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Burkholderia cepacia in pharmaceutical industries

Abstract

Burkholderia Cepacia is one of the most common bacterial species found in contaminated pharmaceutical products, in some years it was considered to be number one bacterial species found in contaminated pharmaceutical products.

B. Cepacia is not easy to be detected in laboratories and can be transmitted to products through raw materials, different water sources or even machine surfaces. Detection techniques of *B. cepacia* in pharmaceutical quality control have been very slow using traditional media and sometimes traditional methods fail to detect this bacterium. Rapid PCR detection of *B. cepacia*in pharmaceutical products contaminated with this bacterium allowed faster detection and higher resolution than standard microbiological methods that require time consuming and multiple procedures. This bacterium has different pathogenic effects on patients, specially people with CF.

Keywords: burkholderia cepacia, cystic fibrosis, pharmaceutical products, product recall

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Abbreviations: *B. cepacia*, *burkholderia cepacia*; CF, cystic fibrosis; *P, aeruginosa*, *pseudomonas aeruginosa*

Introduction

Burkholderia Cepacia is an opportunistic pathogen. *B. cepacia* is a bacterium that found in the moist area of soil around the roots of plants and can be found in different water sources and sometimes can survive on solid surfaces for several weeks. *B. cepacia* is not considered to cause infection in healthy people but infections can occur in immune compromised patients who do not have CF.

Bulkholderia and pseudomonas

Burkholderia Cepacia was first known as Pseudomonas cepacia prior to 1992. Walter H. Burkholder, while teaching at Cornell Universityin1947, identified this bacteria as the source of onion skin rot (cepacia is Latin for "like onion"). Since then, it has been associated with numerous health issues including endocarditis, wound infections, catheter-related urinary infections and intravenous bacteraemia.

By the 1990s, taxonomists found that *B. cepacia* has different characteristics and sufficiently different from P. aeruginosa and since then the type species of the new genus Burkholderia appeared. Burkholderia was named after the American microbiologist, William Burkholder, who described the organism before as the cause of onion rot (the Latin name for onion is cepia). Further analysis by 16 rRNA resulted in division of *B. cepacia* into closely related species called *Burkholderia Cepacia* complex (Bcc). Bcc consists of 17 closely related species of the *proteobacteria* subdivision.

The effect of *Burkholderia* on CF patients

Most conditions caused by *B. cepacia* are affecting patients with impaired immune systems or chronic lung disease, particularly cystic fibrosis (CF). *B. Cepacia* mainly causes pneumonia or lung bacterial infection. *B. cepacia* was first described in patients with CF in the late 1970s; infection was more common in older patients. *B. cepacia* is very resistant to antibiotics used to treat people with CF, these antibiotics are effective on other bacteria rather than Burkholderia. CF in some cases may cause death to people with impaired pulmonary functions.

Materials and methods

This study was done through searching different sources and studies of *Burkholderia Cepacia*, this was done the or etically through collecting data and incidents of *B. cepacia* break though and development. And was done practically through investigating the properties of this bacterium in laboratories during the career and study life. The results of this theoretical and technical research will be detailed in this study.

Results and Discussion

Burkholderia in pharmaceuticals

Microbial contamination is a major reason for product recall in the United States. Several publications have reported the frequency of microbial contamination in non-sterile and sterile products from 1998 to 2011. It was found that number one species isolated were *Burkholderia Cepacia*looking at FDA recall data from January 2012 to July 2012, *B. cepacia*was the number one microbial contaminant in non-sterile products (Table 1). 39% of bacteria isolated from contaminated samples were identified as *B. cepacia,* the contaminated samples were sanitizers, oral pharmaceuticals, and gas relief drops. Although some surveys indicates that *B. cepacia* is one of the most frequently isolated bacterial contaminants in pharmaceutical samples around the world. *B. cepacia* is not listed by pharmacopoeias to be detected in non-sterile dosage forms.

On [8/9/2016] FDA announces voluntary nationwide recall of all liquid products manufactured by Pharma Tech and distributed by six companies stating that: FDA is alerting health care professionals and consumers of Pharma Tech's voluntary recall expansion to include all liquid products due to possible *Burkholderia Cepacia* contamination.

B. cepacia is a very adaptive organism and can live for a very long time if kept in moist environments;

For example, it can survive for several weeks on sputum–contaminated surfaces and for years in water.

Heating and drying are two of the best ways to eradicate this organism; *B. cepacia* can use other routes of transmission including contact with hard surfaces. Perhaps most important to note is this microbe stability to remain viable under harsh conditions of antiseptics

for several months. Given the robust nature of the organism, it is important to consider the relatively high patient risk when this microorganism is present in manufacturing equipment, components, or the process water used in manufacturing pharmaceutical products.

Table 1 Pharmaceutical product recall data from January 2012 to July 2012

Recall Number	Non Sterile	Reason
1	Alcohol Free Sanitizer	B. cepacia
2	Alcohol Free Sanitizer	B. cepacia
3	Oral pharmaceuticals	B. cepacia
4	Alcohols pads	Bacillus cereus
5	Alcohols pads	Bacillus cereus
6	Gelatin capsules	Microbial contamination
7	Alcohols pads	Bacillus cereus
8	Pharmaceutical cream	Enterobacter gergoviae and Pseudomonas monteilii/plecoglossicida.
9	Povidone iodine solution	Elizabethkingia meningoseptica
10	Pharmaceutical gel	Microbial contamination
11	Baby lotion	Microbial contamination, Staphylococcus
12	Peptobismol	Microbial contamination
13	Gas relief drops (Simethicone)	Microbial contamination,B. cepacia
14	Gas relief drops (Simethicone)	Microbial contamination,B. cepacia
15	Pharmaceutical solution	LSA Antimicrobial preservative failure
16	Pharmaceutical solution	LSA Antimicrobial preservative failure
17	Hand sanitizer	B. cepacia
18	Hand sanitizer	B. cepacia

Burkholderia resistance

*B. cepacia*can survive trough different antiseptics, preservatives and resist several antibiotics. *B. cepacia* can grow and survive in pharmaceutical products, active ingredients, and excipients leading to the development of resistance to preservative systems used to protect formulations. Due to mucin-binding proteins, *B. cepacia* can form biofilm to help its adaptation and that provide physiological resistance to antimicrobial treatments and some antibiotics.

Microbial biofilms develop when microorganisms adhere to a surface by producing extracellular polymers that facilitate adhesion and provide a structural matrix. Once these cells attach and produce extracellular polysaccharides in the biofilm, their rate of growth is influenced by flow rate, nutrient composition of the medium, antimicrobial-drug concentration, and ambient temperature. It is well established that microbial biofilms can impart physiological resistance to antimicrobial treatment a thousand fold greater compared to exposure to the same bacteria exposed as individual cells.

B. Cepacia has intrinsic antibiotic resistance by the release of b-lactamase; *B. cepacia* is a multi-drug resistant organism. The multi-resistance of Bcc bacteria appears to result from various efflux pumps that efficiently remove antibiotics from the cell, decreased contact of antibiotics with the bacterial cell surface due to Bcc' stability to form biofilms, and changes in the cell envelope that reduce the permeability of the membrane to the antibiotic.

B. cepacia is also resistant to many disinfectant cleansers and is unaffected by many preservatives including Betadine. Bcc are among the most antimicrobial agent–resistant organisms encountered in the clinical laboratory. Some strains are reported to grow in distilled water at temperatures as low as12°C and as high as 48°C.

In 1981 the FDA sent a letter to the pharmaceutical industry that stated: The FDA has recently encountered a situation in which failure to validate and control a system used to produce ionized water resulted in a drug product contaminated with Pseudomonas cepacia. The product was recalled, and the firm took corrective action. A follow up by the FDA disclosed that the failure to validate and control deionized water systems is not an isolated instance limited to this particular firm.

Therefore, each company is expected to develop microbial specifications for the non- sterile products. The USP 39 NF 34 Chapter 1111 provides methodology for selected indicator organisms, but not all objectionable organisms. For example, it is widely recognized that *Burkholderia Cepacia* is objectionable if found in a topical product or nasal solution in high numbers; yet, there are not any methods provided in the USP that will enable the identification of the presence of this microorganism. A relevant example of this problem is the recall of Metaproterenol Sulfate Inhalation Solution. The USP monograph requires no microbial testing for this product. The agency classified this as a Class I recall because the product was contaminated with *Burkholderia Cepacia.*

Although *B. cepacia* may cause serious consequences in vulnerable populations. Pharmaceutical companies are responsible for monitoring their components, processes, and products to prevent contamination of objectionable microorganisms. The history of several products matrices and past recalls confirm that preservatives do not prevent contamination, and some strains proliferate in preserved solutions. Water is the most common input in pharmaceutical manufacturing, and potable water is a common source of Bcc. Water for pharmaceutical purposes should be handled in a manner that minimizes microbial numbers, endotoxins, and organic and inorganic compound.

Most probable root causes of contamination with Burkholderia in pharmaceutical industries:

a. Inadequate cleaning procedures and lack of cleaning validation studies.

b. Use of unsuitable grade of water as potable water.

c. Poor water system control.

d. Poor water system design.

e. Insufficient microbiological controls.

f. Lack of environmental floral studies.

g. Using specific type of disinfectant for long period of time.

Detection of B. cepacia

Carson et al. described in a research the recovery of four strains of *Burkholderia Cepacia*. Their recovered "Strain1" was recovered from amist therapy unit nebulizer. Upon transfer to tryptic soy broth from distilled water, 99–99.9% of "Strain1" was non-recoverable. Now that *B. cepacia* consists of more than17 species, we do not know which species or strains might behave like "Strain1".[1–8]

Conclusion

B. cepacia is a hard to detect organism, with high resistance to antiseptics and antibiotics and can grow in low nutrient medium. Most

common sources of this organism in pharmaceutical industries are water sources. Furthermore, microbial contamination is non-uniform and can often be difficult to detect. Robust manufacturing facility and process design, and strict daily operational control, is a must. Finished product testing is only the final step in a series of controls, and alone provides insufficient assurance of product quality. Quality control testing cannot ensure sufficient sampling to provide adequate assurance of the absence of any objectionable microorganism when contamination is occurring sporadically or at low frequencies.

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Conflicts of interest

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