CDER Update: The State of Pharmaceutical Quality

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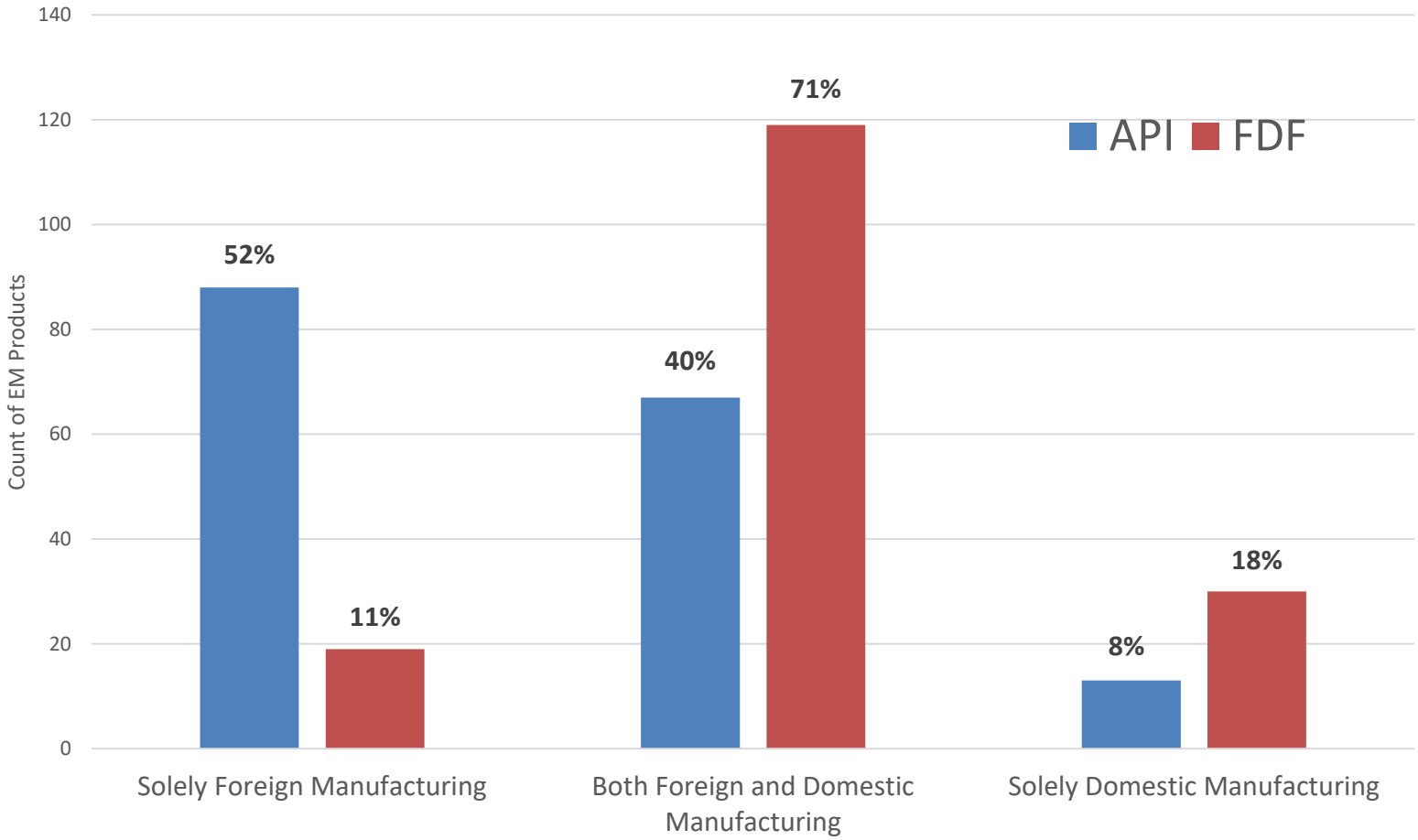
Areas We Will Cover Today

- Overview of State of Pharmaceutical Quality
- Drug Shortages
- Compliance and Inspections
- Statutory Authority Update

Overview of State of Pharmaceutical Quality

Where Essential Medicines Are Made

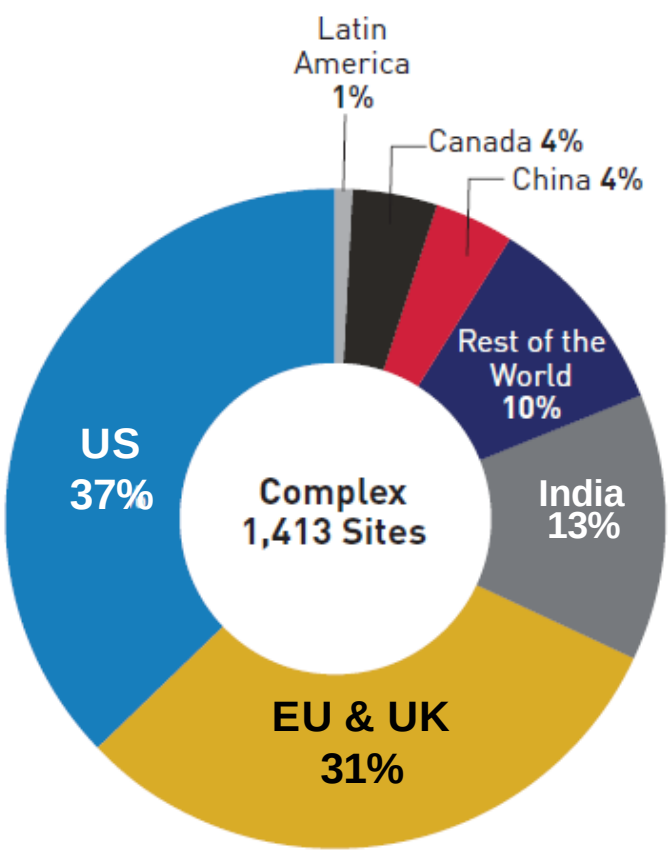
- **EM manufacturing relies heavily on foreign sites**
  - **Solely Foreign:**
    - API (blue) – 52%
    - FDF (red) – 11%
  - **Foreign + Domestic:**
    - API – 40%
    - FDF – 71%
  - **Solely Domestic:**
    - API – 8%
    - FDF – 18%

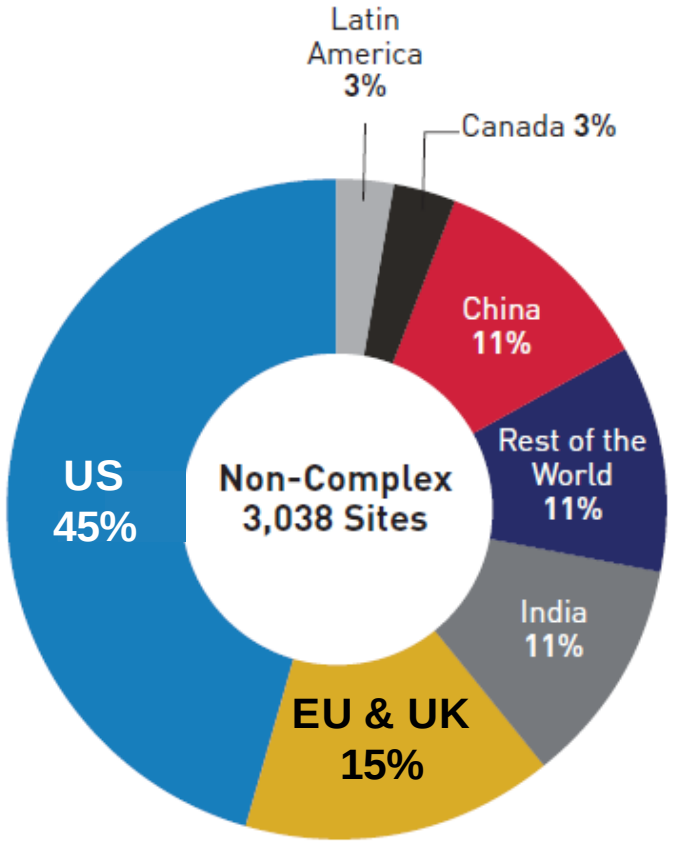


Domestic vs. Foreign Manufacturing for 168 CDER-Regulated EM Products

Source: Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality: FY2022

Where Complex Products Are Made



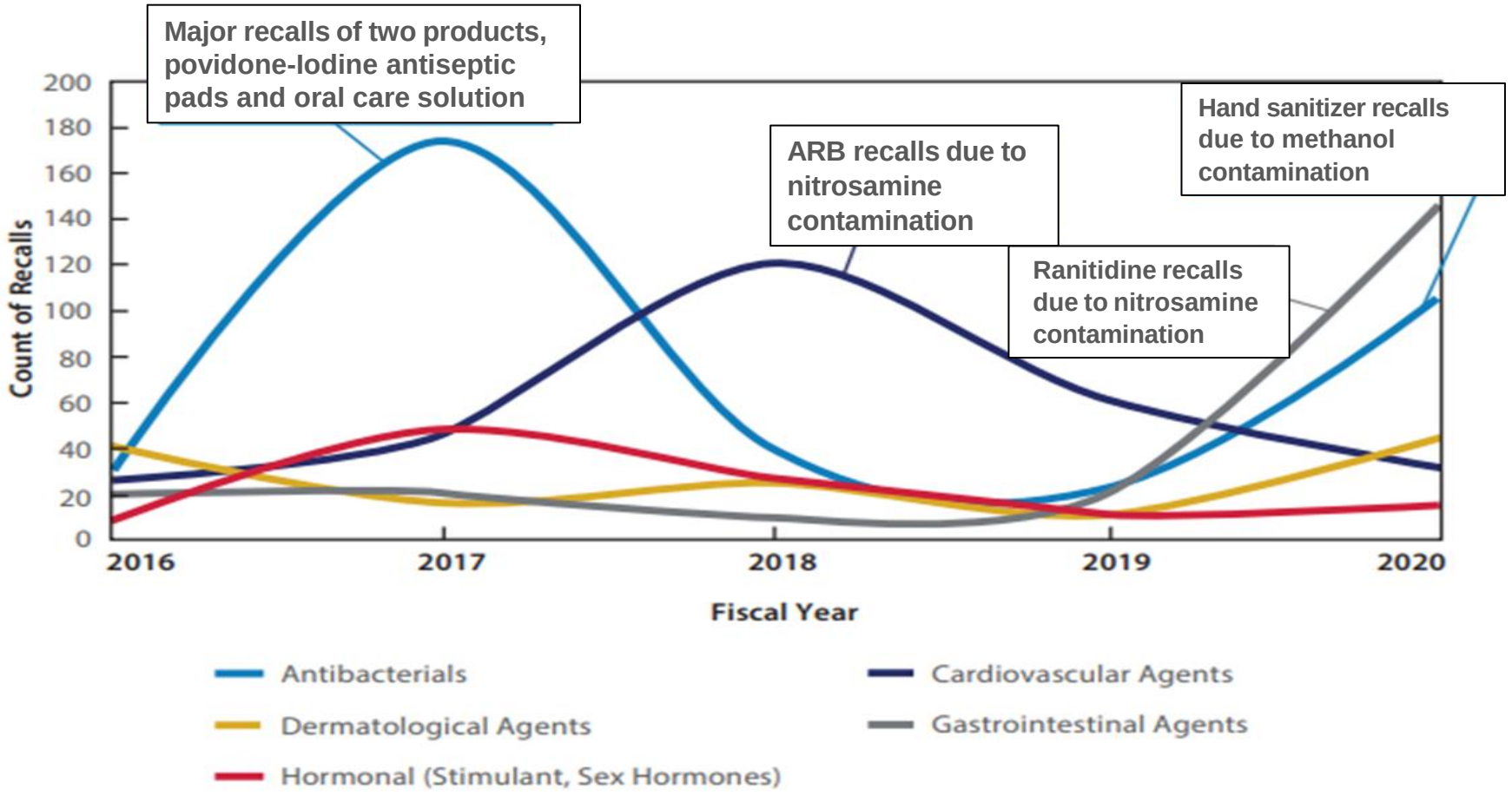


- **Complex** (1,413 sites)
  - U.S.: 37%
  - EU & UK: 31%
  - India: 13%
  - ROW: 10%
  - China: 4%
- **Non-Complex** (3,038 sites)
  - U.S.: 45%
  - EU & UK: 15%
  - India: 11%
  - ROW: 11%
  - China: 11%

Source: Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality: FY2021

A History of Drug Recalls

- **Five Most Recalled Products by USPTC FY2016-2020**
  - Povidone-iodine
    - Pads
    - Oral care
  - ARB recalls, nitrosamine contamination
  - Ranitidine, nitrosamines
  - Hand sanitizer, methanol contamination

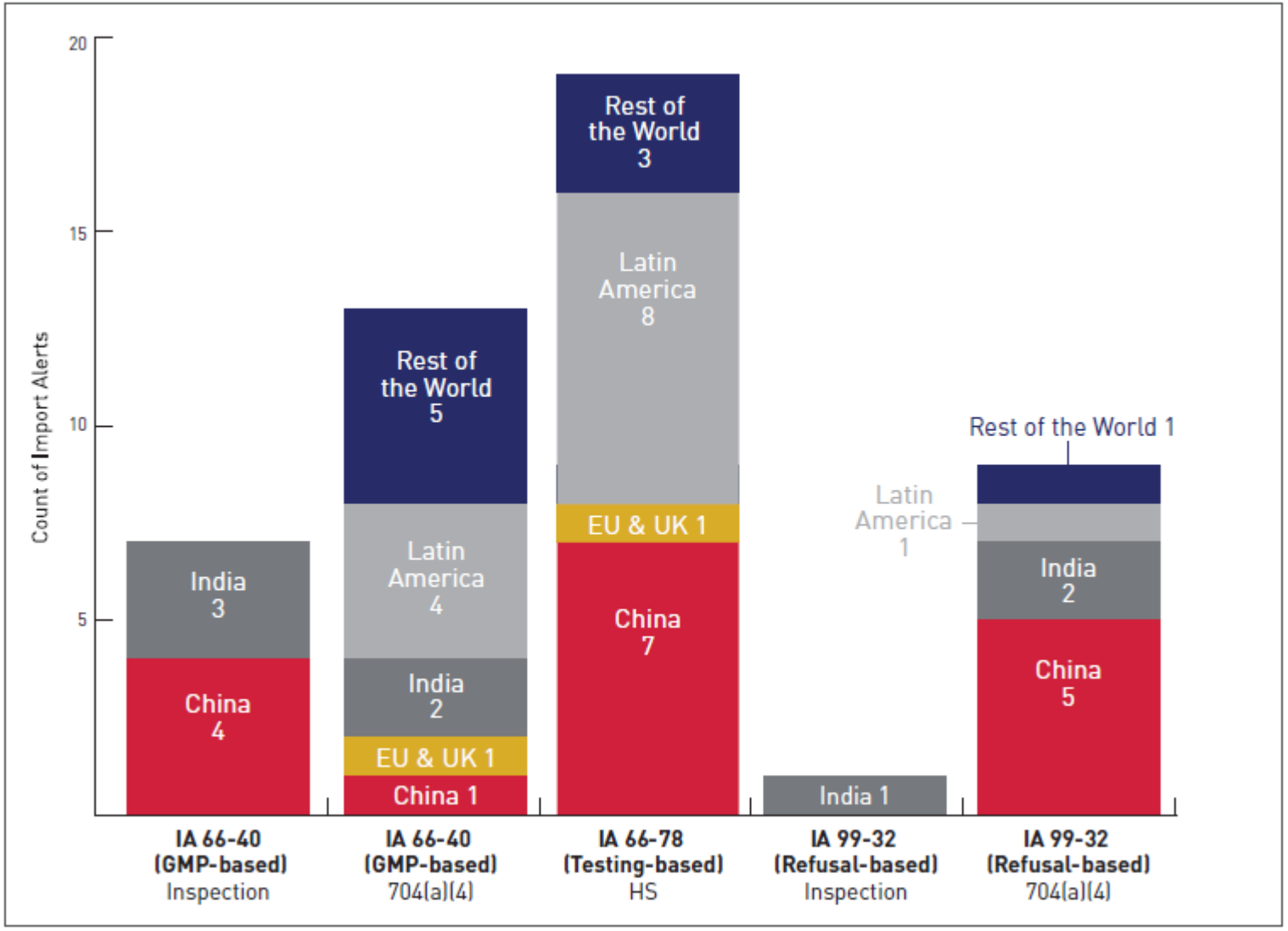


Source: Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality: FY2020

Import Alerts

- **A critical tool to keep violative, defective or potentially harmful drug products from reaching the U.S. market**
  - China, Latin America most import alerts in 2021
  - Many inspection refusal,704(a), non-compliance

Source: Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality: FY2021



Drug Shortages

Drug Shortages

- FDA's Definition
- Prevention: Early Notification is Key
  - Number of prevented shortages, CDER, 2021: **303**
  - Number of new shortages, CDER, 2021: **38**

What we CAN require:

- Notification by manufacturers (FDASIA) of:
  - Supply disruptions
  - Delays
  - Discontinuations
  - Notification of certain manufacturing changes

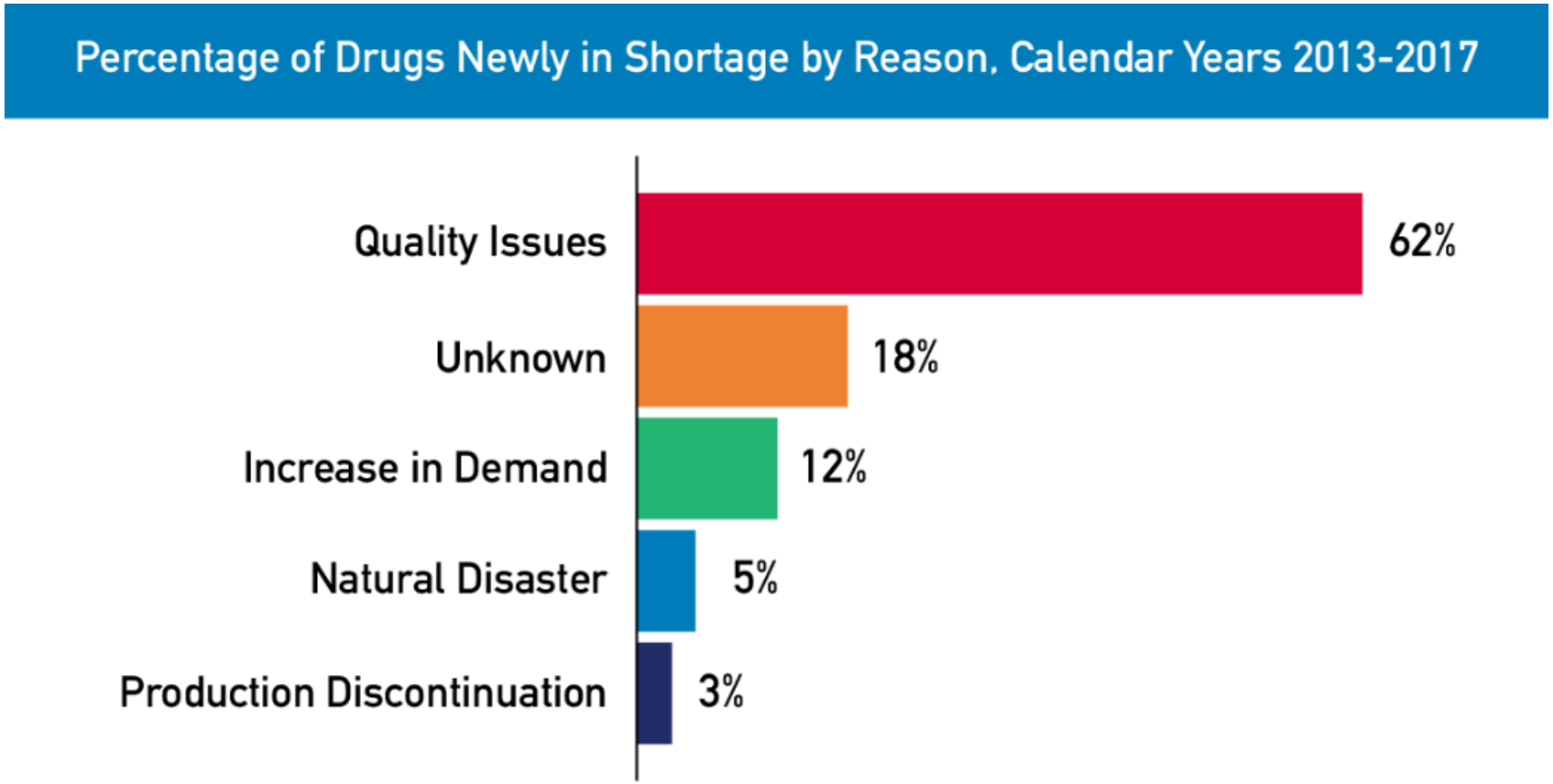
What we CANNOT require:

- A company to report an increase in demand that might lead to shortage
- A company to make a drug
- A company to make more of a drug
- A distributor to report on how much of a drug is distributed and which purchasers will be given priority

FDA's Approach to Preventing & Mitigating Shortages

- Prioritize medically necessary products
- Maintain availability while minimizing risk to patients
- Work with firms to address problems by:
  - Prompting firms to look at supply and demand
  - Expediting review of company's proposed plan to mitigate/resolve the shortage
  - Regulatory discretion, e.g., on stability data for new manufacturing line
  - Temporarily exercising regulatory flexibility and discretion regarding importation from other countries -- rare; contingencies apply
- In the event a shortage cannot be prevented, FDA and the manufacturer can work together to encourage smart distribution, aka *allocation*

Quality Issues Lead to Drug Shortages

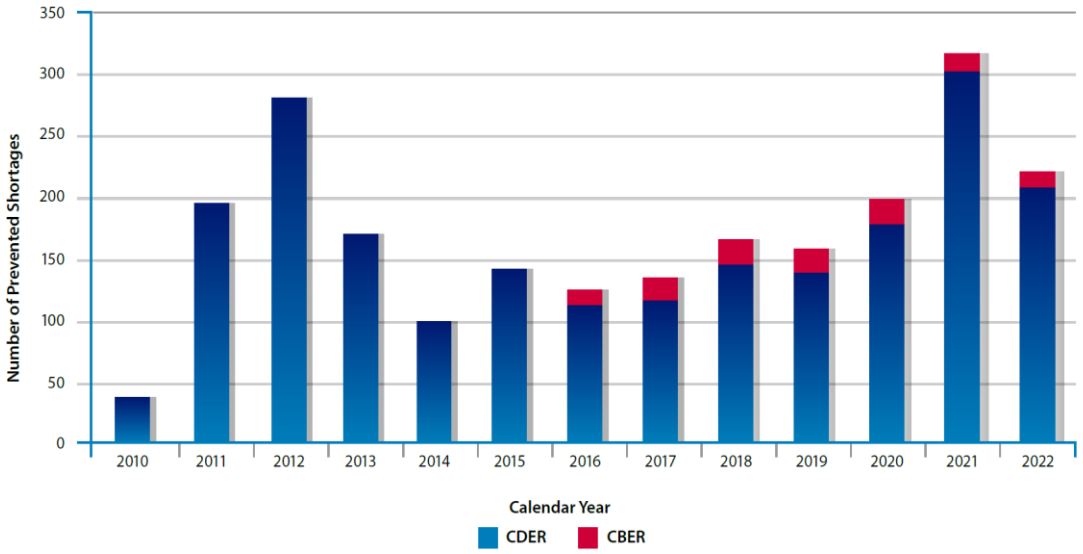


Most drugs in shortage were experiencing supply disruptions, specifically quality issues.

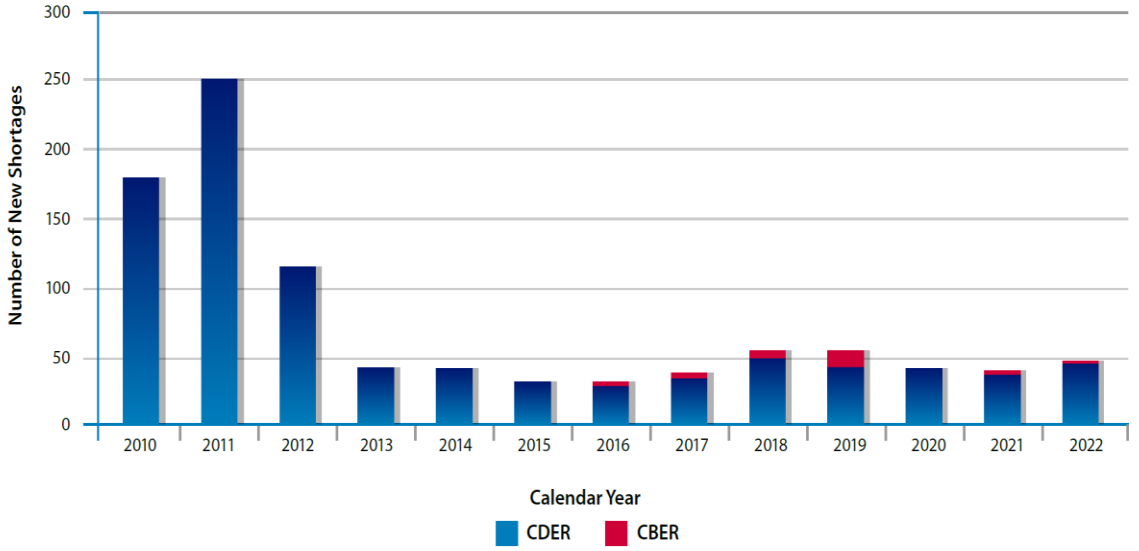
Source: Internal FDA Data

Early Planning and Notification are Key to Prevention

- The earlier this work begins the greater the likelihood a shortage can be prevented, or the most severe impacts mitigated. Risk Management Plans can support proactive planning to prevent shortages and are required for certain products.
- Through ongoing dialogue/work with industry the number of prevented shortages continues to grow, while new drug shortages remain flat.
- Depending on the precipitating events, some drug shortages can endure for months to years (e.g., plant remediations and Agency approvals).



Total Prevented U.S. Drug Shortages Per Year[1]



Total New U.S. Drug Shortages Per Year[1]

1. Annual Report on Drug Shortages for Calendar Year 2022

Manufacturing Capacity Shortfall

- **For critical drugs, there exists a US and global production capacity shortfall**
  - This is particularly true for sterile injectable drugs
  - There are no current incentives for generic drug manufacturers to produce excess over market demand (unlike other commodities)

- **This can lead to disruptions in supply which can ultimately result in shortages**
  - Disruptions can be caused by unforeseen events:
    - Natural disasters
    - Necessary compliance remediations
    - Geopolitical concerns
  - Financial pressures could lead to:
    - Manufacturing site closures
    - Firm bankruptcies

Current US Shortage of Critical Oncology Drugs

CLINICAL

Cisplatin, carboplatin shortage prompts rationing of lifesaving drugs—patients will die

By Paul Goldberg

Thousands of cancer patients across the U.S. are getting bewildering news from their oncologists:

Proven curative regimens containing platinum-based drugs—cisplatin and carboplatin—have become largely unavailable because of a nationwide drug shortage. The institutions that have some supplies of cisplatin and carboplatin are setting up algorithms for rationing their dwindling stocks, which usually means giving top priority to patients treated with curative intent and denying standard-of-care treatment to patients who cannot be cured but who can still benefit from these drugs.

Cisplatin and carboplatin are old, generic drugs. Cisplatin was first described in medical literature in 1844 (*The Cancer Letter*, April 28, 2023). Both cisplatin and carboplatin have been widely used since the 1970s. Since platinum drugs are thoroughly studied and are a staple in oncology, this means they are often present in regimens on both the experimental and control arms of clinical trials.

The New York Times

Rising Rate of Drug Shortages Is Framed as a National Security Threat

A Senate homeland security committee examined growing health care shortages amid reports of rationing within hospitals.

The New York Times

Drug Shortages Near an All-Time High, Leading to Rationing

A worrisome scarcity of cancer drugs has heightened concerns about the troubled generic drug industry. Congress and the White House are seeking ways to address widespread supply problems.

Critical Shortage of Cisplatin and Carboplatin

- Cisplatin and Carboplatin shortage
  - Inspection at one company's facility found quality issues → company temporarily shut down production
  - Demand for carboplatin (second-line therapy) then increased → manufacturers could not meet demand

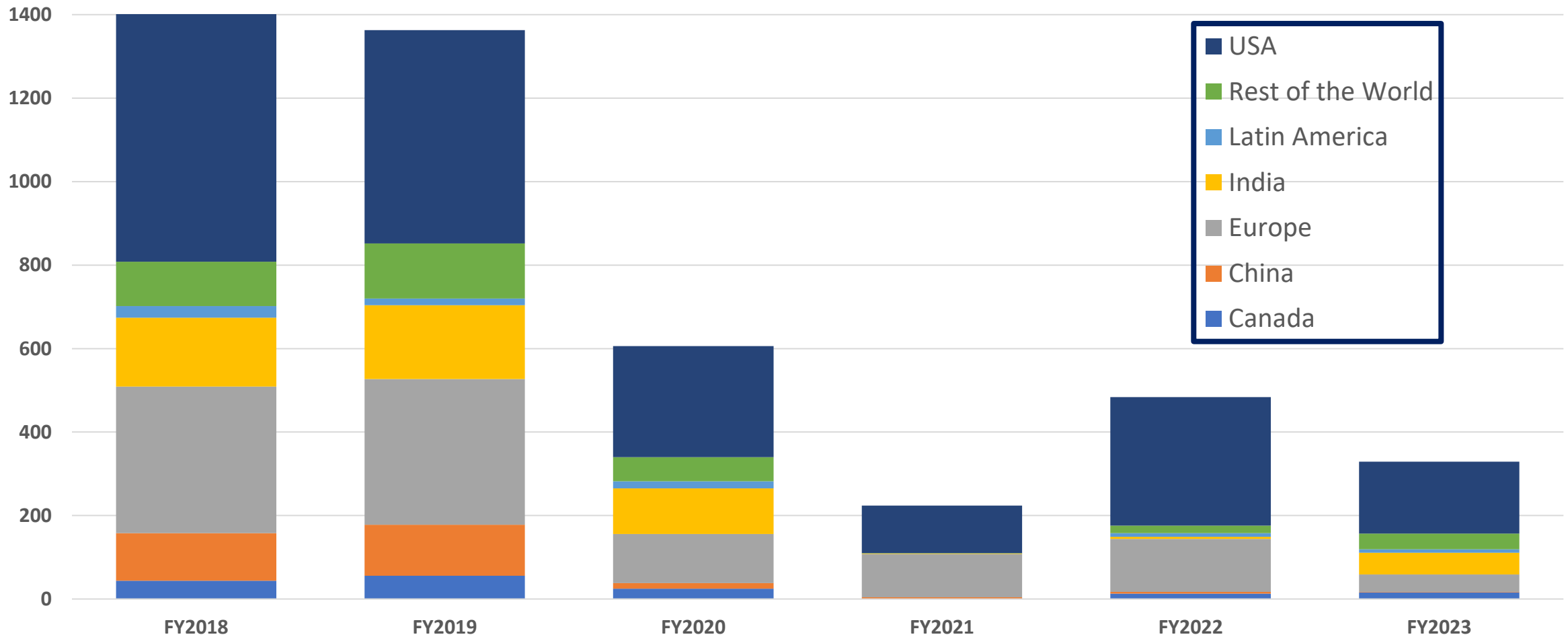
- FDA is assisting manufacturers of each drug to increase supply
  - Examples of assistance include allowing temporary importation of unapproved cisplatin and allowing temporary exclusion from drugs on import alert
  - Asking manufacturers to submit data to support extended expiration dating for lots in distribution approaching labeled expiration date
  - FDA drug shortage website

Compliance and Inspections

Inspections

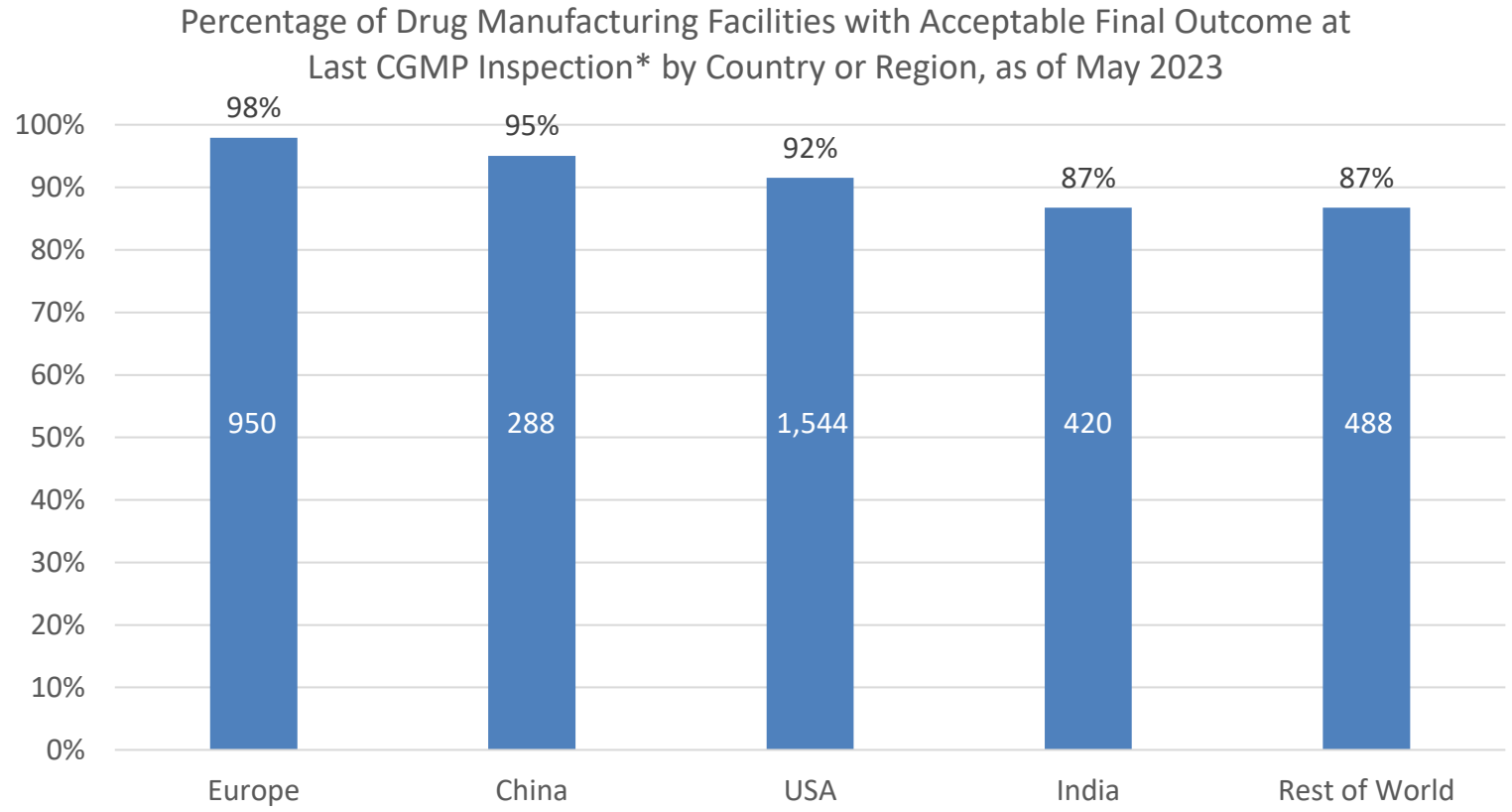
- FDA continued mission-critical inspections throughout the public health emergency
- FDA has conducted domestic inspections at standard operational levels since October 2021
- FDA resumed foreign facility surveillance inspections in March 2022, and resumed inspections in China with U.S.-based staff in April 2023
- FDA continues to leverage a variety of tools for facility assessment, including remote assessments

Surveillance Inspections and MRA Classifications by Region



Note: - Starting in March 2020, and continuing through FY2022, FDA postponed all foreign inspections that were not mission critical.
- FY2023 is incomplete and represents about 75% of the full year.

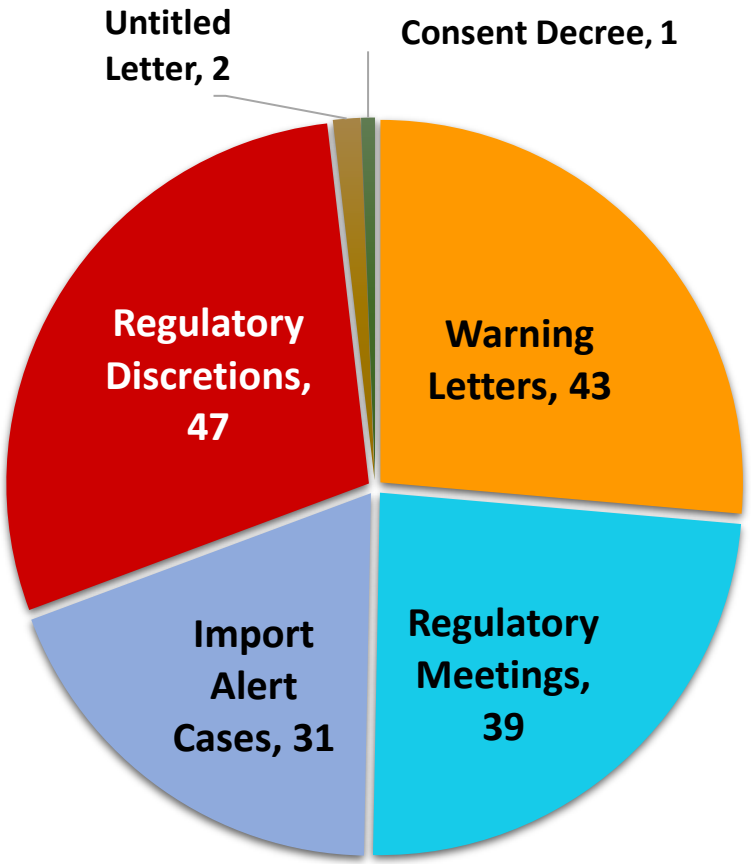
Surveillance Inspection Outcomes by Region



*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

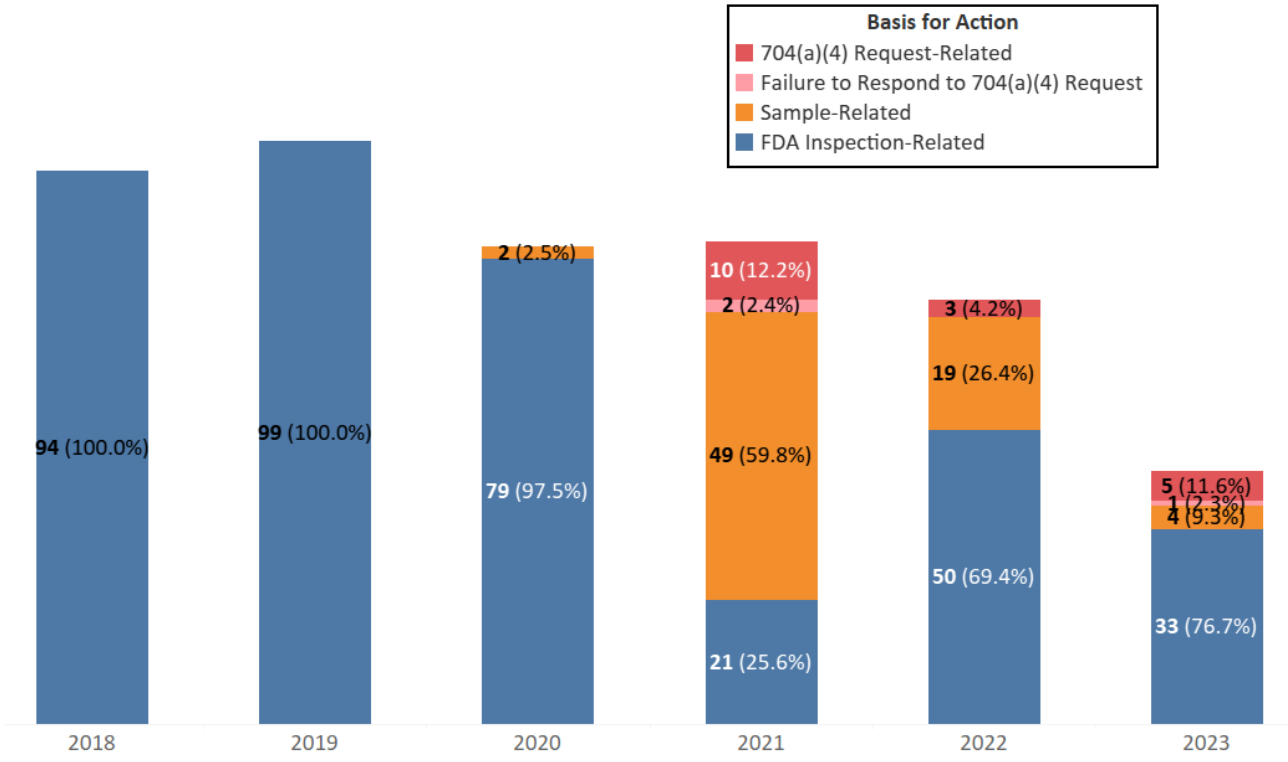
Note: Since the COVID-19 PHE, most surveillance inspections have been in the U.S. These domestic inspections have included sites with higher OAI rates, for instance, newly-registered hand sanitizer manufacturers.

Enforcement and Advisory Tools



*Actions Taken October 1, 2022 to March 31, 2023

Shift in Source of Information Prompting Drug Adulteration Advisory Actions – Warning Letters FY18-22**



Excludes compounding-related actions

** Warning Letters from October 1, 2018 to March 31, 2023

Recurring Issues in Drug Manufacturing Compliance

- Microbial contamination
  - Ophthalmic product contaminated with multi-drug resistant bacteria
  - Burkholderia cepacia complex in non-sterile, water-based drug products
- Poor excipient quality and manufacturing controls
  - Diethylene glycol/ethylene glycol contamination
  - Benzene contamination (warning letter)
  - First CGMP Warning letter issued to excipient manufacturer
- Refusal of inspection; failure to respond to requests for records
- Lack of data integrity, transparency, and record retention
  - Information must be accurate, reliable, and complete
  - Appropriate remediation strategy and suitable timeframes are important
- Inadequate controls related to:
  - Aseptic manufacturing
  - Cleaning and cross-contamination
  - Supply chain globalization & contract manufacturing
  - Facility design and maintenance
  - Out-of-specification result investigations

Sustainable Compliance

- FDA's Current Good Manufacturing Practice (CGMP) requirements provide the foundation for a robust state of control and drug quality
- Maintaining ongoing CGMP compliance requires a proactive and prevention-focused quality system
- If the quality system at a facility is slow to address operations with excessive variability, this reactive approach is a recipe for lapses in compliance and inconsistent pharmaceutical quality
  - Recidivism and numerous actions

Figure A: This facility experiences lapses in control due to inconsistent adherence to CGMP and vacillates between acceptable and substandard quality.

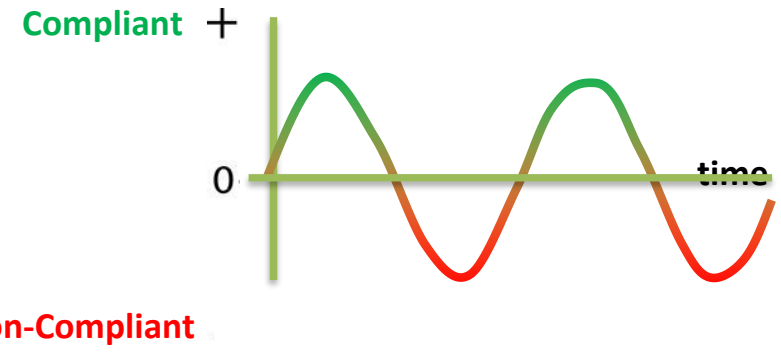
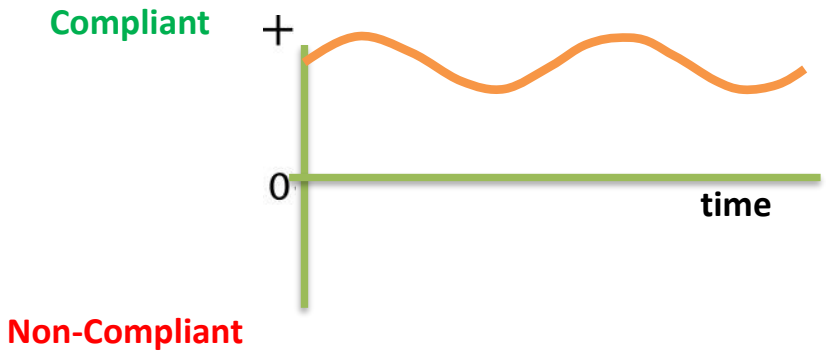
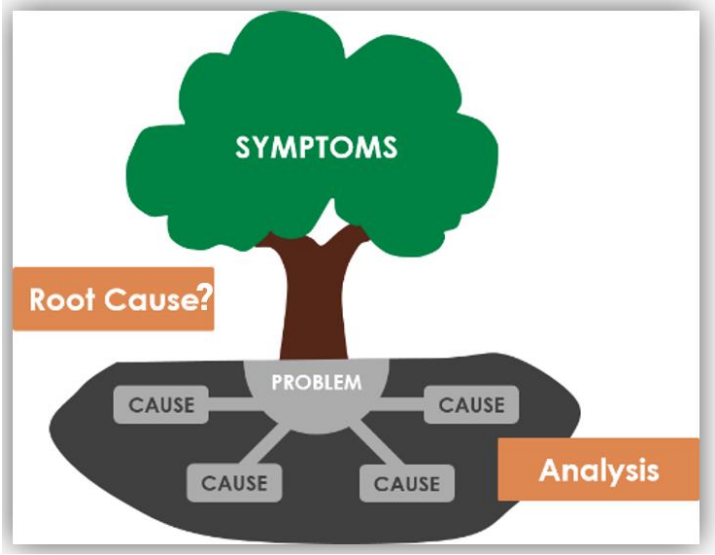


Figure B: This prevention-focused, CGMP-compliant facility yields consistently conforming medicines.



Critical Factors Associated with Sustainable Compliance

- Senior Management Oversight of Facilities
  - Ensure ongoing suitability of operational design, control, and maintenance
  - Allocate resources for production infrastructure upgrades when operations are deficient.
  - Technological capability directly impacts quality of outputs, and is central to sustainable compliance
- Lifecycle Quality Signals and Root Cause Analysis
  - Important to have an effective system for implementing corrective actions and preventive actions
  - A structured approach to the investigations is critical for understanding the root cause



A Call to Action: Achieving Sustainable Compliance

1. Identify and address current problems; implement long-term systemic remediation
2. Ensure strong quality management oversight
    - "Walk the talk:" quality is top priority throughout organization
    - Accountability for quality
3. Well-designed facilities, equipment, and processes
    - Upgrade to highly capable facilities and equipment
    - State of control vigilantly monitored
4. Engineer quality system to proactively identify and remediate problems as they occur (FDA is not your quality system)
    - Prompt attention to address emerging adverse trends and deviations

→ Commitment to quality assurance creates the needed conditions for dependable supply for patients

Statutory Authority Update

Drug Supply Chain Security Act (DSCSA)

- Enacted November 27, 2013
- Outlines steps to achieve interoperable, electronic tracing of product at the package level to identify and trace certain prescription drugs as they are distributed in the U.S.
- Establishes national licensure standards for wholesale drug distributors and third-party logistics providers (3PLs)
- Improves detection and removal of potentially dangerous drugs from the drug supply chain
- Enhances ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful

DSCSA Implementation

- Stakeholder Readiness and Challenges for November 2023
  - Industry has shown progress -> there is still work to do before the 11/27/2023 deadline (e.g., including industry testing)
  - While most data exchange will be standardized, flexible methods may be needed for small entities (e.g., web portals or email)
  - Continue outreach to trading partners and other stakeholders, as lack of understanding of complexities and needs may still exist, particularly with small entities or State regulators
  - Variety of implementation challenges

DSCSA Implementation (cont'd)

- What's Next → 2023 and Beyond
  - Guidances for Industry
  - Small Dispenser Assessment
  - Stakeholder Engagement (e.g., public private partnership, public meeting)
  - Finalize Wholesale Distributor/Third-party Logistics Provider (3PL) proposed regulations
  - Compliance and enforcement

CARES Act Drug Amount Reporting

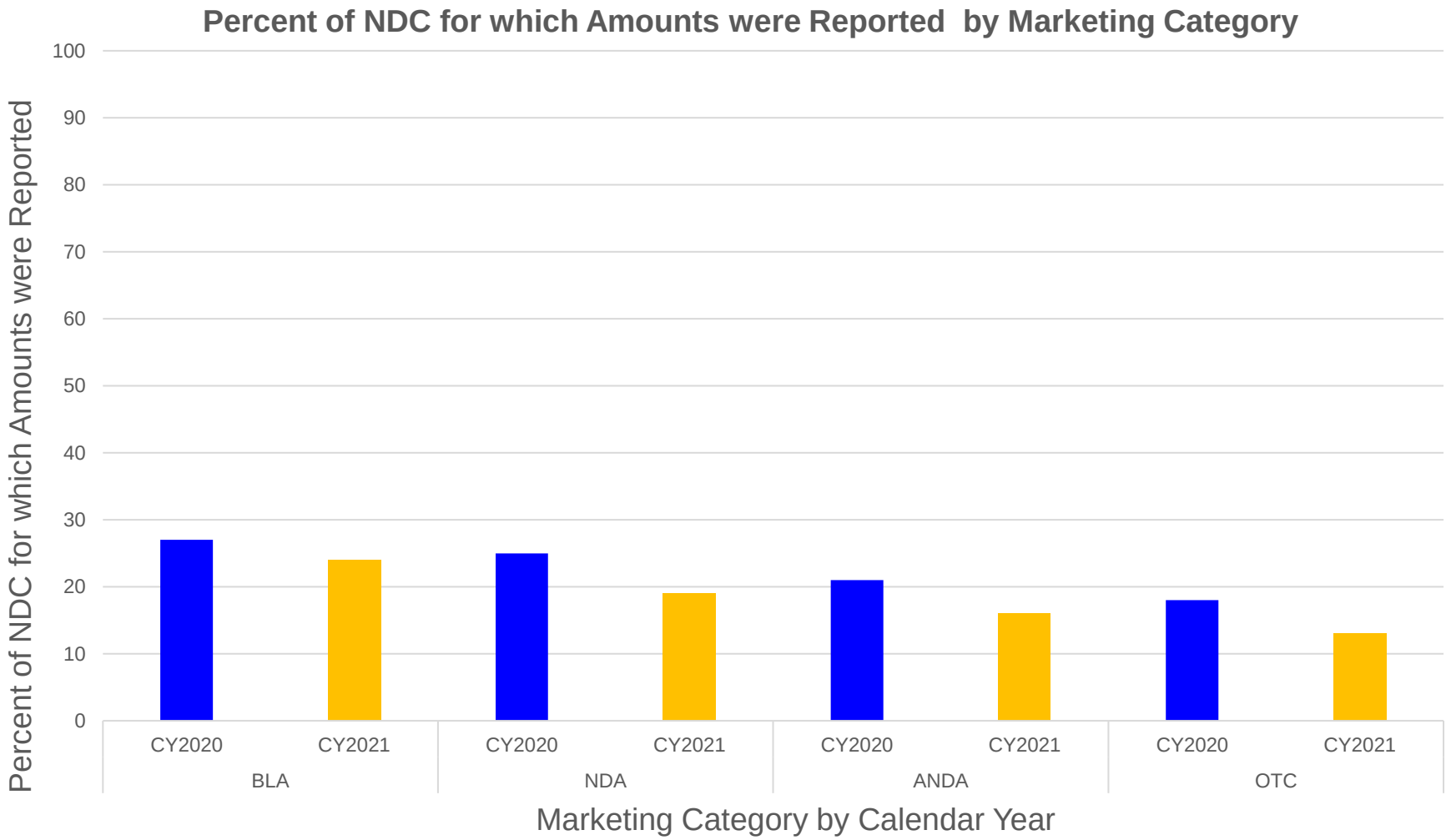
- **CARES Act requires each registrant to annually report to FDA amount of each listed drug manufactured for commercial distribution**
  - Enacted March 27, 2020
- **Registrants of all animal and human drug establishments registered with FDA under Section 510 of the FD&C Act are required to report on the amount of all drugs listed under section 510**
  - Exceptions include certain biological products and categories of biological products exempted by order under Section 510(j)(3)(B)

The Value of Drug Amount Reporting

- **FDA's vision for use of the CARES Act Drug Amount data:**
  - Combining drug amount reporting data with other information to enhance understanding of drug supply chain issues and drug shortages
  - Using the drug amount reporting data to evaluate an establishment's potential impact on drug supply chains
  - Strengthening CDER's risk-based Site Selection Model used for prioritizing surveillance inspections by better gauging potential patient exposure to a site's products

Limited Drug Amount Reporting

- **Low percentage of CARES Amount Reporting across all product types**
  - BLA, NDA, ANDA, OTC

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