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## Review

***Burkholderia cepacia*: This Decision Is Overdue**

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**ABSTRACT:** This is the third in a series of seven articles discussing the Recall Root Cause Research project conducted by the Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research. This paper reviews the regulatory and scientific impact of a common and recurring opportunistic pathogen, *Burkholderia cepacia*. *B. cepacia* is comprised of closely related species called *Burkholderia cepacia* complex, which has contaminated many finished pharmaceutical products and environments used to manufacture pharmaceuticals. This review includes a brief perspective as described in several U.S. Food and Drug Administration (FDA) documents, and assesses root cause using product recall reports and FDA Establishment Inspection Reports. We identify several possible points of origin for microbial contamination. This discussion also includes concern with anomalies in test methods that may influence *B. cepacia* measurement. The issue of objectionable microorganisms and whether *B. cepacia* can readily be included in a compendial chapter is briefly discussed.

Finally, this paper underscores that drugs contaminated with *B. cepacia* pose a serious threat to susceptible patients, particularly those with cystic fibrosis or who are otherwise immunocompromised. It is therefore important to prevent *B. cepacia* from contaminating pharmaceutical manufacturing environments, raw materials, and finished products.

**LAY ABSTRACT:** *Burkholderia cepacia* is a species of bacterium that is commonly found in natural environments such as soil, water, rhizosphere and agriculture products. The species name represents a group of closely related organisms. These bacteria have contaminated many drug products and can create public health concerns. Pharmaceutical products that are contaminated with *B. cepacia* may pose serious consequences to vulnerable patients (e.g., compromised immune system). Preventing *B. cepacia* contamination in drugs by addressing the potential sources of this bacteria in a drug manufacturing operation is an important public health goal. This review highlights potential sources of *B. cepacia* species as they relate to U.S. Food and Drug Administration findings recorded in data from Establishment Inspection Reports and Warning Letters.

**Introduction**

This is the third in a series of seven papers reporting on Recall Root Cause Research (RRCR) led by the Division of Manufacturing and Product Quality (DMPQ), in the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) (1–3).

*Burkholderia cepacia* (pronounced Burk-HOLD-er-ia Sa-PAY-shah) was known as *Pseudomonas cepacia* prior to 1992. Walter H. Burkholder, while teaching at Cornell University in 1947, identified the microbe 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, intravenous bacteremias, and foot infections or “foot rot” (4).

*Burkholderia cepacia* is an opportunistic pathogen that causes disease primarily among immunocompromised populations. Specific populations susceptible to infection include elderly people, young children, cancer patients, pregnant women, and people with chronic

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illness. However, *B. cepacia* occasionally causes illness in non-immunocompromised, previously healthy patients.

The most serious conditions caused by *B. cepacia* are pneumonia or bacterial infection that occur in patients with impaired immune systems or chronic lung disease, particularly cystic fibrosis (CF). CF is the most common lethal inherited disease of Caucasian populations, with pulmonary infections being the major cause of morbidity and mortality. The severity of infection or colonization by *B. cepacia* may be different for individual patients. However, overall, pulmonary colonization reduces survival by 50%; about one-third to one-half of patients succumb to cepacia syndrome, a rapidly fatal necrotizing pneumonia (5).

Recent advances in taxonomy caused *Pseudomonas cepacia* to be moved from the genus *Pseudomonas* and placed in the genus *Burkholderia*. The genus *Burkholderia* currently comprises more than 60 species. 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  $\beta$ -proteobacteria subdivision.

Bcc are widely distributed in natural and man-made habitats (6). These species are free-living, non-fermenting, Gram-negative aerobic bacteria with motility due to multitrichous polar flagella (7). They are common in nature and present in soils, plant rhizospheres, water, and agriculture products. They are found in both urban and suburban soil (8). In some situations, they are also used as a bio-pesticide to prevent fungal diseases. Infections caused by Bcc have occurred worldwide, and accumulating evidence implicates contaminated pharmaceuticals, cosmetics, disinfectants, and preservative products as major sources of Bcc (6).

Besides their role in causing disease, Bcc species have unique metabolic features that are of potential commercial value. Some Bcc strains have been shown to degrade carcinogenic or toxic products such as ethers present in gasoline, polycyclic aromatic compounds and other constituents of crude oils and coal, and herbicides such as 2,4,5-trichlorophenoxyacetic acid (the principal component of Agent Orange) (5). This use has raised concern because the same characteristics that make species of Bcc a good candidate for bioremediation, including the ability to metabolize a

wide variety of carbon sources and secretion of bio-film exopolysaccharides, also make it difficult to prevent and eliminate when it appears as a contaminant in pharmaceutical products and in laboratory and manufacturing equipment. According to Jimenez:

a survey of the scientific literature indicates that *B. cepacia* is one of the most frequently isolated bacterial contaminants in pharmaceutical samples around the world. However, *B. cepacia* is not listed by any of the pharmacopoeias . . . (9).

In epidemiological terms, the mode of interpersonal transmission for this opportunistic pathogen primarily occurs through direct contact with other people (e.g., a handshake), or through contact with body perspiration. Although *B. cepacia* does not appear to survive on completely dry surfaces for more than one week, it can survive for many months in water (4). *B. cepacia* can use other routes of transmission including contact with hard surfaces. Perhaps most important to note is this microbe's ability to remain viable under harsh conditions (e.g., organic solvents, antiseptics, low nutrients, etc.) for many 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.

Collective evidence on the unique adaptation skills of Bcc were recently described in a mini-review by Vial *et al.* (10). They described experiments showing that Bcc can survive and grow within the vacuoles of both amoeba and mammalian macrophages and monocytes. Nasal mucosa has been known to carry amoeba and "consequently could represent an important natural reservoir for Bcc strains and act as a Trojan horse allowing bacteria to access the respiratory tract." They hypothesized that with Bcc's ability to adapt and survive intracellular respiratory epithelial and phagocytic cells, "these properties confer obvious advantages to persist in mammalian lungs, which are a classical entrance route for numerous microbial pathogens" (10).

Bcc are multi-drug resistant organisms. 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's ability to form biofilms, and changes in the cell envelope that reduce the permeability of the membrane to the antibiotic (6). *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 (11). Some strains are able to grow in distilled water at temperatures as low as 12 °C and as high as 48 °C (12). Due to mucin-binding proteins, this species can form biofilms and contaminate plastics, metals, water systems, hospital equipment, catheters, and living tissue.

Microbial biofilms develop when microorganisms adhere to a surface by producing extracellular polymers that facilitate adhesion and provide a structural matrix (13). 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 (13). 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 (14).

### FDA Guidance

In addition to biofilm formation and successful proliferation on several types of surfaces, Bcc presents challenges to their detection and removal or destruction. The concern and threat of Bcc is not a new issue and has been addressed in the general scientific literature and by the FDA. For example, in 1981 the FDA sent a letter to the pharmaceutical industry that stated in part:

The FDA has recently encountered a situation in which failure to validate and control a system used to produce deionized water resulted in a drug product contaminated with *Pseudomonas cepacia* [sic], a pathogen. The product was subsequently 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 (15).

Another example comes from the 1993 FDA guidance document *Guide to Inspections of Microbiological*

*Pharmaceutical Quality Control Laboratories*, where the FDA stated:

Therefore, each company is expected to develop microbial specifications for their non-sterile products. Likewise, the USP Microbial Limits Chapter (61) provides methodology for selected indicator organisms, but not all objectionable organisms. For example, it is widely recognized that *Pseudomonas cepacia* [sic] is objectionable if found in a topical product or nasal solution in high numbers; yet, there are no test 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 Meta-proterenol Sulfate Inhalation Solution. The USP XXII monograph requires no microbial testing for this product. The agency classified this as a Class I recall because the product was contaminated with *Pseudomonas gladiolicepacia*. The health hazard evaluation commented that the risk of pulmonary infection is especially serious and potentially life threatening to patients with chronic obstructive airway disease, cystic fibrosis, and immunocompromised patients. Additionally, these organisms would not have been identified by testing procedures delineated in the general Microbial Limits section of the Compendia (16).

### Pathogenicity and Risk of Disease Complications

Only a subset of the human population is considered "healthy." The specific characteristics of a healthy person are subjective and vary depending on the country and criteria used to make this judgment. For this fortunate group of people, exposure to some Bcc species results in little or no morbidity, and rare mortality if infection does occur (11).

However, the world's increasing population of the elderly, malnourished, and immunocompromised individuals and infants can be at considerable risk. Bcc species adversely affect CF patients, often with fatal results. A recurring theme among CF patients is that strains of *B. cepacia* are recovered following repeated courses of antimicrobial treatment. These strains are frequently resistant to all known antimicrobial agents (11).

Research indicates that *B. cepacia* strains exhibit random genetic changes that can confer a high frequency of transmissibility, or given the right epidemiologic circumstances, these altered genetic changes can benefit the organism's communal survival (related to comment above re: virulence) and pathogenicity (4). As described earlier, the close genetic relatedness of these species raises concerns about the possibility of DNA exchange among different species. Exchange of genes for virulence factors might increase adaptability and diminish the effectiveness of treatment and control. Early investigations mistakenly indicated that there was no solid evidence available for genetic exchange between different Bcc species in natural environments. However, in vitro transduction of antibiotic resistance between Bcc species raises a realistic possibility due to the existence of Bcc phage with broad host specificity and the presence of common DNA insertion sequences in different Bcc species (17). Confirmatory evidence recently published indicates that genes located in secondary chromosomes are subject to a faster evolutionary rate (6). In fact, one report describes the incidence of these alterations as more than 10% due to horizontal gene transfer. One result of these gene transfers is greater metabolic diversity of these microorganisms. It was further determined that in at least one case "the *B. cenocepacia* strain, J2315, displayed 14 genomic islands most probably arisen from horizontal gene transfer. The acquisition of genomic islands appears to play a crucial role in the evolution of this particular epidemic lineage, introducing new functions that promoted survival and pathogenesis in the CF lung" (6).

The consequences of antimicrobial resistance are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of transmissibility and increased numbers of infectious people in the community who expose the general population to a resistant strain (18). Taking steps to eliminate contaminated products will limit sources of exposure by Bcc species to immunocompromised individuals such as those with CF (19).

*B. cepacia* complex has generated considerable anxiety amongst patients with CF and has changed the way in which CF care teams manage their *B. cepacia* infected patients. Median survival rates decline markedly to

approximately 15–19 years with a history of *B. cepacia* complex infection (19).

Bcc-contaminated products are most harmful to CF patients receiving lung transplantations. The mortality rate is high. Mortality rates in the United Kingdom for the first year of infection were reported at 50–100% (20).

Of the 11 patients with cystic fibrosis who were also infected with *B. cepacia* complex, five died post-transplant because of progressive *B. cepacia* related sepsis . . . All five patients were clinically unresponsive to cyclical antibiotics and thoracostomy drainage.

A team in Toronto, Canada reported their experiences (21):

Of the 53 [transplant] recipients, 19 have died (15 of 28 [54%] *B. cepacia* positive and 4 of 25 [16%] *B. cepacia*-negative). *B. cepacia* was responsible for or involved in 14 deaths . . . One-year survival was 67% for *B. cepacia*-positive patients and 92% for *B. cepacia*-negative patients.

Another study in Liverpool, England found similar results (22):

Thirty-seven patients had been colonized by epidemic *B. cepacia* and these patients had four times the mortality of the remainder ( $P < 0.01$ ) . . . This study confirms the excess mortality associated with epidemic *B. cepacia* colonization and shows that those with poor spirometric values are at the greatest risk.

CF patients are an at-risk population who need special consideration given the inherent danger associated with any exposure to Bcc species. CF patients must not be exposed to Bcc species in their prescription drugs or any over-the-counter product.

### Manufacturing Control Measures

Although *B. cepacia* contamination in a topical wipe or ointment may be a minor nuisance for most patients, it may cause serious consequences in vulnerable populations. Pharmaceutical companies bear the responsibility to monitor their components, processes,



and products to prevent contamination of objectionable microorganisms. The literature and past recalls confirm that preservatives do not prevent contamination, and some strains proliferate in preserved solutions.

Specifically, manufacturers can not rely on preservatives for the control of Bcc, but can address contamination by other, reliable means such as in-process controls and sterile product manufacturing.

To prevent the risk of this opportunistic and adaptable pathogen, manufacturing control measures must include not only effective cleaning, disinfecting, and drying of equipment but also must consider almost any source of water as a potential reservoir (12). Water is the most common raw material in pharmaceutical manufacturing, and potable water is a common source of Bcc. Water for pharmaceutical purposes is processed and held in a manner that minimizes microbial numbers, endotoxins, and organic and inorganic compounds (9).

### Lessons Learned from Product Recalls

We considered the public health problem associated with Bcc contamination by evaluating 16 representative recalls. Ten of the voluntary recalls were prompted by complaints of contamination. One hospital reported three patients with *B. cepacia* pneumonia. These were traced back to a contaminated mouthwash product. However, because Bcc species are common in the environment, a contaminated commercial product may be overlooked as the source of a serious infection or fatality.

The product recalls included as part of our review occurred during the years 2000 and 2008. Eight recalls were Class I, six were Class II, and two were Class III. Six recalls were initiated voluntarily following FDA findings, and the firms initiated 10 voluntary recalls. The product types included eyewash, nasal spray, mouthwash, anticavity rinse, skin cream, baby and adult washcloths, surgical prep cloth, electrolyte solution, and radiopaque preparations. Bcc had contaminated each of these products, even in the presence of one or more antimicrobial preservatives.

The preservatives used were benzalkonium chloride, cetylpyridinium chloride, chlorhexidine gluconate, citric acid, diazolidinylurea, hydrogen peroxide, lactic

acid, methylparaben, potassium sorbate, propylparaben, sodium citrate, and sodium hypochlorite. These antimicrobial ingredients are common components of pharmaceutical formulations and range from highly effective to mild in terms of microbiostatic or microbicidal activity. While there does not appear to be one class or group of antimicrobial compounds that particularly favors Bcc's resistance, these species have been able to persist in the presence of common pharmaceutical preservatives.

These companies did not report a root cause analysis for the recalls. However, information was available for review and apparent root causes were determined. No prioritization should be associated with the order of the observations listed. We identified the following potential causes:

- Inadequate cleaning procedures
- Use of unsuitable grade of water (e.g., use of potable water to clean process equipment)
- Poor water system control (e.g., lack of proper sanitization, failure to validate, and lack of scheduled maintenance)
- Poor water system design (e.g., stagnant water allowed biofilm development)
- Inadequate testing and specification (e.g., inadequate microbiological analysis, contaminated raw materials incomplete/incorrect testing for antimicrobial effectiveness)
- Inadequate procedures (e.g., incomplete equipment drying time, improper storage of intermediates, time/temperature abuse, inadequate sterilization of final product)
- Inadequate validation for environmental monitoring of critical product surfaces and equipment handling procedures

Not surprisingly, water was implicated in six recalls, while contaminated raw materials were implicated in three recalls, and inadequate testing before distribution was implicated in two recalls.

One recall report was particularly revealing in its frankness:

The purified water system had not been properly cleaned and tested since May 19XX. The president told FDA officials the company skipped the scheduled maintenance because it could not afford it. The reverse osmosis membranes of the water system had not been changed for more than a year, although this should be done every four months, according to the company's written procedure, to prevent microbial buildup. The company again cited financial difficulties as the reason. Employees failed to perform adequate microbial challenge tests—specifically for *B. cepacia*—type of microorganisms, which can flourish in the presence of the antibacterial agent the company added to its product. Corrective actions included a contract with an outside company to reengineer, validate and maintain the water purification system, sanitize the entire water system with hydrogen peroxide, change the reverse osmosis membranes, and rewrite the SOP [standard operating procedure] for the purified deionized water system.

The FDA investigation of another company concluded:

This was an unusual case of contamination, in that all ten lots of incoming solution passed initial release testing for bioburden. Later samples taken from these same lots of bulk solution, however, showed failing levels of *B. cepacia* indicating that the bacteria was proliferating in the solution. This new information calls into question the scientific soundness of the product formulation itself. Until such questions, are answered, it may be prudent to keep all lots of this product off the market.

## Conclusion

The underlying problems with organisms like *B. cepacia* is their unpredictable capacity to avoid detection (11), ability to grow in low-nutrient conditions (12), resistance to chemical preservatives (17), and the potential to cause disease. Because the most common source of this contaminant is water (13), aqueous products are especially at risk because of *B. cepacia*'s ability to remain viable in harsh conditions.

As noted throughout this paper, *B. cepacia* continues to evade detection in pharmaceutical manufacturing

operations, and inadequate control strategies have resulted in frequent recalls of products. Because the organism may grow poorly or not at all when transferred from water systems to high-nutrient culture media (12), finished product testing by conventional methods can yield misleading, false-negative results.

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 imperative. 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 encompass sufficient sampling to provide adequate assurance of the absence of any objectionable microorganism when contamination is occurring sporadically or at low frequencies. New technologies may allow enhanced detection of *B. cepacia* in various materials (8).

In their 1973 paper (12), Carson *et al.* described recovery of four strains of *Pseudomonas cepacia*. Their recovered "Strain 1" was recovered from a mist therapy unit nebulizer. Upon transfer to tryptic soy broth from distilled water, 99–99.9% of "Strain 1" was non-recoverable. Now that *B. cepacia* consists of 17 species, we do not know which species or strains might behave like "Strain 1" (12).

Research is needed to improve conventional cultivation methods to detect and recover this species in pharmaceutical materials. With the potential for nutrient shock to occur when using nutrient-rich media, cultivation conditions may cause false-negative results. It may be necessary to use a pre-enrichment recovery step, analogous to those developed for *Salmonella* (23), prior to selective cultivation to maximize the acclimation of these sometimes fastidious microorganisms (24).

Reliance on finished product testing has not been successful for eliminating Bcc contamination hazards. Regardless of the inadequacies of current test methods, the pharmaceutical manufacturer is responsible for adequately designing and controlling the drug manufacturing process to exclude potentially harmful microorganisms from entering the process stream and contaminating finished products. Process technologies exist to control this species and should be applied in pharmaceutical manufacturing to ensure that these products are safe.

This systematic review of the regulatory history associated with *Bcc* reveals that these microorganisms play a significant role in product contamination and subsequent pharmaceutical recalls. Appropriate manufacturing process improvements should include measures such as microbiological screening of materials, equipment, and environments for this and other potentially objectionable microorganisms. It is time to add this objectionable microorganism to the high-profile list of microbes to target during manufacturing, environmental monitoring, and finished product surveillance. The federal regulations for the current good manufacturing practices (cGMPs) of drugs states quite clearly in 21 CFR 211.84(d)(6) that “each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.”

This concern is again addressed in another section of the CGMP regulations, 21 CFR 211.113(a): “Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.”

Although these regulations do not specifically list the names of these objectionable microorganisms, it is the responsibility of industry, regulatory, and academic microbiologists to discover, evaluate, and publish findings on these emerging opportunistic pathogens.

Regulatory agencies possess large amounts of data and detailed inspectional reports derived from hundreds of different inspections that allow them to assess the impact of microorganisms such as *Bcc*. With this unique perspective, FDA can propose cause and effect relationships regarding the sources of a contaminant and the resulting product adulteration with these microorganisms.

The goal of this report is to clarify these relationships for the benefit of manufacturers and regulators responsible for uncovering emerging problems and high-risk activities. It is not enough just to point out that many non-sterile pharmaceutical products recalled over the last ten or more years were associated with this opportunistic pathogen. Even more alarming is the association of this opportunistic pathogen with several sterile pharmaceutical products recalled in the past several years.

*Bcc*'s ability to survive and proliferate in a wide range of antimicrobials, as well as to develop highly resistant biofilm formation, makes this microbe a target for destruction and removal from drug products and manufacturing environments. This body of work, along with the published reports of others, provide evidence that the health risks and diminished product quality associated with this opportunistic pathogen is increasing.

The scientific community has discussed the possibility of incorporating *Bcc* organisms in the USP list of bacteria found in Chapter <62> Microbial Limits Test, which includes tests for specified microorganisms. However, with the recent harmonization of the two new USP Chapters <61> and <62>, the process to make this inclusion may take a considerable amount of time (25, 26). For USP to make a unilateral decision may require creation of a separate chapter like it did with Chapter <63> Mycoplasma Tests (27).

The cGMP regulations do not specifically list objectionable microorganisms by name. However, the last two paragraphs of the USP 32 Chapter <1111> (28) may provide a practical guide for developing a risk-based assessment for the presence of an opportunistic pathogen in a pharmaceutical product. Among the criteria suggested to be included for the evaluation are the following: the use of the product (hazard varies according to the route of administration); the nature of the product (whether the product supports growth); the method of application; the intended recipient (neonates, infants, the debilitated); the use of immunosuppressive agents; and the presence of disease, wounds, or organ damage.

Much of the FDA's Quality Initiative is based on Quality by Design (QbD). Under QbD, the earliest product quality questions are intended to define the product's necessary quality attributes. These may include microbial limits or sterility. Because *Bcc* species are often capable of growing in the presence of antimicrobial agents in liquid products, there remains the potential for applying great numbers of these contaminants to open wounds or mucous membranes.

The evidence regarding the objectionable nature of this microorganism is substantial and supported by other independent research (29). *Bcc* organisms pose a clear and present danger to patient health and safety. The challenge is undeniable; now is the time to re-



move Bcc from our pharmaceutical manufacturing areas and products.

A recall is a firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers, and against which the FDA would initiate legal action (e.g., seizure). Recalls do not include market withdrawals. FDA assigns a numerical designation (I, II, or III) to a particular product recall to indicate the relative degree of health hazard presented by the product.

A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

A Class II recall is a situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

A Class III recall is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences (30).

#### Conflict of Interest Declaration

The authors declare that they have no competing interests.

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