

# The State of Pharmaceutical Quality

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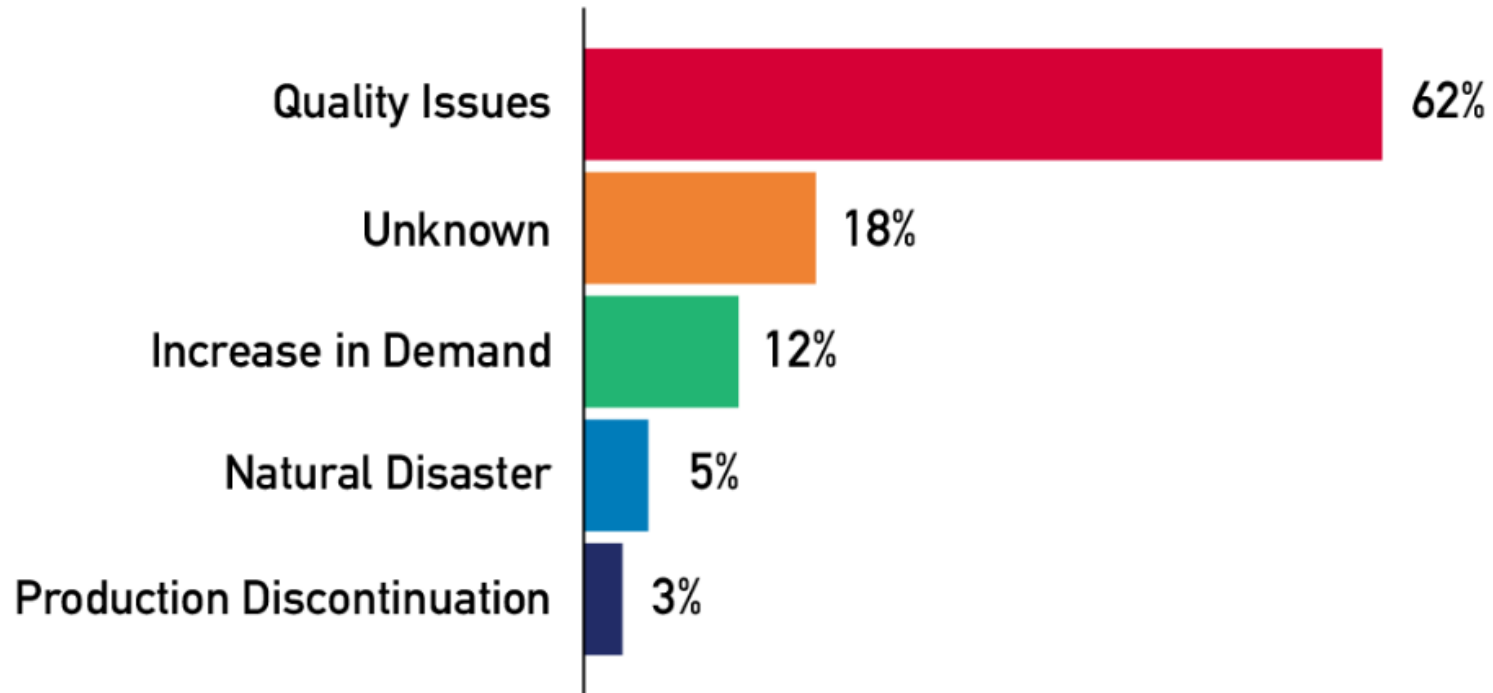
**Presented at IPA 8<sup>th</sup> Global Pharmaceutical  
Quality Summit**

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# Quality Issues Lead to Drug Shortages



Percentage of Drugs Newly in Shortage by Reason, Calendar Years 2013-2017



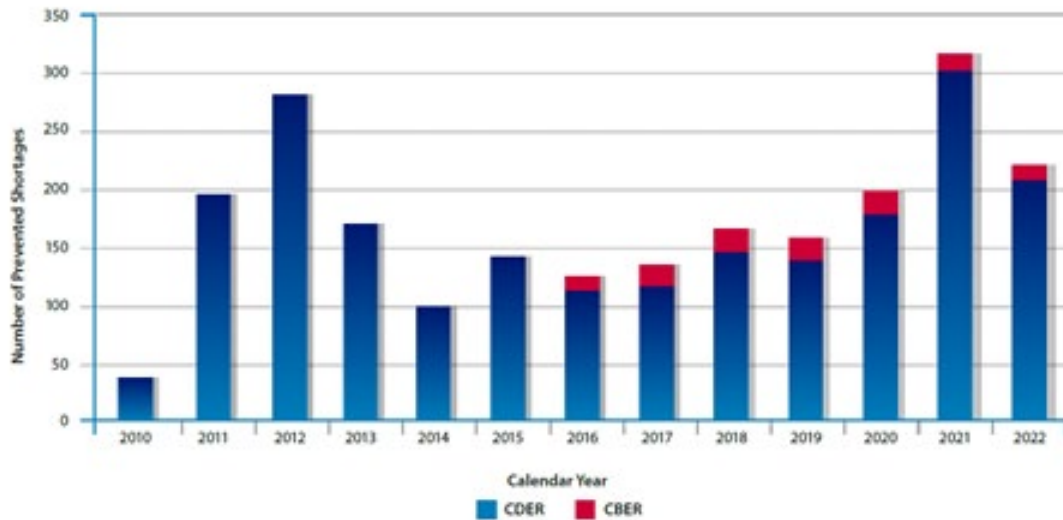
Most drugs in shortage were experiencing supply disruptions, specifically quality issues.

Source: Internal FDA Data

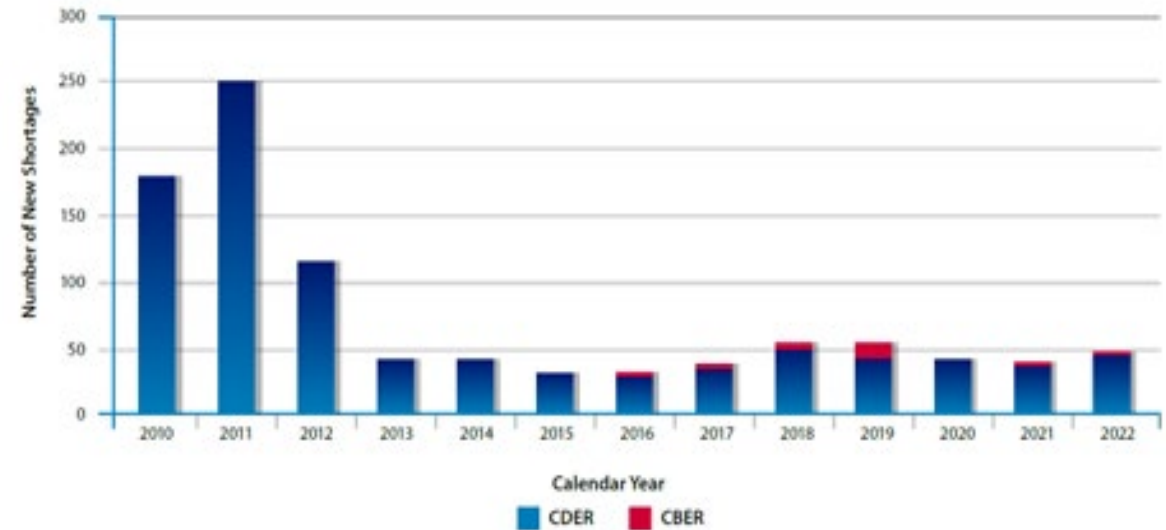
# Early Notification is Key to Prevention



- 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., plant remediations and Agency approvals)
- The earlier this work begins the greater the likelihood a shortage can be prevented, or the most severe impacts mitigated



Total Prevented US Drug Shortages Per Year<sup>1</sup>



Number of New US Drug Shortages Per Year<sup>1</sup>

# 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:
    - Hurricane Maria in Puerto Rico
    - Necessary compliance remediations
    - Geopolitical concerns
  - Or financial pressures could lead to:
    - Manufacturing site closures
    - Firm bankruptcies

# Oncology Drug Shortages



## ■ 16 drugs in shortage (as of May 2023)

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

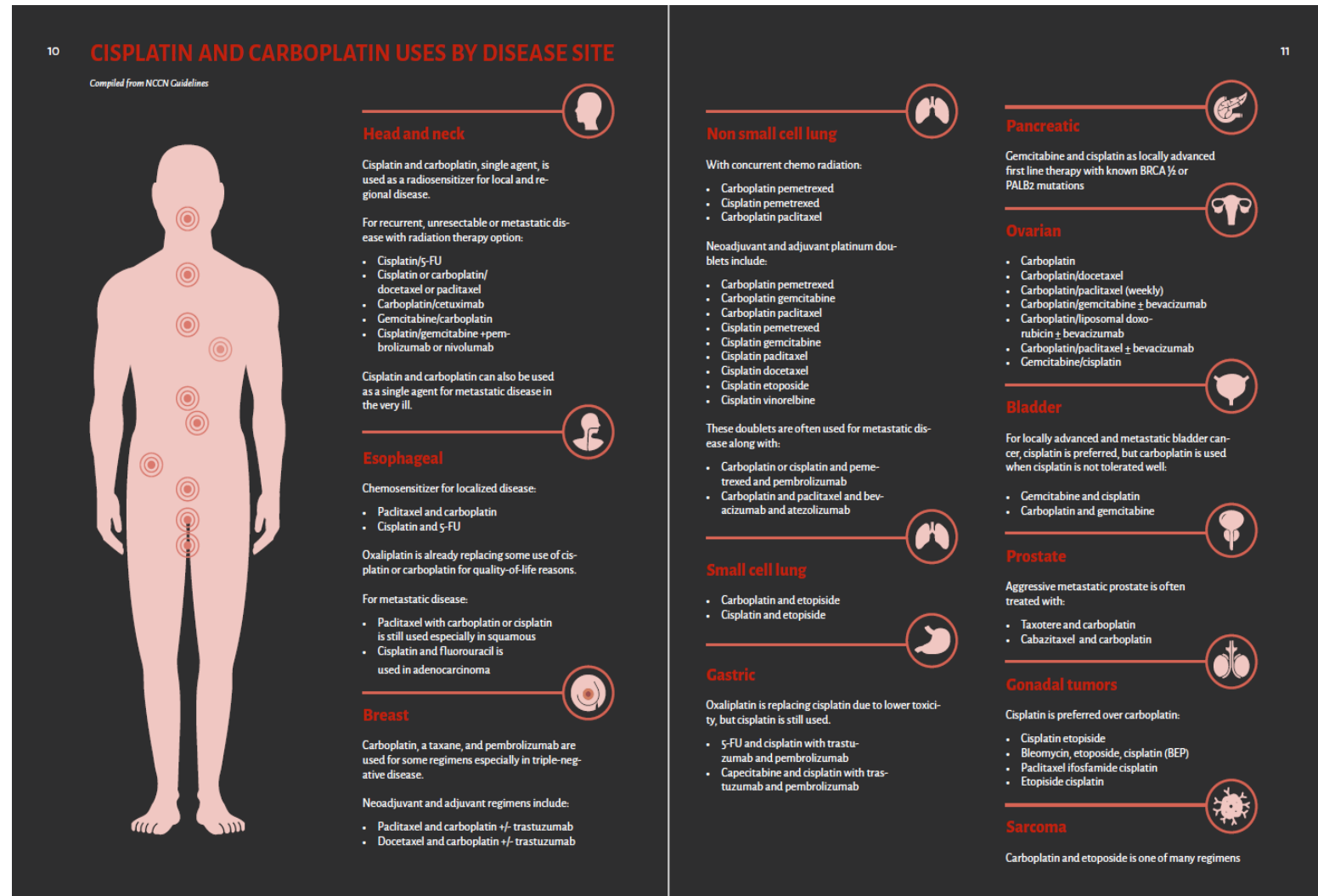
## *Drug Shortages Near an All-Time High, Leading to Rationing*

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



- 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

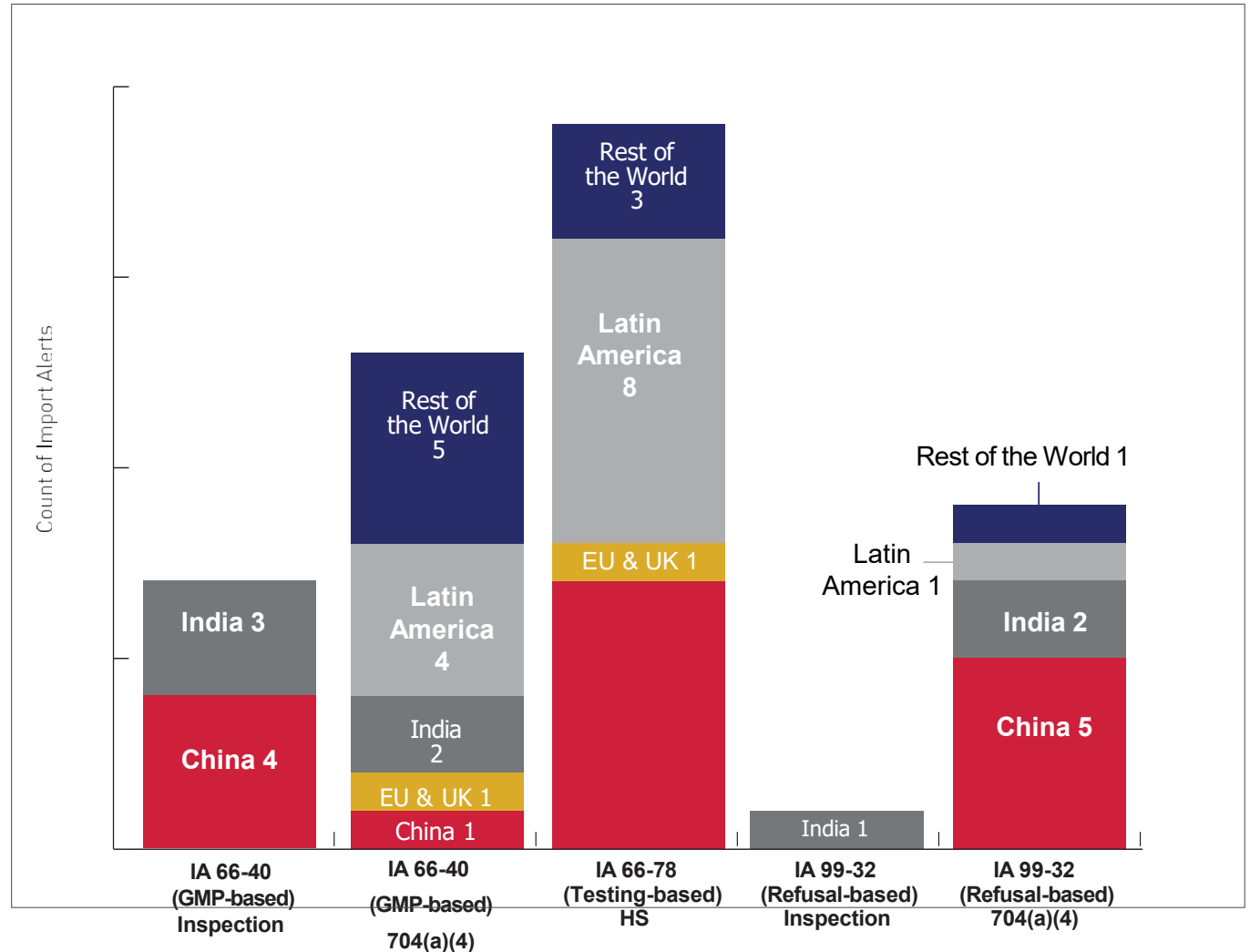


# Import Alerts



- **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





# 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



# Recurring Issues in Drug Manufacturing Compliance



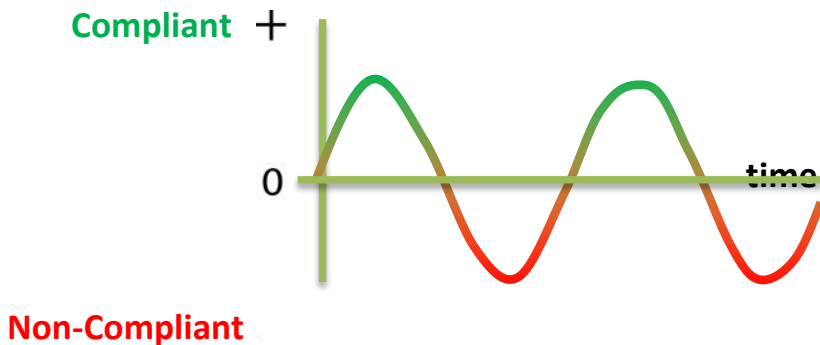
- Microbial contamination
  - [Ophthalmic product](#) contaminated with multi-drug resistant bacteria
  - [Burkholderia cepacia complex](#) in non-sterile, water-based drug products
- Poor excipient quality and manufacturing controls
  - [Diethylene glycol/ethylene glycol](#) contamination
  - [Benzene](#) 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

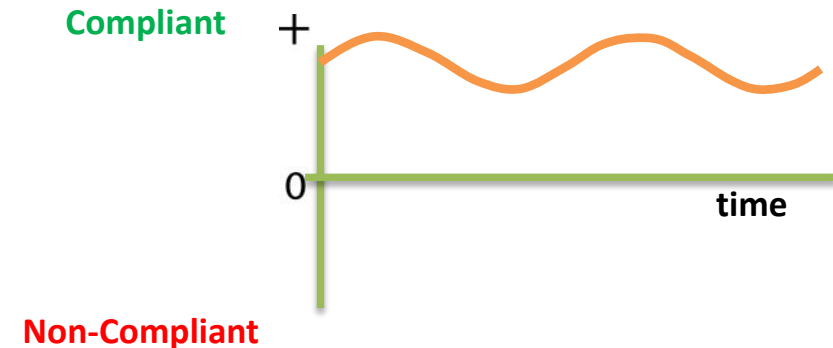


- FDA's Current Good Manufacturing Practice (CGMP) requirements provide the foundation for a robust state of control and drug quality
- Maintaining ongoing CGMP compliance requires a proactive and prevention-focused quality system
- If the quality system at a facility is slow to address operations with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

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



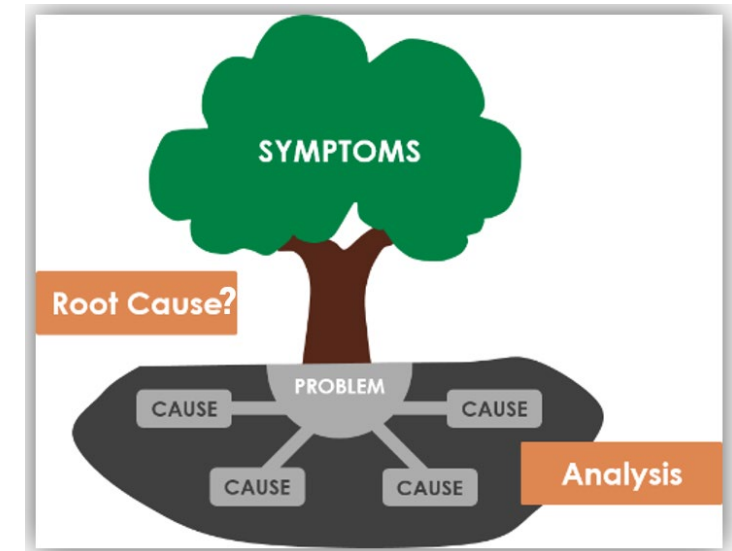
**Figure B: This prevention-focused, CGMP-compliant facility yields consistently conforming medicines.**



# 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



# Example of Transformation from OAI to Sustainable Compliance



- Large, multinational manufacturer of generics
  - Produces critical sterile drugs for vulnerable patients
  - Multiple VAI inspections → emerging concerns conveyed during regulatory meetings, firm commits to systemic CGMP remediation
  - Ineffective remediation, recurring problems → Recalls, WL, 3<sup>rd</sup> party audit
- Firm made long term investments in transformational change. This required fundamental changes in the:
  - **Quality System:** Key management changes. Improved quality system governance at site. Increased QA oversight of facility, process, and quality performance.
  - **Facility Design:** Replaced old lines with modern processing lines. Converted low-capability inefficient facility to highly capable isolator technology.
- Outcome: Sustainable Compliance (approaching 10 years)

# 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**



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