



2021 PDA/FDA JOINT REGULATORY CONFERENCE



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27-29 SEPTEMBER | LIVE. INTERACTIVE. ONLINE.

EXHIBITION: 27-29 SEPTEMBER
#PDAFDA

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Pandemic Response Highlights

Coronavirus Treatment Acceleration Program (CTAP)

- 460+ trials reviewed by FDA
- 630+ development programs for therapeutic agents in the planning stages
- 1000+ Expanded Access requests
- 1 approved treatment
- 11 treatments under emergency use authorization

22+ guidances on clinical development for COVID-19 therapeutics

Expanded CDER's drug shortage program to include supply chain surveillance

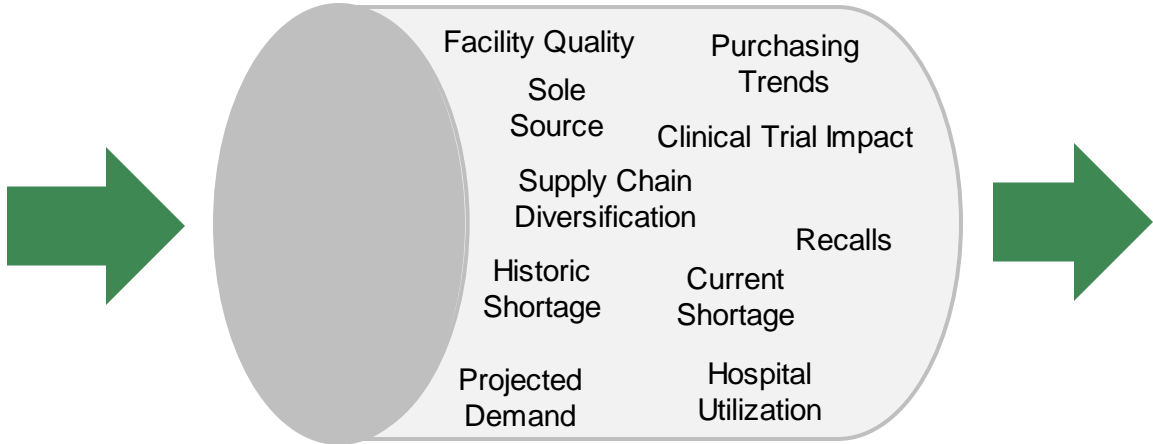
- Integrates data to help assess risk to critical medicines to treat COVID-19 aiming for earlier detection and response to supply disruptions
- Provides visibility into availability, supply, and demand
- Used to address drug shortages
- We are enhancing this system by seeking additional data sources and deploying advanced analytics
 - Phased process to expand coverage to additional products

Supply chain surveillance is based on examining multiple signals for supply chain disruption

Drug Identification
Identify critical drugs for supply chain surveillance

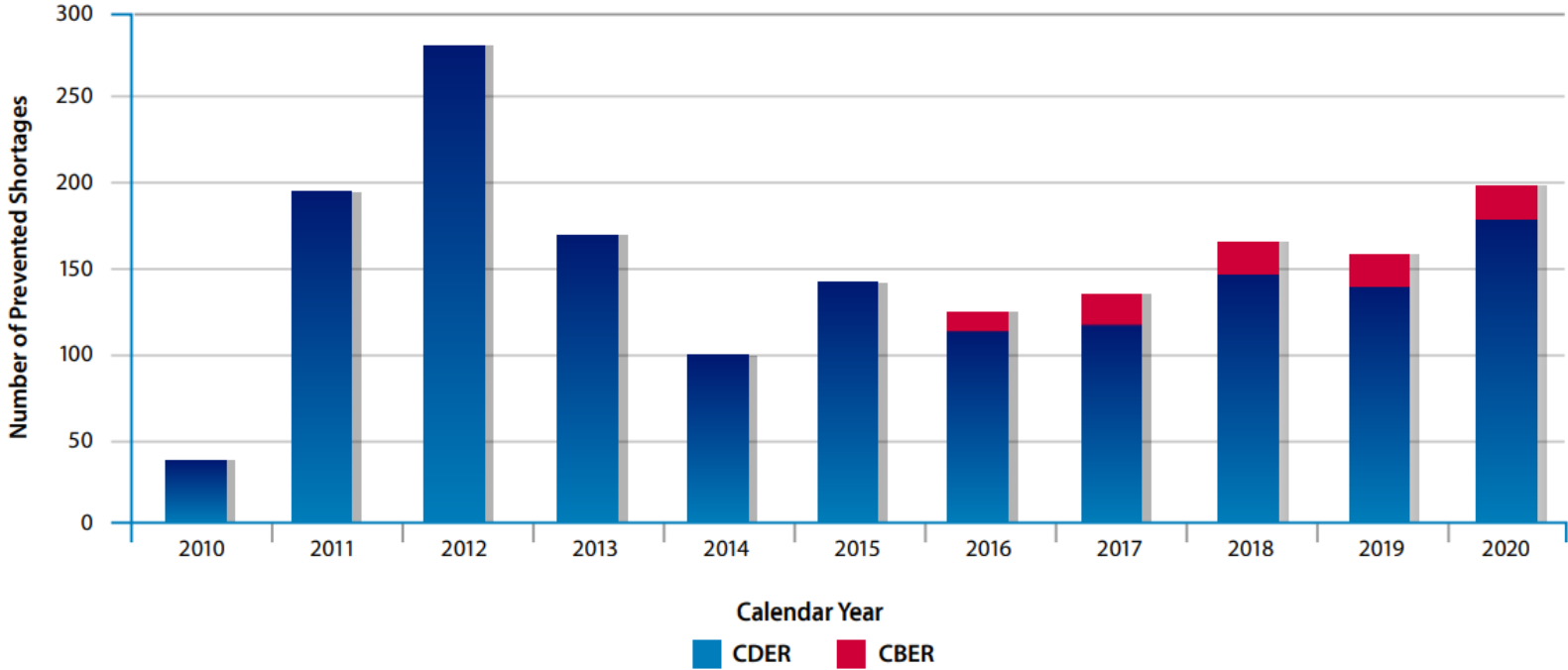
Integrated Supply Chain Assessment
Conduct analysis based on integrated data on key signals to determine if a drug is vulnerable to supply chain disruptions

Mitigation and Management
Conduct additional review for drugs with signals of supply chain disruptions



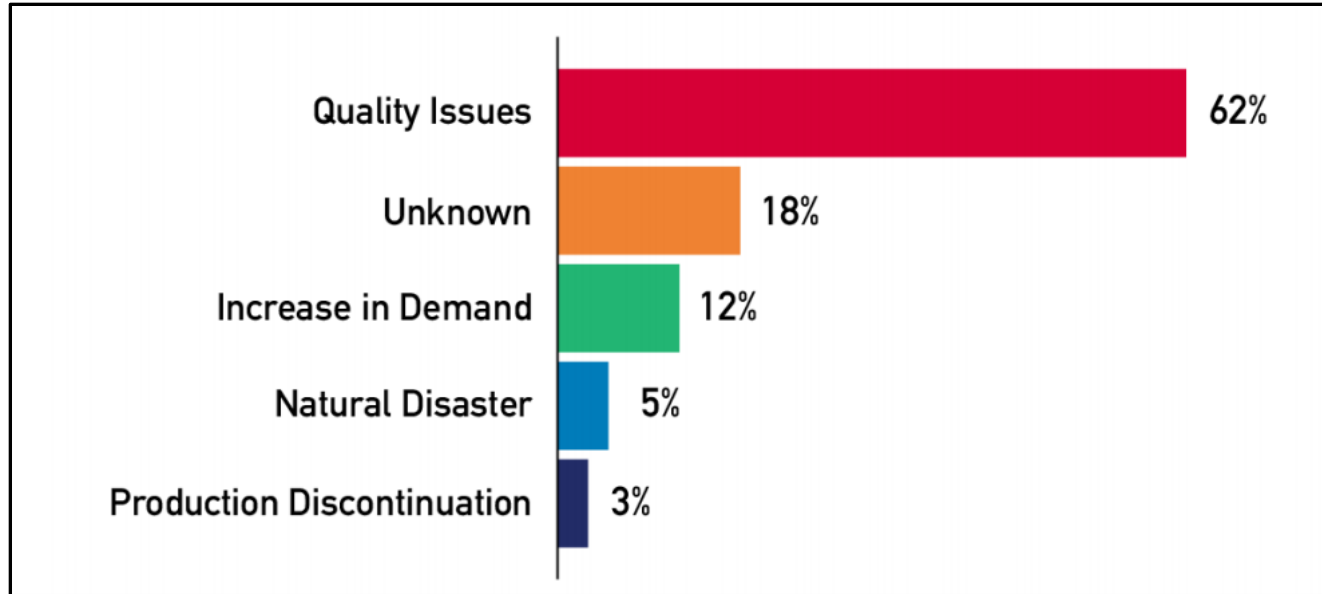
Shortage Mitigation

Total Prevented US Drug Shortages Per Year



Communications with manufacturers and others helps prevent drug shortages⁷

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



Most drugs in shortage were experiencing supply disruptions, with a majority caused by quality issues

The Challenge: Protecting patients when the market is flooded with products making unproven claims. Products are unlawful and put patients at risk.

(Examples: chlorine dioxide, colloidal silver, CBD, copper, honey, botanical oils)

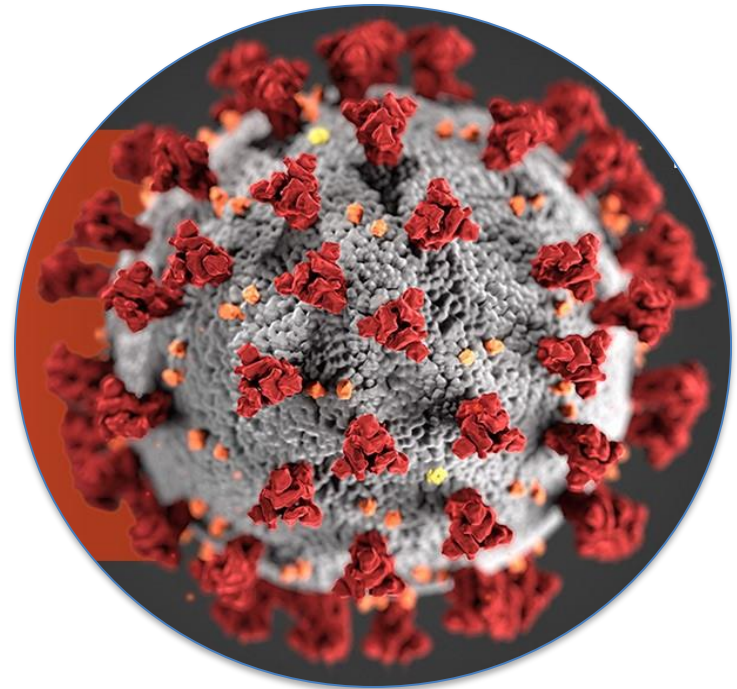
Actions Taken:

- ▶ Warning letters for products claiming to treat COVID-19
- ▶ Warning letters to Internet pharmacies claiming to treat COVID-19
- ▶ Removal of contaminated hand sanitizer products

Manufacturing Quality

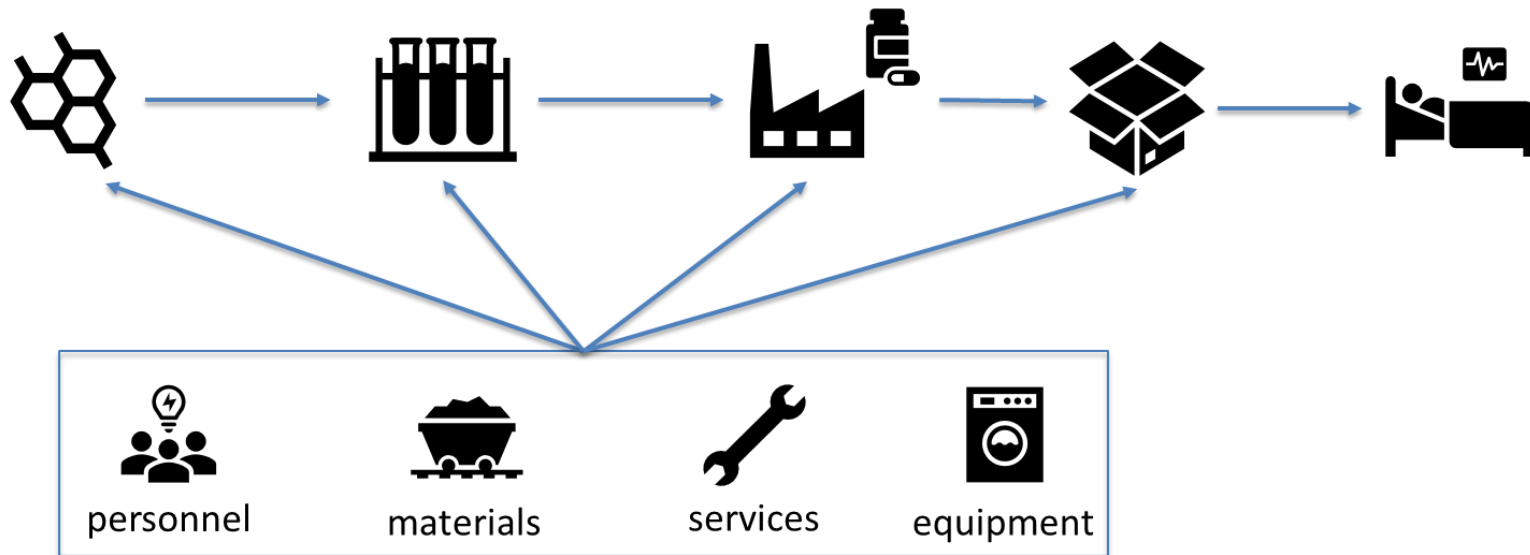
Long-existing quality issues are now magnified

- ▶ Information about current state of drug manufacturing and distribution
- ▶ Supply chain vulnerabilities
- ▶ Shortages due to manufacturing and distribution issues



Supply Constraints

The supply chain supporting the manufacture of FDA-regulated products has become constrained at multiple levels during the COVID19 public health emergency.



- ▶ Coronavirus Aid, Relief, and Economic Security Act (CARES Act)
 - ▶ Includes a provision requiring manufacturers of drugs, API, or any associated medical device to develop, maintain, and implement, as appropriate, a **redundancy risk management plan that identifies and evaluates risks to the supply of the drug**, as applicable, for each establishment in which the drug or API is manufactured
 - ▶ FDA draft guidance *Risk Management Plans to Mitigate the Potential for Drug Shortages* in development
- ▶ PIC/S - Recommendation “How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management”

- More mature quality management systems proactively focus on performance, especially outcomes that affect the patient, including reducing quality issues that lead to complaints, shortages, and quality-related adverse events
- FDA has proposed a system to measure and rate a drug manufacturing facility's quality management maturity, and a firm's ability to deliver high-quality drug products reliably and without disruption

Quality Management Maturity

Quality Metrics

Business Continuity

Leadership Commitment to Quality

Communication and Collaboration

Quality Culture

Sustainable Compliance

Enhanced Pharmaceutical Quality System (PQS)

Manufacturing Strategy and Operations

Advanced Analytics

Risk Management

Customer Experience

Employee Ownership and Engagement

Continual Improvement

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Steps to Quality Management Maturity (QMM)



- Current Good Manufacturing Practice (CGMP) establishes a minimum standard for systems that assure proper design, monitoring, and control of manufacturing processes and facilities
- ICH Q10 outlines an effective pharmaceutical quality system applied throughout the product lifecycle to facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities
- Quality management maturity – measure of the consistency, reliability, and robustness of the business processes established and maintained to achieve quality policies and objectives, including a focus on achieving continual process and system improvement.

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QMM and Postapproval Changes

- Continual system and process improvement may identify the need for post-approval changes
- Need for regulatory submissions may dissuade some manufacturers from making needed CMC changes
- QMM + product and process knowledge, including relevant manufacturing experience at the proposed commercialization site, can be leveraged to support increased regulatory flexibility for making manufacturing changes – see *ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management*

Building a QMM Program

- Learn from efforts to date
 - PDA Quality Culture Initiative
 - ISPE Advancing Pharmaceutical Quality Program
 - University of St. Gallen research
 - FDA/CDRH Case for Quality Pilot Program
- Conduct outreach to purchasing organizations, pharmacy chains, and other federal agencies
- Execute 2 pilot programs announced October 2020 using QMM framework developed in coordination with 3rd party appraisers
 - QMM FDF Pilot Program – open to domestic manufacturers of drug products marketed in the U.S.
 - QMM API Pilot Program – open to foreign manufacturers of API used in drug products marketed in the U.S.
- Seek and incorporate stakeholder input

Manufacturing Quality Takeaways

- COVID-19 public health emergency has highlighted previously existing challenges in supply chain management and drug shortages
- Proactive risk management, which includes supply chain management, is a theme of recent legislation and internationally harmonized guidelines
- Quality management maturity is attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement
- Higher levels of QMM can support increased regulatory flexibility for post-approval changes to address supply chain and other quality challenges
- FDA's QMM program will build on existing programs, pilot programs, and stakeholder input

Guidance for Non-sterile Manufacturers

FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products



Drug Safety and Availability

Information about Nitrosamine Impurities in Medications

Drug Alerts and Statements

Medication Guides

Drug Safety Communications

Drug Shortages

FDA Drug Safety Podcasts

Information by Drug Class

Medication Errors Related to CDER-Regulated Drug Products

Postmarket Drug Safety Information for Patients and Providers

[7/7/2021] The FDA advises drug manufacturers of non-sterile, water-based drug products that Burkholderia cepacia complex (BCC or B. cepacia) continues to pose a risk of contamination.^{[1], [2], [3]} BCC is a group of gram-negative bacteria comprising more than 20 species that has been linked to multiple instances of opportunistic infections.^[4] For example, Paroex® Chlorhexidine was [recalled](#) in 2020 due to objectionable microbial contamination including the BCC species B. lata. Inadequate design, control, or maintenance of pharmaceutical water systems have led to contamination with BCC and other water-borne opportunistic pathogens.

Patients exposed to BCC contamination may be at an increased risk for illness or infection, especially patients with compromised immune systems or who are otherwise susceptible to infection.^[5] In 2016, severe BCC infections occurred when contaminated docusate oral solution was used in intubated children and other compromised patients. Repeated recalls of contaminated antiseptics, such as povidone iodine, benzalkonium chloride, and chlorhexidine gluconate, have occurred in the U.S. and overseas. These drugs may be used in hospitals when caring for patients who are often particularly vulnerable due to their medical conditions.^{[6], [7], [8]}

It is essential that manufacturing facilities, equipment, and processes are designed to prevent contamination and strict sanitary standards are continually followed. There is a long history of product recalls due to BCC contamination traced back to deviations from [current good manufacturing practice \(CGMP\) requirements](#).

In light of these BCC contamination incidents, the FDA is reminding drug manufacturers to:

Content current as of 07/07/2021

- **Microbiological Quality Considerations in Non-sterile Drug Manufacturing Guidance for Industry** - on the CDER agenda as a priority for issuance
- **The guidance will address the importance of a robust design and control program to prevent contamination of non-sterile products, in accordance with CGMP**
 - Lifecycle attention to manufacturing quality
 - Consider intended use of each drug product and patients who may receive the drug
 - Understand the microbial risk factors associated with the product and process, and the hazard posed by objectionable microbes surviving or proliferating in the product

Warning Letter Trends

Recent Warning Letters Themes

- Low process capability or lapse in state of control (process validation)
- Deficient investigations of production or laboratory problems
- Excessive variability in component quality (supplier reliability concern)
- Chemical or microbial contamination of drug products
- Deficient facilities or equipment
- Failure to meet quality unit responsibilities, including batch release requirements

“Describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.”

“These repeated violations demonstrate a failure of your executive management to exercise proper oversight and control over the manufacture of drugs. You should immediately and comprehensively assess your company’s global manufacturing operations to ensure that systems, processes, and ultimately, products conform to FDA requirements.”

In Summary

- Accelerated development and authorization of several therapeutics against COVID-19
- Enhanced analytical approaches and interventions to identify and mitigate drug supply chain disruptions
- Continued to progress the quality management maturity program
- Highlighted the hazards posed by objectionable microbiological contamination of non-sterile drugs
- Continued emphasis on the critical role of CGMP-compliant quality systems as the foundation for reliable quality and supply