

2023 PDA/FDA JOINT REGULATORY CONFERENCE

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Call to Action: Assuring Quality through Sustainable Compliance, Vigilant Quality Management and Modern Manufacturing

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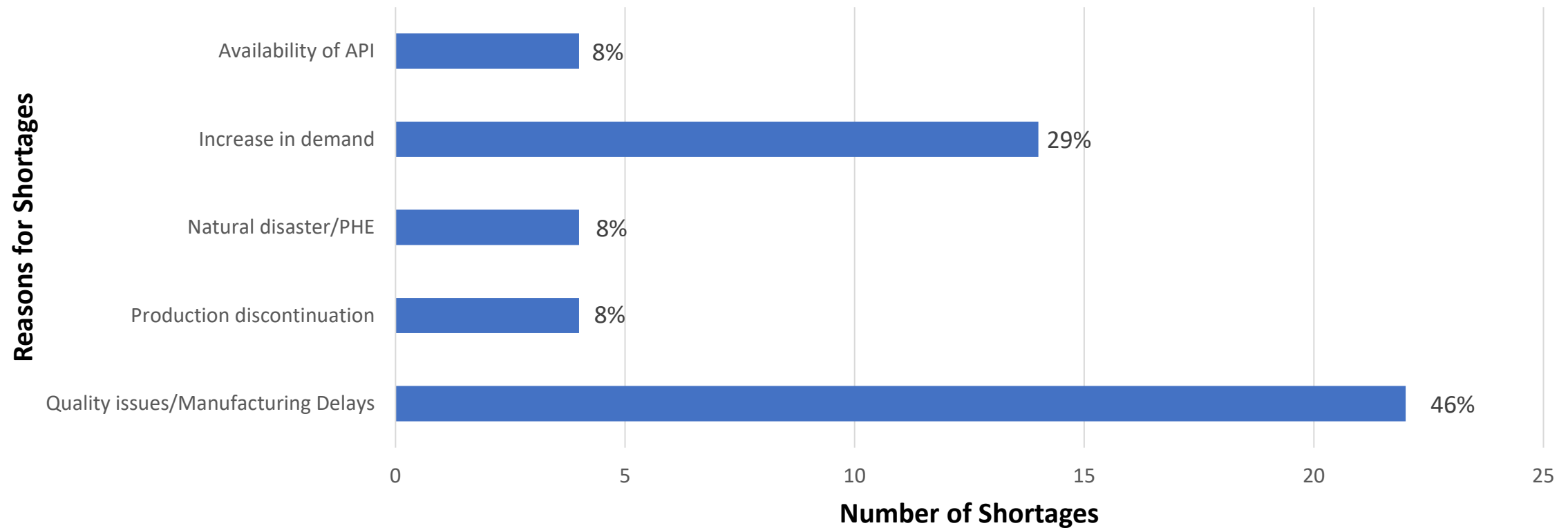
September 18, 2023

Areas We Will Cover Today



- Manufacturing Issues Leading to Drug Shortages
- Inspections
- Achieving Sustainable Compliance
- Call to Action

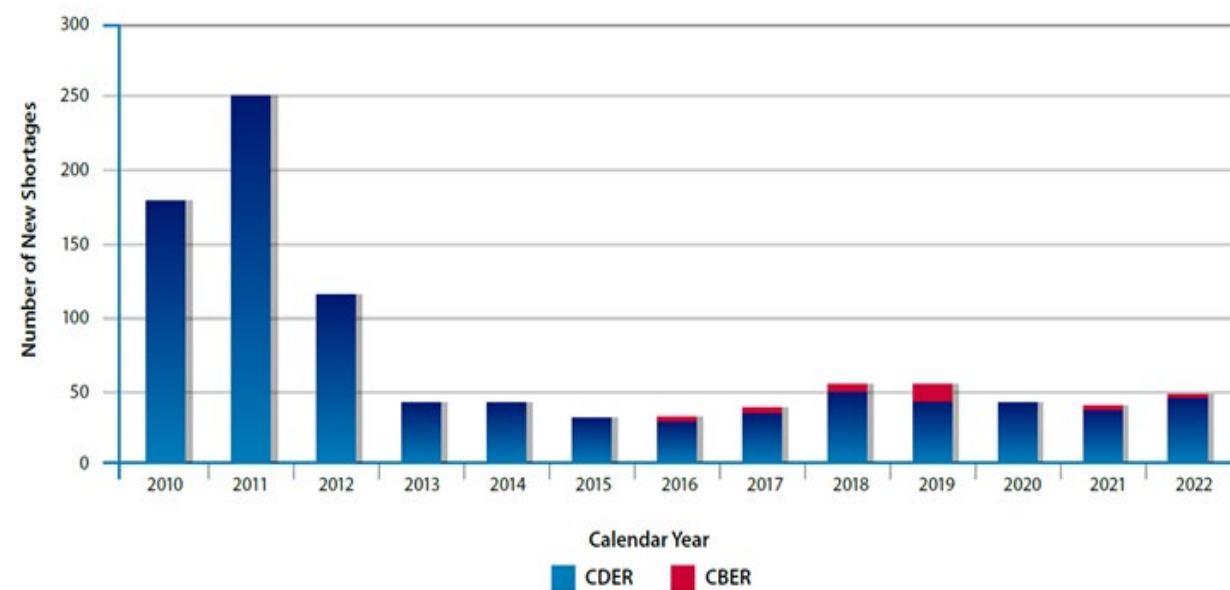
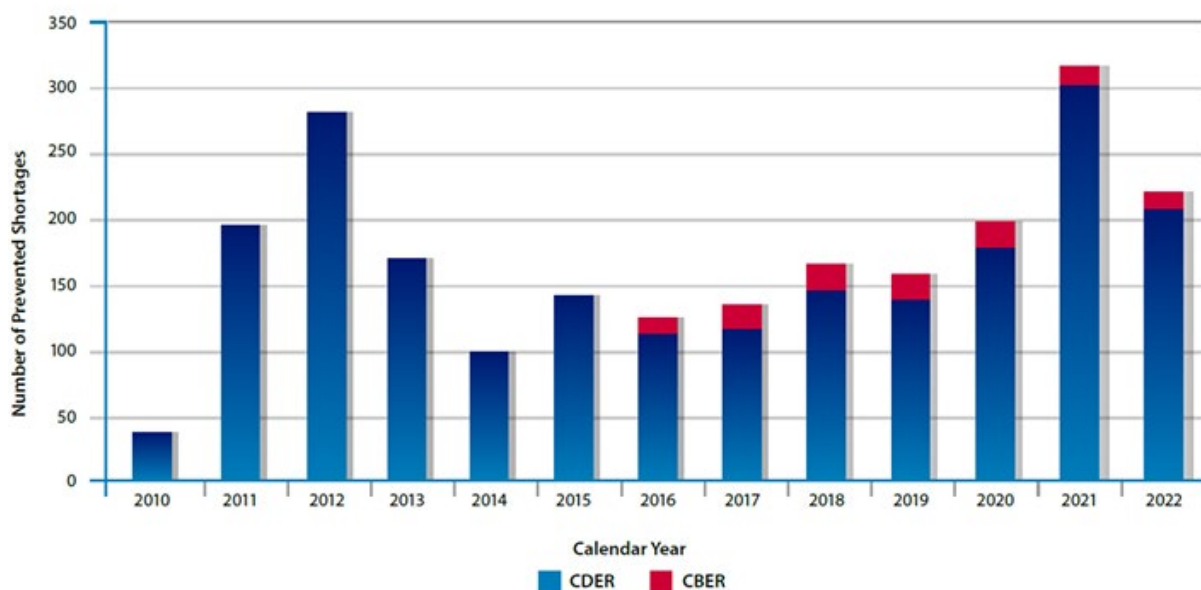
Reasons for New Shortages in CY2022



Early Notification is Key to Prevention



- 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., due to the need for plant remediations)
- The earlier this work begins the greater the likelihood a shortage can be prevented, or the most severe impacts mitigated



Manufacturing Capacity Shortfall



- **For critical drugs, there exists a U.S. 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 significant events:
 - Hurricane Maria in Puerto Rico
 - Necessary compliance remediations
 - Geopolitical concerns
 - Or financial pressures can lead to:
 - Manufacturing site closures
 - Firm bankruptcies

Oncology Drug Shortages



- 16 drugs in shortage (as of August 2023)

- amifostine injection,
- azacitadine injection,
- capecitabine tablets,
- carboplatin injection,
- cisplatin injection,
- cytarabine injection,
- dacarbazine injection,
- dexamethasone injection
- fludarabine injection
- hydrocortisone injection
- leucovorin injection
- lutetium lu 177 vipovotide textraxeta injection
- methotrexate injection
- methotrexate tablets
- palifermin injection
- streptozocin injection

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 1944 (*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.

20 SEPTEMBER

Critical Shortage of Cisplatin and Carboplatin



- 1.8 million Americans are diagnosed with some form of cancer every year
- There are estimates that up to 500,000 patients possibly could have a stage and a diagnosis that would rely on a platinum agent
- The current shortages of cisplatin and carboplatin followed an inspection and identification of quality issues at one company's facility
 - Shortages posted on FDA website in 2/23 and 4/23, respectively
 - The company shut down production leading to the current shortage. In addition, the shortage of cisplatin led to a ripple effect as demand for the second line treatment, carboplatin, increased but the manufacturers were not able to meet demand

10 **CISPLATIN AND CARBOPLATIN USES BY DISEASE SITE**
Compiled from NCCN Guidelines

Head and neck

Cisplatin and carboplatin, single agent, is used as a radiosensitizer for local and regional disease.

For recurrent, unresectable or metastatic disease with radiation therapy option:

- Cisplatin/5-FU
- Cisplatin or carboplatin/docetaxel or paclitaxel
- Carboplatin/cetuximab
- Gemcitabine/carboplatin
- Cisplatin/gemcitabine + pembrolizumab or nivolumab

Cisplatin and carboplatin can also be used as a single agent for metastatic disease in the very ill.

Esophageal

Chemosensitizer for localized disease:

- Paclitaxel and carboplatin
- Cisplatin and 5-FU

Oxaliplatin is already replacing some use of cisplatin or carboplatin for quality-of-life reasons.

For metastatic disease:

- Paclitaxel with carboplatin or cisplatin is still used especially in squamous
- Cisplatin and fluorouracil is used in adenocarcinoma

Breast

Carboplatin, a taxane, and pembrolizumab are used for some regimens especially in triple-negative disease.

Neoadjuvant and adjuvant regimens include:

- Paclitaxel and carboplatin +/- trastuzumab
- Docetaxel and carboplatin +/- trastuzumab

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Non small cell lung

With concurrent chemo radiation:

- Carboplatin pemetrexed
- Cisplatin pemetrexed
- Carboplatin paclitaxel

Neoadjuvant and adjuvant platinum doublets include:

- Carboplatin pemetrexed
- Carboplatin gemcitabine
- Carboplatin paclitaxel
- Cisplatin pemetrexed
- Cisplatin gemcitabine
- Cisplatin paclitaxel
- Cisplatin docetaxel
- Cisplatin etoposide
- Cisplatin vinorelbine

These doublets are often used for metastatic disease along with:

- Carboplatin or cisplatin and pemetrexed and pembrolizumab
- Carboplatin and paclitaxel and bevacizumab and atezolizumab

Small cell lung

- Carboplatin and etoposide
- Cisplatin and etoposide

Gastric

Oxaliplatin is replacing cisplatin due to lower toxicity, but cisplatin is still used.

- 5-FU and cisplatin with trastuzumab and pembrolizumab
- Capecitabine and cisplatin with trastuzumab and pembrolizumab

Pancreatic

Gemcitabine and cisplatin as locally advanced first line therapy with known BRCA 1/2 or PALB2 mutations

Ovarian

- Carboplatin
- Carboplatin/docetaxel
- Carboplatin/paclitaxel (weekly)
- Carboplatin/gemcitabine ± bevacizumab
- Carboplatin/liposomal doxorubicin ± bevacizumab
- Carboplatin/paclitaxel ± bevacizumab
- Gemcitabine/cisplatin

Bladder

For locally advanced and metastatic bladder cancer, cisplatin is preferred, but carboplatin is used when cisplatin is not tolerated well.

- Gemcitabine and cisplatin
- Carboplatin and gemcitabine

Prostate

Aggressive metastatic prostate is often treated with:

- Taxotere and carboplatin
- Cabazitaxel and carboplatin

Gonadal tumors

Cisplatin is preferred over carboplatin:

- Cisplatin etoposide
- Bleomycin, etoposide, cisplatin (BEP)
- Paclitaxel ifosfamide cisplatin
- Etoposide cisplatin

Sarcoma

Carboplatin and etoposide is one of many regimens

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 taking steps to help increase supply. For example:
 - Not objecting to temporary importation of unapproved cisplatin and temporary exclusion of drugs from import alert
 - Asking manufacturers to submit data to support extended expiration dating for lots in distribution approaching labeled expiration date
 - The most up to date information is on the [FDA drug shortage website](#)



Compliance and Inspections

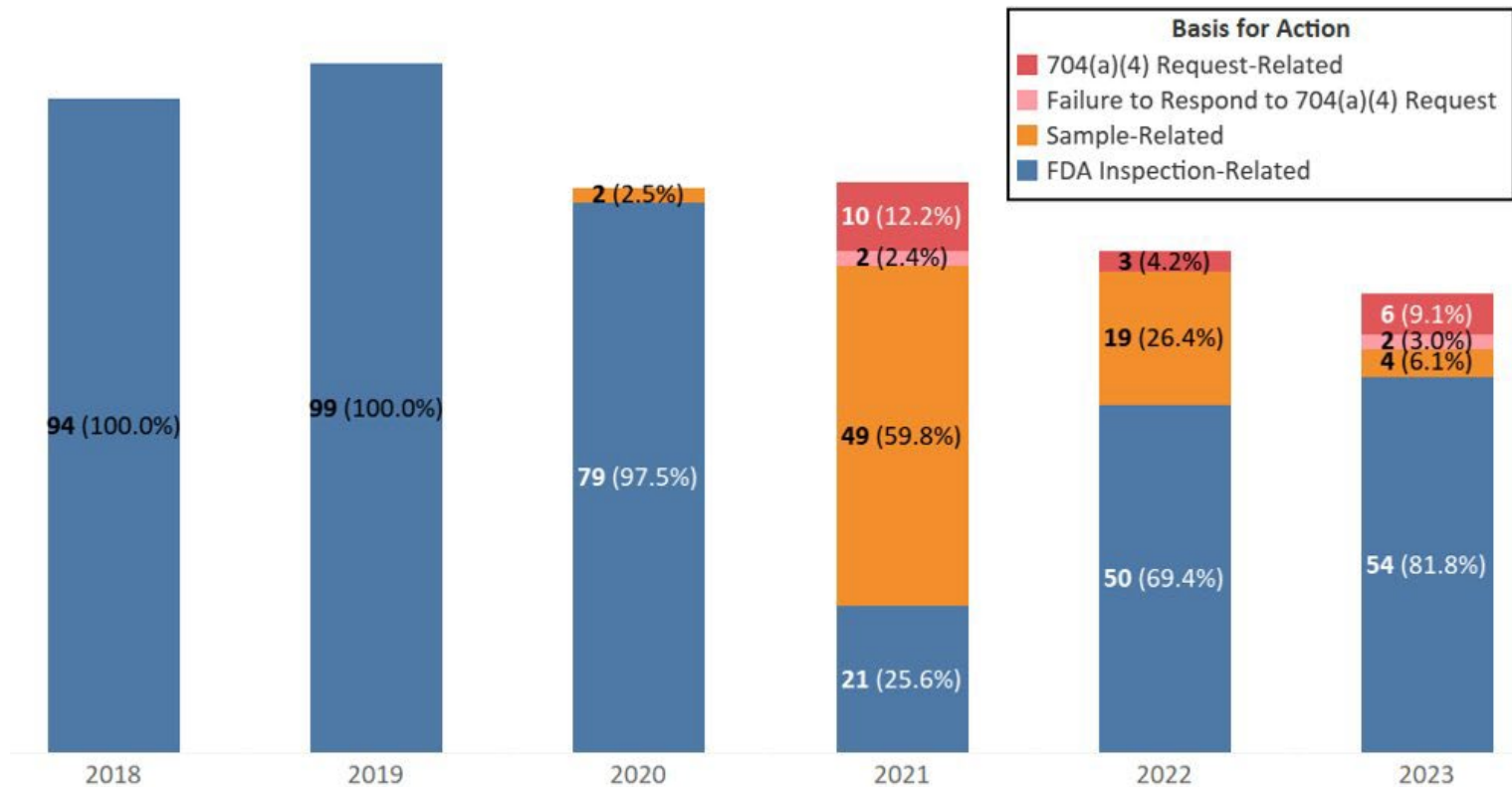
Inspections

- 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



Enforcement and Advisory Tools

Shift in Source of Information for Drug Adulteration Advisory Actions Warning Letters FY18-23**



** Warning Letters through July 31, 2023

Excludes compounding-related actions

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](#) testing
 - [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

What is Compliance?

Compliance is:

- *The act or process of complying with a regimen.*
- *The degree of constancy and accuracy with which a prescribed regimen is followed.*

Examples:

Example 1: Patient adherence to prescription

Q: What is the result of patient non-compliance with taking a drug as directed (e.g., antiseizure, heart failure, antibiotic)?

A: Patient non-compliance leads to a higher probability of failure of the therapy and unfavorable health outcomes.

Example 2: Manufacturing

Q: What happens if a manufacturer doesn't follow CGMP requirements?

A: There is less assurance of product quality and a higher probability of defects and failures.

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 which increases the risk of product quality failures

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

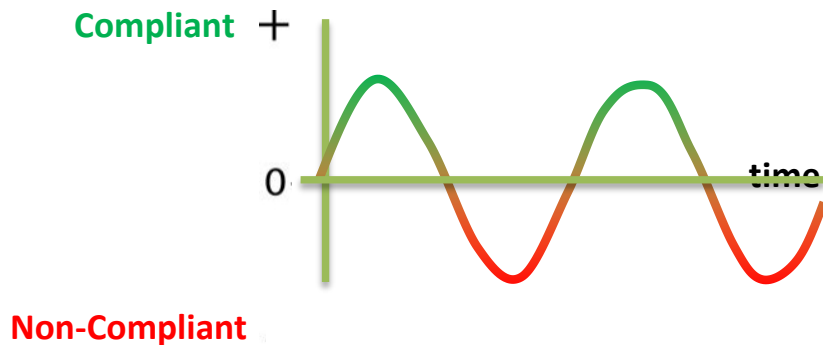
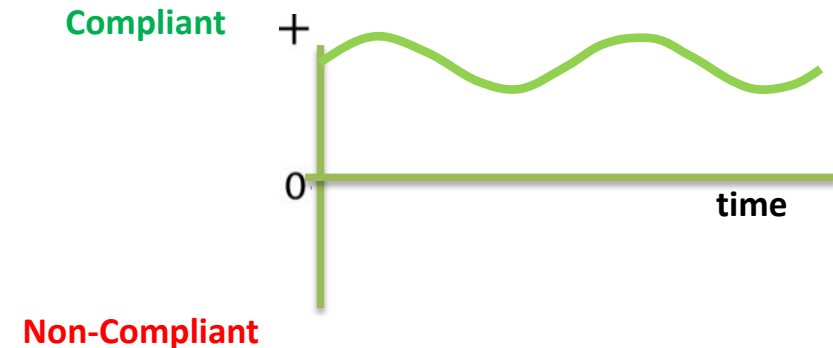


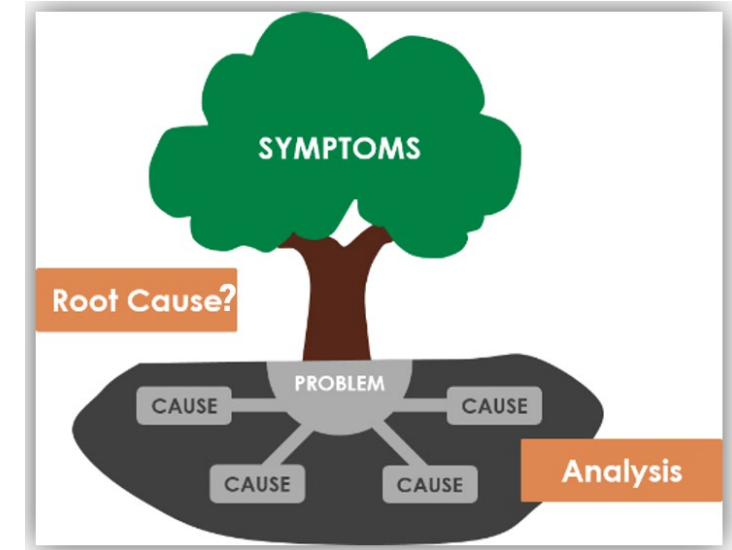
Figure B: This prevention-focused, facility results in consistent CGMP compliance.



Critical Factors Associated with Sustainable Compliance



- Senior Management Oversight of Facilities
 - Technological capability directly impacts quality of outputs and is central to sustainable compliance.
 - Ensure ongoing suitability of operational design, control, and maintenance.
 - Allocate resources for production infrastructure upgrades when operations are deficient.
- Lifecycle Quality Signals and Root Cause Analysis
 - Implement effective systems for detecting emerging issues
 - Use structured approach for investigations to determine root cause, in order to accurately define the needed Corrective Action and Preventive Action (CAPA)



Senior Management Oversight and Opportunities for Manufacturing Modernization

- Digitization
- *Digitalization*
- Automation (e.g., robotics)
- Semi-Continuous or Continuous Manufacturing
- Building Management Systems
- 100% Inspection Technologies
- Containment Advances (e.g., isolators)
- Rapid Testing and Monitoring Technologies
- Optimization of Quality Management System

Example of Recidivism and Lack of Sustainable Compliance



- Large, multinational manufacturer of generics
 - Produces sterile and non-sterile finished products and active ingredients for vulnerable patients
 - FDA observed multiple facilities within a single corporate umbrella with significant CGMP violations, including data integrity issues, inadequate out-of-specification result investigations, unsuitable equipment → firm required to retain independent experts to evaluate applications and CGMP activities
 - Numerous actions → felony charges (\$500m settlement), consent decree (2012, covered up to 4 facilities from 2014-2017), warning letters (at least 7 from 2002 -2022), drugs placed on import alert
- Problems continue
 - Ineffective CGMP remediations across network persist (e.g., facility received a letter of Consent Decree and CGMP non-compliance in **2023**)
 - **Many drugs remain on Import Alert 66-40**

Examples of Successful Compliance Remediation

- Large multinational API manufacturer of antibiotics and sartan drugs
 - Produces drugs for vulnerable patient populations
 - Problems developed over several years culminating with WL issued in 2019; firm held regulatory meetings in 2019 and had communications over several years. Firm was re-inspected in 2022, resulting in VAI classification
- Large analytical firm focused on laboratory tests across the pharmaceutical and packaging industries
 - Issues developed resulting in a noncompliance action in 2020. The firm worked on corrective actions
 - In 2022 at their follow up inspection received a VAI classification



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 is essential for dependable drug supply



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