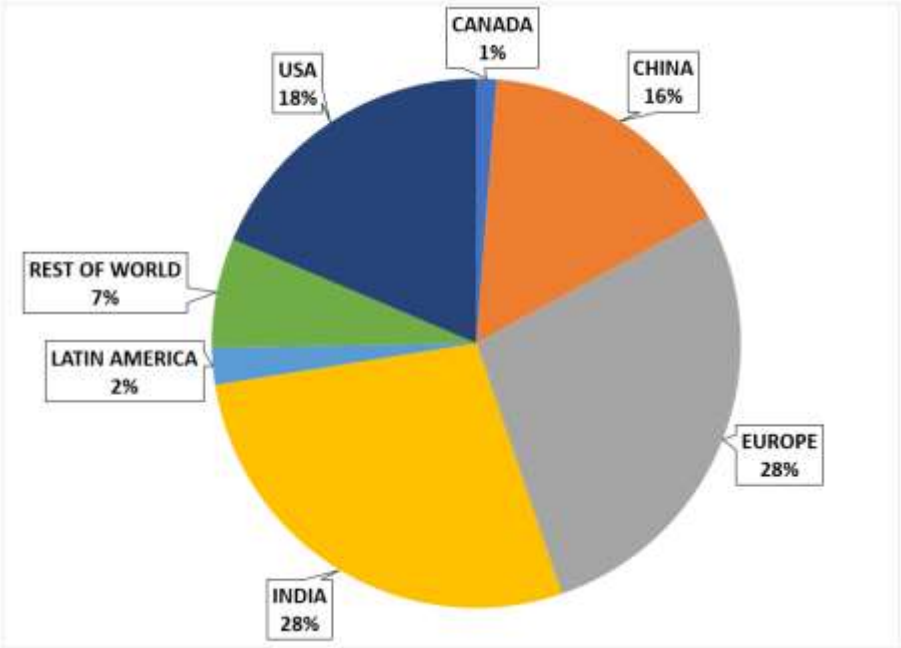
Risk Factors Used in the SSM

Inspections under Mutual Recognition Agreement

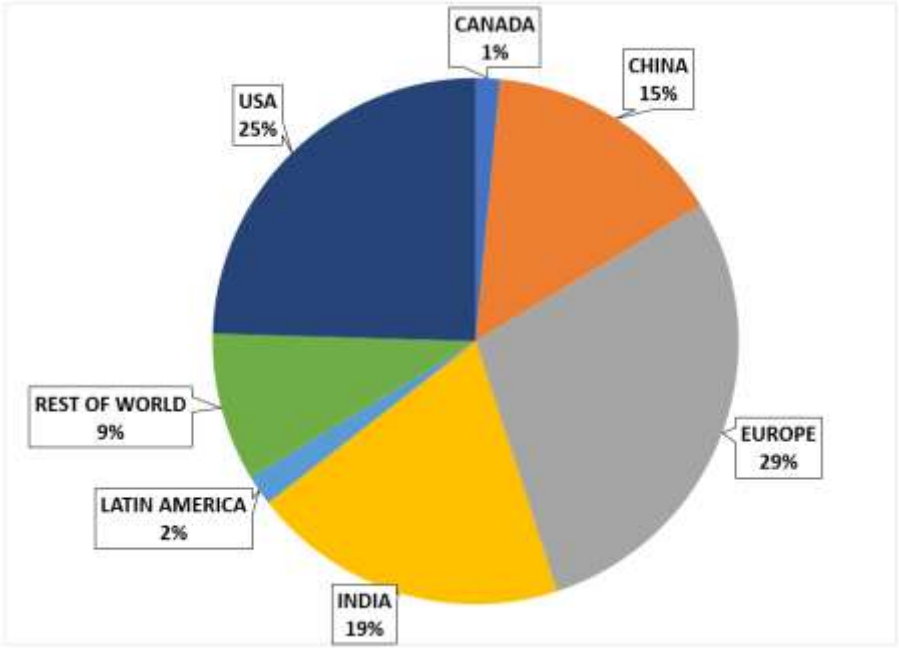
- In 2017, the U.S. entered into a Mutual Recognition Agreement (MRA) with the EU. By mid 2019, all EU Member States were assessed and found capable (with some exclusions) for CGMP inspections.
- Since FY2018, FDA has been requesting, reviewing, and classifying inspection reports from our MRA partners for sites assigned for inspection.
- In 2021, the U.S. entered an MRA with the UK, following its exit from the EU.
- In 2021, a third-country inspection assessment was done to expand the MRA scope beyond the U.S. and EU.
  - FDA can now classify inspections conducted by our MRA partners in third countries (e.g., an inspection conducted by an EU member state of a facility outside of the EU).
- In July 2023, the MRA with Swissmedic was implemented.

Location of API Manufacturers*

Generic Drug Manufacturers



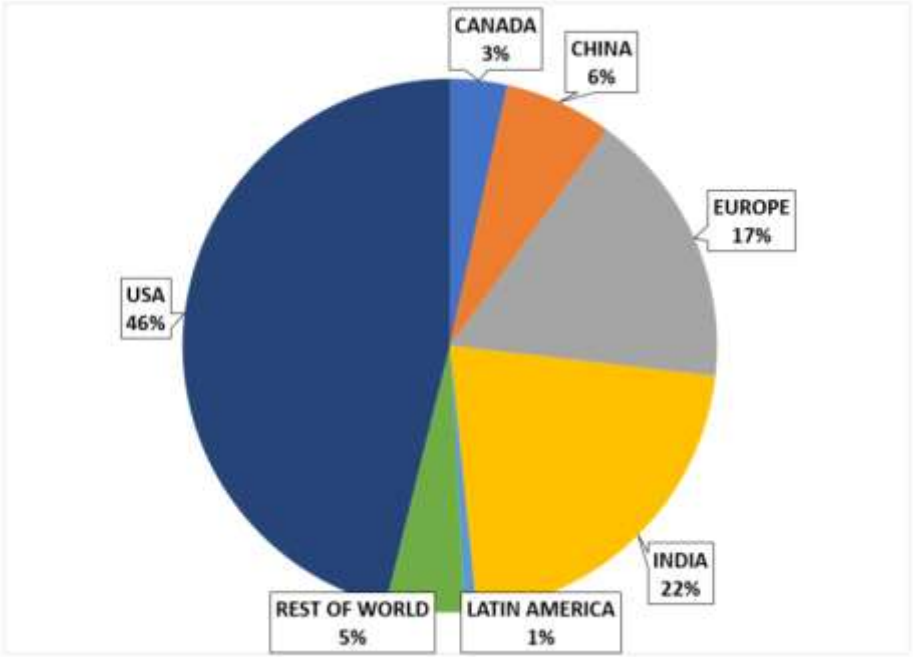
All Drug Product Manufacturers



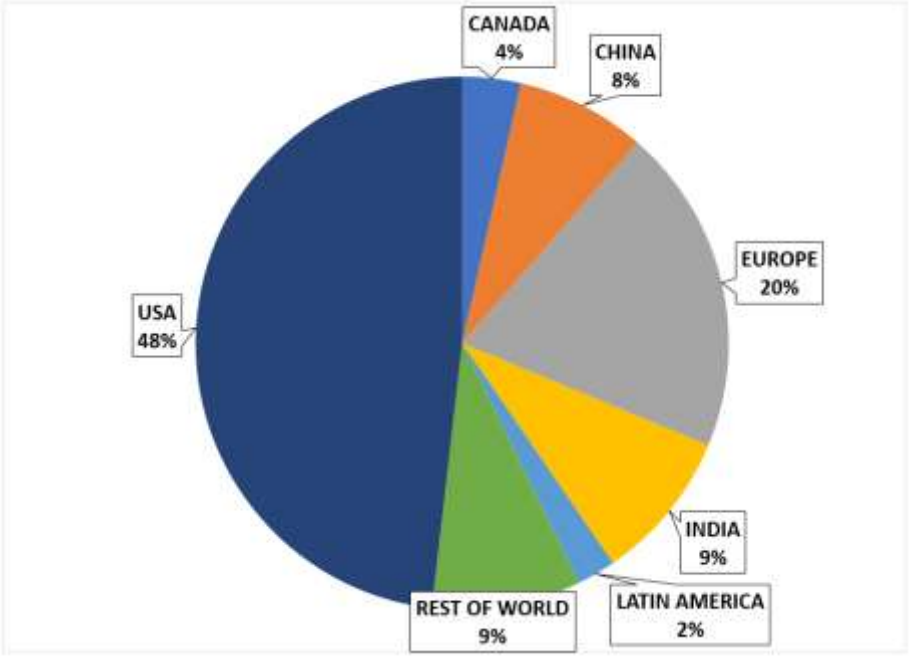
*Data as of August 14, 2023

Location of FDF Manufacturers*

Generic Drug Manufacturers

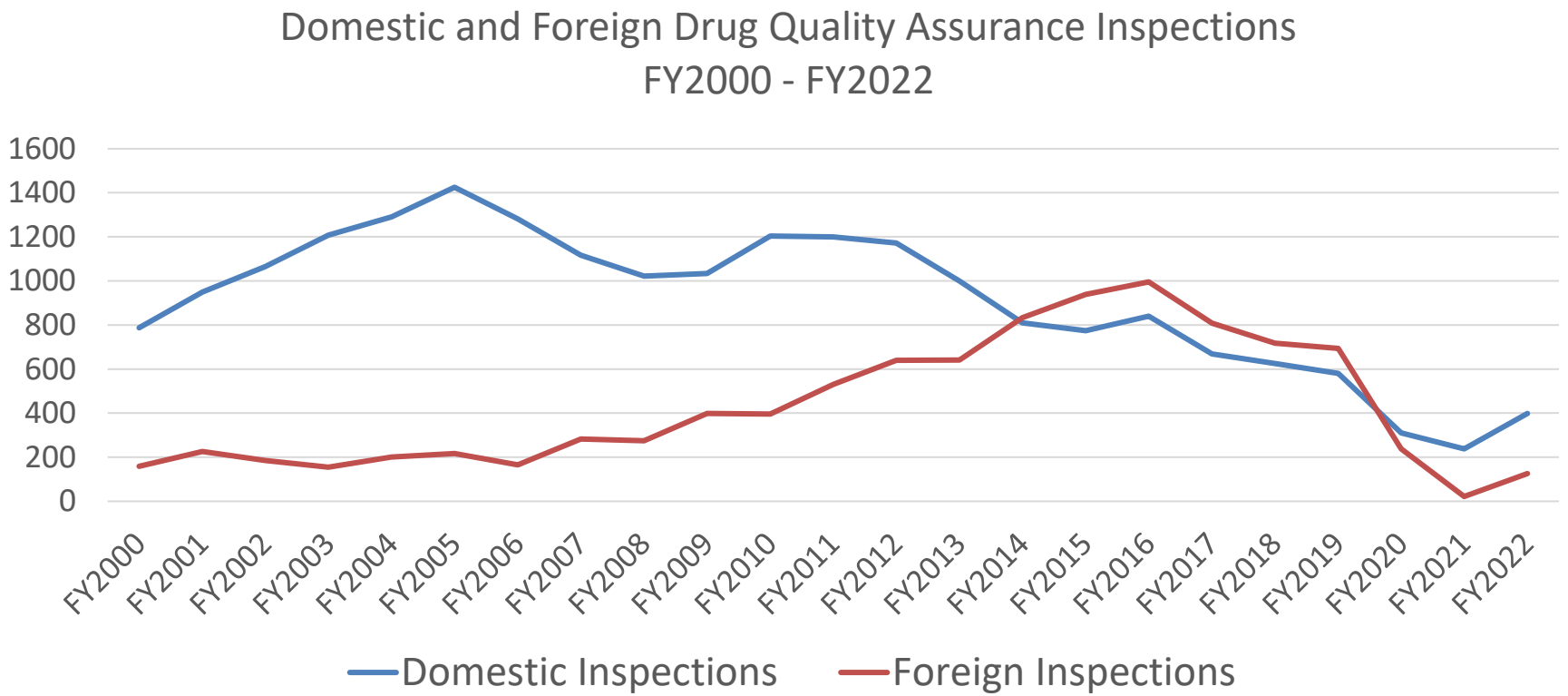


All Drug Product Manufacturers

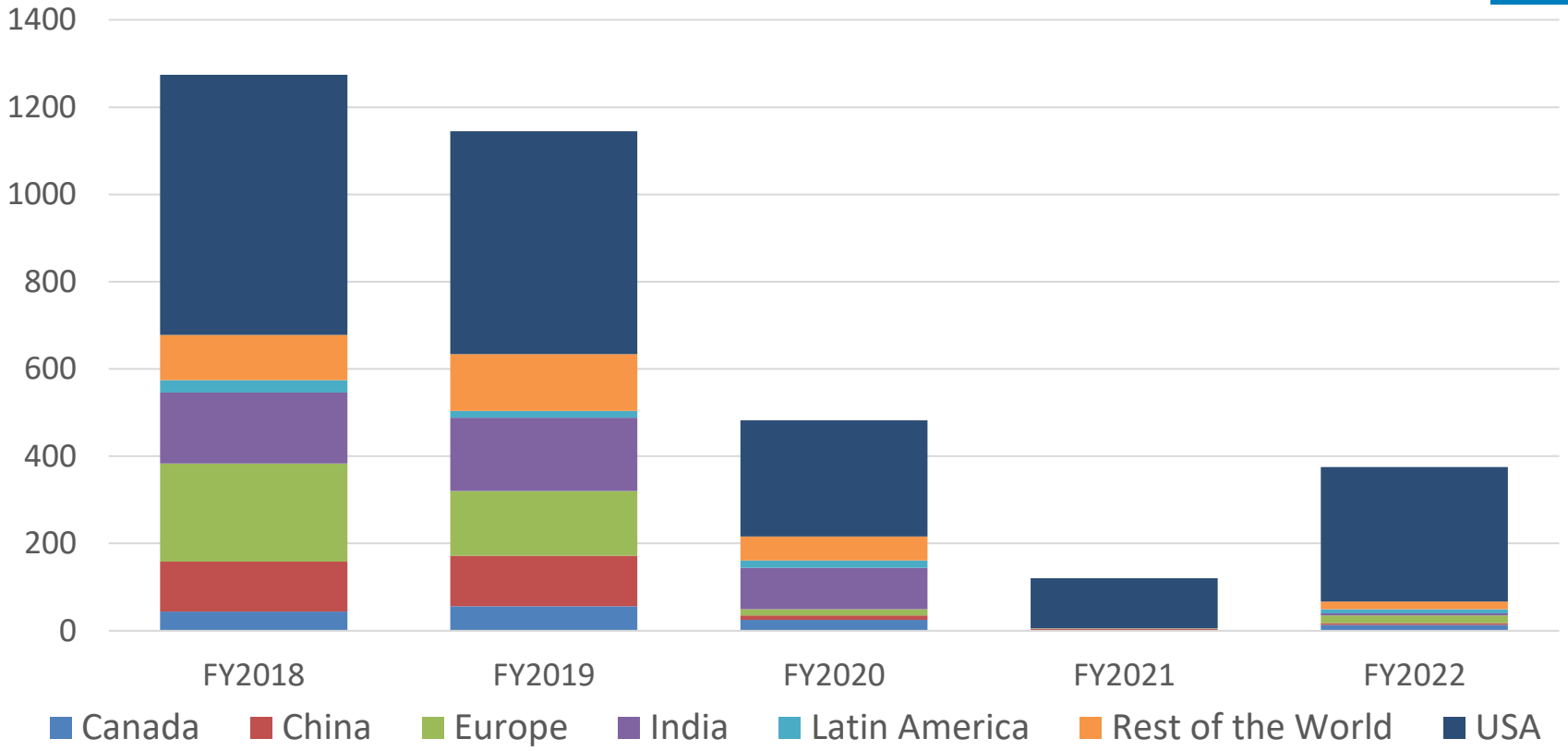


*Data as of August 14, 2023

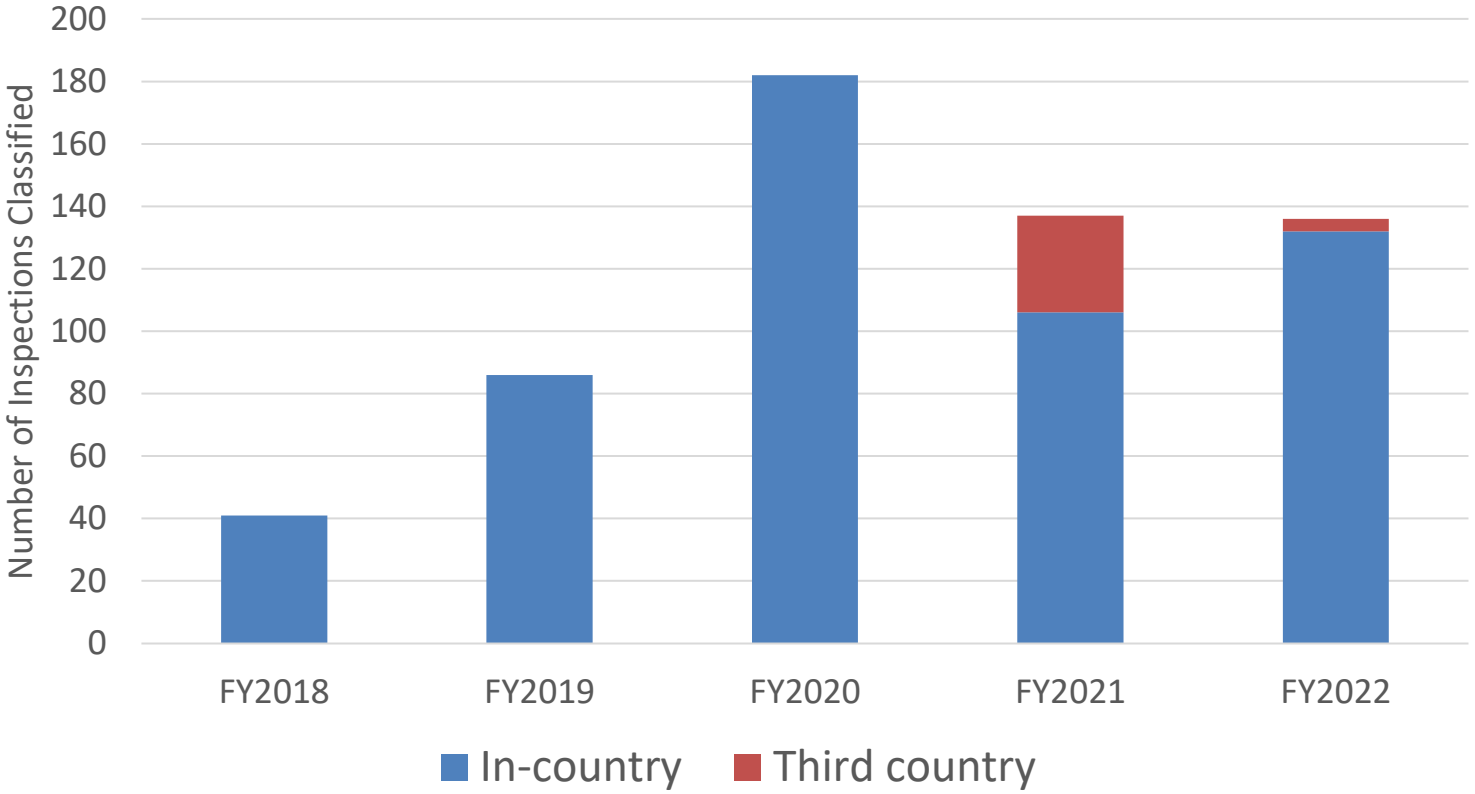
Drug Quality Assurance Inspection Counts FY2000 – FY2022



Surveillance Inspections by Region



MRA Inspections Classified by Fiscal Year



Understanding CGMP Inspections and 483s

Simone Pitts
Pharmaceutical National Expert
Office of Regulatory Affairs
US FDA

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Why an Inspection is Important

- An inspection verifies a firm's adherence to good manufacturing practice standards
- Uses a risk-based approach to focus coverage on areas of most importance to drug quality and the resulting risk to patients
- Typically, over 90-95% of drug manufacturers are found to be compliant on inspections

What is an Inspection

- During a CGMP inspection, the Investigator will utilize a 6 System risk-based approach to evaluate the firm's manufacturing operations based on CPGM 7356.002 *Drug Manufacturing Inspections*
  - Quality, Facilities & Equipment, Materials, Production, Packaging & Labeling, and Laboratory Control.
    - Drug Compliance Programs | FDA
- The Quality System is always assessed during an inspection to ensure overall compliance with CGMP standards along with additional coverage of two or more systems.

What is an Inspection

- Coverage of the system(s) is documented in an Establishment Inspection Report (EIR) with specific details of the manufacturing operations covered in order to reflect the firm is operating in a state of control.
- Items that are routinely covered during an inspection include e.g., investigation reports, equipment qualification, validation of the manufacturing process, testing of incoming raw materials and finished products and adequate analytical methods.
- Any deficiencies observed that are in violation of CGMP requirements are listed on an FDA-483.

Simone Pitts, Pharmaceutical National Expert

What a 483 is, and is not

FDA Form 483

An FDA 483 is a form provided to a company's management at the close of an inspection documenting significant deficiencies observed as defined in Investigations Operations Manual 2023 Chapter 5, Section 5.2.3 Reports of Observations:

- ***The FDA 483, Inspectional Observations is intended for use in notifying the inspected establishment's top management in writing of significant objectionable conditions, relating to products and/or processes, or other violations of the FD&C Act and related Acts which were observed during the inspection. These observations are made when in the investigator's "judgment," conditions or practices observed, indicate that any food, drug, device, or cosmetic have been adulterated or are being prepared, packed, or held under conditions whereby they may become adulterated or rendered injurious to health. The issuance of written inspectional observations is mandated by law and ORA policy.***

https://www.fda.gov/media/166533/download

FDA Form 483

- The FDA 483 only includes factual observations from the current inspection, no opinions or assumptions are allowed to be written on the 483.
- The investigator applies the current law (Food, Drug, and Cosmetic Act and related Acts) while conducting the inspection.
- Observations are listed on the FDA 483 in order of significance and details the violation that was observed.
  - 21 CFR Part 211 is the principal regulation the observation is listed under. For example, 21 CFR 211.22(a) Lack of quality control unit.
    - Observation written by the Investigator – Specifically, Your firm lacked a quality control unit that has the responsibility to oversee manufacturing operations.

FDA Form 483

- Code of Federal Regulations Title 21 Part 210 and 211 are the minimum standards that are acceptable for finished drug products.
- At the conclusion of the inspection and if a Form-483 is issued, companies are strongly encouraged to respond within 15 business days with their corrective action plan and implement the plan in a timely manner.

FDA Form 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

U.S. FDA CDER/OPQ/OS IAB, Attn: Mr. Concepcion Cruz
White Oak Building 51, Room 4316
10903 New Hampshire Avenue
Silver Spring, MD 20993
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

[redacted]

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

[redacted]

[redacted]

TYPE OF ESTABLISHMENT INSPECTED

Manufacturer, Distributor

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1:

The firm failed to validate disinfectant and sanitization procedures used in the clean controlled manufacturing areas and did not ensure that product quality is not compromised.

For example,

A. The firm has fumigated the Plant [redacted], the clean controlled Powder Processing Areas, [redacted] times in 2014, 2015, and 2016 with [redacted] disinfectant solution according to SOP AMP-044-02, titled "Fumigation in Powder Processing Area", effective date 6/25/2016, after microbiological environmental monitoring alert levels were exceeded. The Powder Processing Areas are used in finished API production, for example fo[redacted] [redacted] and [redacted] USP. When fumigation is to be done, the [redacted] solution is aerosolized to cover the entire area of a room. The firm removes equipment and product stored in the room prior to fumigation, but when product in [redacted] drums cannot be removed from the room, the procedure states the drums "shall be covered properly as to avoid cross contamination."

The firm did not do the following prior to implementing the fumigation procedure:
- Validate the sanitization to ensure that the method used to cover the product drums prevents contamination of the product from the fumigation agents.
- Establish that product quality is not impacted from the fumigation.
- Record in the fumigation logs which product in drums were left in the rooms.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[redacted]		07/06/2016

What an FDA Form 483 is not

The FDA 483 is discussed with the company's management at the close of the inspection to ensure there is a full understanding of the observations listed by the investigator and a meaningful correction action can be developed and initiated.

- ✓ The 483 issued is ***not*** an all-inclusive list of every violation observed from the law or regulation, there are instances where observations are discussed with management at the close of the inspection and not listed on an FDA 483.

The issuance of the FDA 483 is ***not*** the Agency's final communication but an opportunity to open a dialog between FDA and the firm.

- ✓ It is the beginning of FDA interactions, thus should not be misinterpreted as the final quality position of the firm. The EIR, the FDA 483, evidence and documents collected during the inspection and the response is all considered before determining further action, if any will be taken to protect public health.

How FDA Reviews Inspectional Findings

Francis Godwin
Director, Office of Manufacturing Quality
Office of Compliance
CDER | US FDA

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Review of Inspectional Findings

If a 483 is issued, a firm has 15 business days to respond with their corrective actions and further information for review

- https://www.federalregister.gov/documents/2009/08/11/E9-19107/review-of-post-inspection-responses

FDA:

- Reviews the findings/evidence collected on the inspection,
- Reviews the firm's response,
- Benchmarks the information against relevant technical/legal standards,
- Evaluates the situation for patient risk/regulatory significance,

Depending on review, FDA may concur, downgrade or upgrade the final CGMP classification.

Classification Letters Define NAI/VAI/OAI for Industry

Since Oct. 1, 2018, as part of the GDUFA commitments FDA informs firms of CGMP status within 90 days of end of inspection.

Site classifications and template letters also posted to web

Goal: Increase communication with industry (to specific manufacturing sites, to customers/sponsors) and to public

Three outcomes:

- NAI – No Action Indicated
- VAI – Voluntary Action Indicated
- OAI – Official Action Indicated

Classifications NAI/VAI vs OAI

NAI/VAI

- Firm is considered to be in an acceptable state of compliance with regards to CGMP
- NAI means no 483 was issued, VAI means a 483 was issued
- VAI also means that FDA has reviewed the content of the firm's response
- Does not generally affect approvability of pending applications under review
- Does not impact government procurement/contracts with the facility

OAI

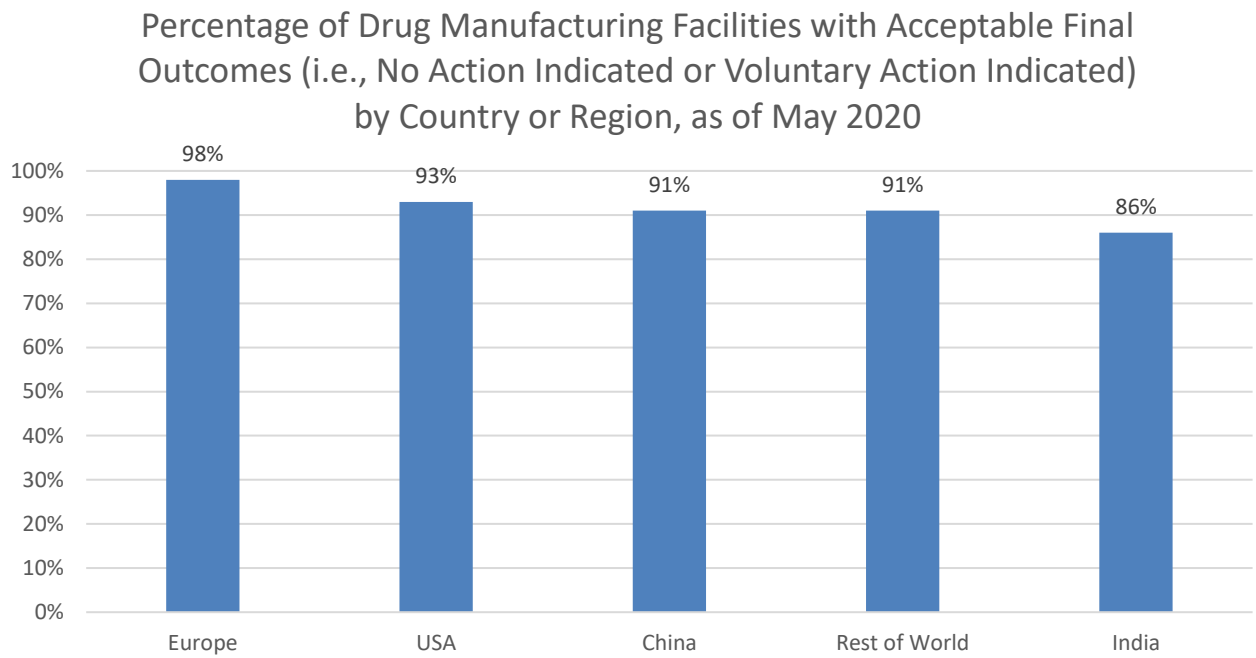
- Firm is not considered to be in an acceptable state of compliance with regards to CGMP and may be subject to regulatory or enforcement action
- Can be OAI regardless whether a 483 was issued
- May result in non-approval of pending applications
- May impact government procurement/preclude contract with the facility

Compliance Timeline Targets

Francis Godwin, Office of Manufacturing Quality Director

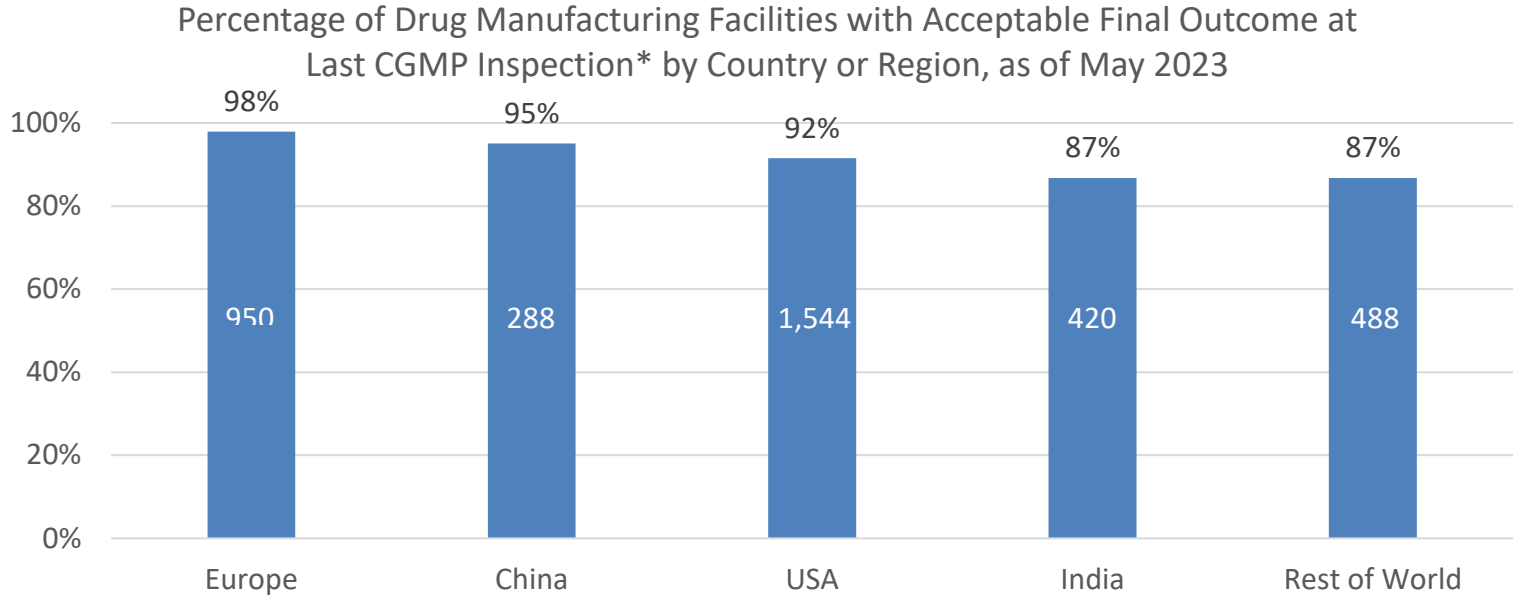
FDA Regulatory Actions

Inspection Outcomes by Region



Statement of Judith McMeekin, Pharm.D. Associate Commissioner for Regulatory Affairs, before the Committee on Finance US Senate, COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process, June 2, 2020

Inspection Outcomes by Region



*i.e., No Action Indicated or Voluntary Action Indicated outcomes, most recent inspection FY2000 to May 2023; number in bar represents total number of sites inspected with acceptable final outcomes

Shift in percentage of US sites: largely due to shift in US inspections for sites with higher OAI rates, for instance new hand sanitizer manufacturers that entered the inventory during the Pandemic.

The Compliance Toolbox

Injunction/ Consent Decrees

Seizures

Administrative Detention Orders

Import Alerts

Warning Letters

Regulatory Meetings

Untitled Letters

Response Letters

Others

Note, While most of these tools are primarily for OAI inspections, some can also be used for NAI/VAI outcomes

Perception of FDA Actions

- As with 483s, FDA often sees misperception regarding posted Warning Letter content.
  - Both from technical applicability
  - As well as what is needed to issue a Warning Letter in the first place.
- **The CGMP framework was designed to have multiple control layers in the manufacturing process**
  - This way if one layer were to fail, others can catch drugs before distribution
- The majority of Compliance Actions, such as Warning Letters, do not have (or need) evidence of failing drugs in distribution

Perception of FDA Actions

- As evidence of failing product being distributed is not necessary, a Warning Letter does not actually mean the drugs from the firm are failing specifications.

- Rather the action is usually a warning of noncompliance, with the aim that the firm fixes things before failures occur with distributed drugs.

- However, if the inspectional findings reveal failing product, or high likelihood of it, FDA will
  - ask the firm to recall.
  - and/or put out public notice via press release/or alerts.
  - Pursue more aggressive actions as needed.

Import Alert Exclusions

- If findings warrant it, FDA can place a firm on import alert, barring their drugs from legally entering the United States.
  - https://www.accessdata.fda.gov/cms_ia/ialist.html
- However, if this would lead to shortages, FDA can exclude specific drugs from the import alert.
  - **If FDA does this, we impose additional requirements on the manufacturer tailored to the specific technical issues for those drugs**.
- FDA can, and often does, conduct our own testing of imports as an additional oversight control.

Recent Import Alert Carveout Example

https://www.fda.gov/media/169115/download

What is Posted Today, and Where

Darshini Satchi
Deputy Director, Division of Information Disclosure Policy
Office of Regulatory Policy
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What is Posted Today, and Where

- Redacted CGMP inspection FDA Form 483s are generally posted only if 3 or more Freedom of Information Act (FOIA) requests are submitted, or proactively by FDA under specific conditions.
  - Trade secret/confidential commercial information is removed
- Warning Letters (WLs), and WL Closeouts, are all posted to the FDA WL page
- CGMP Import Alerts are published, including carveout drugs
- Final CGMP Classifications are posted to the inspection classification database

Document Posting Timeframes

- CGMP classifications are typically posted to the Inspections Dashboard within 1 week after an inspection is finalized
- Warning Letters typically posted within 1 or 2 weeks of issuance.
- There are no set timeframes for posting of 483s because these are only posted if there are 3 or more FOIA requests

FDA Resources and Dashboard

Rob Bughman
Project Manager, FDA Inspection Dashboard
Office of Regulatory Affairs
US FDA

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Current Locations of Various CGMP Inspection-related documents

Below are links to various document repositories on FDA's Website

- CDER Reading Room: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/cder-foia-electronic-reading-room
- ORA Reading Room: https://www.fda.gov/about-fda/office-regulatory-affairs/ora-foia-electronic-reading-room
- FDA Warning Letter Page: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
- FDA Inspections Dashboard: https://datadashboard.fda.gov/ora/cd/inspections.htm
- FDA CGMP Inspection Related Import Alert: https://www.accessdata.fda.gov/cms_ia/importalert_189.html
- Enforcement Reports: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports

FDA Data Dashboard

- Compiles and links publicly available compliance datasets (Inspection, Citations, Recalls, Compliance Actions, and Import Refusals) in one location on dashboards with easy to use, visually accessible, customizable, and understandable graphics.
- Compliance datasets are available through APIs.
- Compliance datasets are updated weekly.
- Other datasets include:
  - Import Entry
  - Laboratory Accreditation for Analyses of Foods Program
  - Accredited Third-Party Certification Program
  - Voluntary Qualified Importer Program.
  - Links to Warning Letters and Import Alerts

U.S. FOOD & DRUG ADMINISTRATION

Q&A Panel Discussion