Case Study: Microbiological Quality Considerations in Non-Sterile Drug Manufacturing

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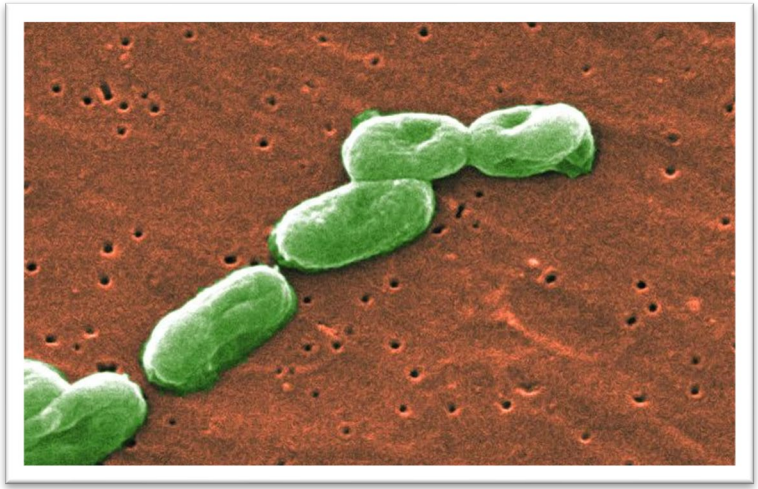
- **severe illnesses and deaths associated with *Burkholderia cepacia* complex**
- patients in 13 hospitals across 9 states

Burkholderia cepacia Complex (BCC)

- complex of ~20 closely related species
- opportunistic human pathogens
- can cause severe life-threatening infections



Voluntary Nationwide Recall of all Liquid Products Manufactured by Pharmatech LLC and Distributed by Leader Brand, Major Pharmaceuticals, and Rugby Laboratories Due to Possible Product Contamination

What Happened?

Presentation Overview

A. Current Good Manufacturing Practice

B. Objectionable Organisms

C. Case Study

D. FDA Advisory Notice

E. FDA Draft Guidance for Industry

A. Current Good Manufacturing Practice (CGMP)

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act

- A drug shall be deemed adulterated…..
- If its manufacture does not conform to CGMP

CGMP Regulations for Finished Pharmaceuticals – 21 CFR 210 and 211

- contain minimum requirements for manufacturing, processing, and packing a drug product.
- Intended to make sure that a product:
  - is safe for use
  - has the ingredients and strength it claims to have

B. Objectionable Organisms

Objectionable

- 21 CFR 211.84(d)(6)
- 21 CFR 211.113(a)
- 21 CFR 211.165(b)

Preamble to 21 CFR 211 Regulations

"Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them."

211 Preamble (cont.)

- “unique circumstances of a particular formulation”
- “a particular ingredient”
- “a particular method of manufacture”

- “the conditions found at a particular firm”

The United States Pharmacopeia (USP) and Non-Sterile Dosage Forms

- Compendial products must comply with applicable and binding USP General Chapters
- Manufacturers of non-compendial articles may use USP General Chapters to assist them in meeting some CGMP requirements
- Significant CGMP issues possible when General Chapters are either misinterpreted or narrowly applied

Misapplication of USP Content

- USP indicator organisms do not provide a sufficient standard for objectionable microorganism testing
- USP Monograph tests, assays, limits, and referenced General Chapters <u>are not batch release standards</u>

C. Case Study

The Pharmatech Story

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Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

A multistate investigation of health care–associated *Burkholderia cepacia* complex infections related to liquid docusate sodium contamination, January-October 2016

Janet Glowicz PhD, RN [a,b,*], Matthew Crist MD [a], Carolyn Gould MD [a], Heather Moulton-Meissner PhD [c], Judith Noble-Wang PhD [c], Tom J.B. de Man MS [c], K. Allison Perry MS [c], Zachary Miller MS [d], William C. Yang PhD [e], Stephen Langille PhD [e], Jessica Ross BS [f], Bobbiejean Garcia MPH [f], Janice Kim MD [g], Erin Epson MD [g], Stephanie Black MD [h], Massimo Pacilli MPH [h], John J. LiPuma MD [i], Ryan Fagan MD [a], The *B. cepacia* Investigation Workgroup

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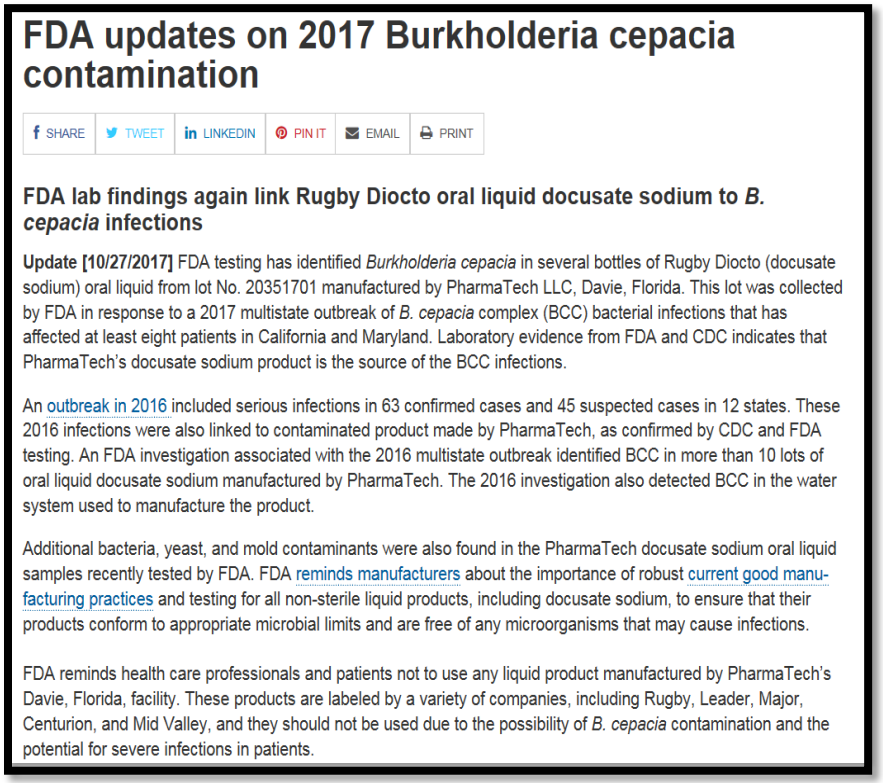
[i] *Burkholderia cepacia Research Laboratory and Repository, Ann Arbor, MI*

October 2017

FDA testing identifies *B. cepacia,* other bacteria, and fungi in several bottles of docusate manufactured by Pharmatech



FDA updates on 2017 Burkholderia cepacia contamination

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FDA lab findings again link Rugby Diocto oral liquid docusate sodium to *B. cepacia* infections

Update [10/27/2017] FDA testing has identified *Burkholderia cepacia* in several bottles of Rugby Diocto (docusate sodium) oral liquid from lot No. 20351701 manufactured by PharmaTech LLC, Davie, Florida. This lot was collected by FDA in response to a 2017 multistate outbreak of *B. cepacia* complex (BCC) bacterial infections that has affected at least eight patients in California and Maryland. Laboratory evidence from FDA and CDC indicates that PharmaTech's docusate sodium product is the source of the BCC infections.

An outbreak in 2016 included serious infections in 63 confirmed cases and 45 suspected cases in 12 states. These 2016 infections were also linked to contaminated product made by PharmaTech, as confirmed by CDC and FDA testing. An FDA investigation associated with the 2016 multistate outbreak identified BCC in more than 10 lots of oral liquid docusate sodium manufactured by PharmaTech. The 2016 investigation also detected BCC in the water system used to manufacture the product.

Additional bacteria, yeast, and mold contaminants were also found in the PharmaTech docusate sodium oral liquid samples recently tested by FDA. FDA reminds manufacturers about the importance of robust current good manufacturing practices and testing for all non-sterile liquid products, including docusate sodium, to ensure that their products conform to appropriate microbial limits and are free of any microorganisms that may cause infections.

FDA reminds health care professionals and patients not to use any liquid product manufactured by PharmaTech's Davie, Florida, facility. These products are labeled by a variety of companies, including Rugby, Leader, Major, Centurion, and Mid Valley, and they should not be used due to the possibility of *B. cepacia* contamination and the potential for severe infections in patients.

Former CEO of Drug Manufacturing Company Pleads Guilty to Conspiring to Defraud the FDA and Distributing Adulterated Drugs

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Department of Justice
Southern District of Florida

FOR IMMEDIATE RELEASE
Friday, June 24, 2022

Miami, Florida – Raidel Figueroa, the former CEO and co-owner of Pharmatech, LLC, a drug and dietary supplement manufacturer that operated in Broward County, Florida, pled guilty to conspiring to defraud the FDA, falsifying records in an FDA investigation, obstructing proceedings before the FDA, and distributing adulterated drugs in Fort Lauderdale federal court yesterday.

D. FDA Advisory Notice

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

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Advisory Notice

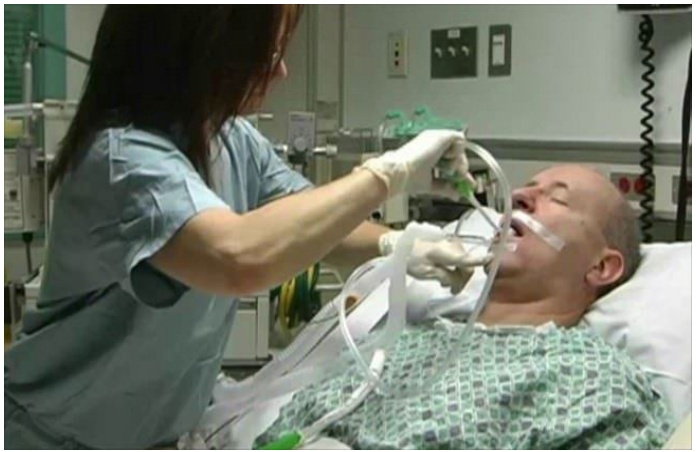
- Reminded manufacturers of relevant CGMP requirements
- Addressed specific BCC concerns/considerations
- Discussed preservative system function
- Notified manufacturers of USP <60> and FDA draft guidance

2021 – Updated Advisory Notice

In 2016, severe BCC infections occurred when contaminated docusate oral solution was used for children requiring mechanical ventilation and for other immunocompromised or susceptible patients.[2,3] The distribution of this contaminated product ultimately led to criminal charges and conviction.[4] In addition, repeated recalls of contaminated antiseptics, such as povidone iodine, benzalkonium chloride, and chlorhexidine gluconate, have occurred in the United States and overseas. These marketed defects are notable because these drugs are often used in hospitals when treating patients who are particularly vulnerable due to their medical conditions. [3,5-9]

Case Study #2

- October 2022 - another multistate BCC outbreak
- Mostly COVID patients administered chlorhexidine gluconate



Case study #2

- Product had passed the manufacturer's release testing
- Firm not testing for BCC
- USP <1111>
- Retain samples failed microbiological testing

Case study #2

- Inadequate equipment cleaning
- Inappropriate equipment design

More Case Studies

- Contamination of aqueous-based throat spray and liquid antacid with *Escherichia coli*
- Contamination of moisturizing cream with *Pseudomonas* and *Staphylococcus*
- Excessive contamination of a non-aqueous-based cream indicated for infants
- Alcohol antiseptics contaminated with *Bacillus cereus*

E. FDA Draft Guidance for Industry: Microbiological Quality Considerations in Non-sterile Drug Manufacturing

Principles

- Microorganisms can affect the safety and efficacy of non-sterile drugs
- The number and type of organisms must be limited
- Prevention, risk-based control, and monitoring are essential
- Quality should be designed into equipment, facilities, and processes

Notable Risks

- Water / water systems
- Product's ability to support microbial growth

Risk-Based Impact Assessment

- Product
- Manufacturing process, components, facilities, equipment, and personnel
- Microbiological testing

Microbiological Concerns for Specific Dosage Forms and Cases

- Solid dosage forms
- Non-solid dosage forms
- Microbiological consideration – special cases

Resources

- American Journal of Infection Control - A multistate investigation of health care–associated Burkholderia cepacia complex infections related to liquid docusate sodium contamination, January-October 2016
- DOJ Press Release - Former CEO of Drug Manufacturing Company Pleads Guilty to Conspiring to Defraud the FDA and Distributing Adulterated Drugs

Resources

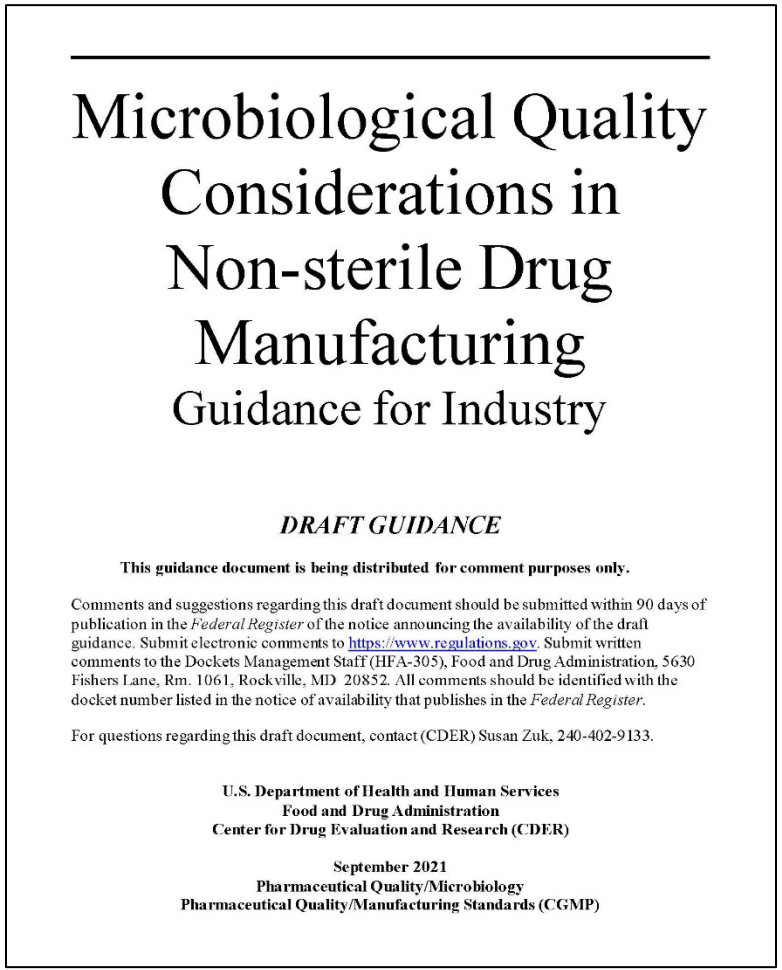
- FDA Advisory Notice - FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products
- FDA Draft Guidance for Industry - Microbiological Quality Considerations in Non-sterile Drug Manufacturing

Take-Home Messages

- CGMP requires the absence of objectionable microorganisms
- Microbial contamination of non-sterile drugs can cause serious illness and death
- Quality should be designed into facilities, equipment, and processes

Take-Home Messages

- CGMP noncompliance has resulted in recent tragedies
- FDA Advisory Notice and Draft Guidance are available



Microbiological Quality Considerations in Non-sterile Drug Manufacturing

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Zuk, 240-402-9133.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2021
Pharmaceutical Quality/Microbiology
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Please Read FDA's Draft Guidance!

Questions?

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FDA
U.S. FOOD & DRUG
ADMINISTRATION