

LETTER TO THE EDITOR

This Letter is to comment on the recent research article by Friedman *et al.*, *Burkholderia cepacia*: This Decision Is Overdue. *PDA J. Pharm. Sci. Technol.* **2011**, 65 (5), 535–543.

I appreciate the opportunity to comment on the question of the “objectionable” nature of *Burkholderia cepacia* complex (Bcc) and applaud the authors on a cogent presentation of the Food and Drug Administration (FDA) interpretation of the situation. However, regulatory science is an area where reasonable people may differ. For example, there was a time when we were expected to test hot water loops for thermophiles in the mistaken belief that they were capable of supporting growth of thermophilic organisms (1). We also were encouraged to rotate disinfectants in the illogical belief that microorganisms would become resistant in the manufacturing environment to relevant concentrations of the disinfectant (2, 3). A lingering expectation among some that we should check for obligate anaerobes under strictly aerobic conditions shows the continuing need for “science-based regulation.” These comments are not meant to suggest that I personally have anything but the highest regard for the FDA or its personnel—they have a difficult and vitally important job that is performed with distinction. However, everyone’s belief system is molded by experience. The experience with *B. cepacia* has been a particularly unpleasant one.

This history began in 1980 with a series of *Pseudomonas cepacia* (the organism’s previous name) pneumonia cases among cystic fibrosis (CF) patients that was eventually traced back to an inhalant (4). It was noted at the time that this product contaminant would not have been detected by the USP Microbial Limits Test and that the USP cannot provide tests for all organisms of concern in all product presentations (5). This experience clearly left a deep impression on the culture at FDA, as a later guide to inspections (6) devoted a significant amount of text to the failings of the USP Microbial Limits Test chapter as an adequate release test for non-sterile finished products. This inspection guide is still used as a training document for FDA inspectors.

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To this point, I am concerned that both the authors and the reviewers of this paper accepted the position that if an organism is associated with a recall, the organism must be pathogenic and objectionable. This is not true. There are two obvious reasons for a recall—the product is causing problems in the field, or someone believes that the product might cause problems in the field. If the true explanation is the latter, the existence of a recall only denotes the assumptions of the individuals involved. Given that generations of inspectors have been trained to consider *B. cepacia* “objectionable,” this is a reasonable concern. The correct interpretation of the motivation for the correlation between recalls and a specific microorganism can be determined by a search of the literature to find relevant examples of a clinical problem. This did not happen here, as I will describe, and the authors frequently assert the widespread pathogenicity of *B. cepacia* based solely on its association with recalls—recalls that were prompted by the FDA’s concerns over the presence of *B. cepacia* in the product.

I would like at this point to establish areas of agreement:

- *B. cepacia* is very dangerous to CF patients (especially Genomovar III, also known as *Burkholderia cenocepacia*) and CF patients should be protected from unwarranted contact with products containing *B. cepacia* that may cause them to catch pneumonia.
- Sterile products should be sterile—if they are not it is not relevant what the contamination might be; the concern is that the expectation of sterility for that product is not met.
- Large numbers of any organism in pharmaceutical products is contraindicated (pharmaceutical products are not food, which can apparently tolerate up to 10⁷ CFU/g of who-knows-what).

I wish to organize my commentary around the concluding paragraph of the article, which reads: “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 remove

Bcc from our pharmaceutical manufacturing areas and products.”

First of all, the assertion in this concluding paragraph that *B. cepacia* is objectionable is not based on an independent research article; the article cited is a review of FDA recalls published in 2006 and so describes much the same material as the paper. Let's look at the remainder of the assertions in order:

1. Clear and present danger
2. Remove from manufacturing areas
3. Remove from products.

I. Clear and Present Danger

The first half the section on “Pathogenicity and Risk of Disease Complications” is devoted to antibiotic resistance of the organism, the other half to the risks of performing lung transplants into patients previously colonized with *B. cepacia*. While the risk of antibiotic resistance is clear, it is the overwhelming use of antibiotics in agricultural feedstock and its impact on the environment and common soil and water organisms (such as *B. cepacia*) that is the real concern. The transmission of *B. cepacia* from the environment to the patient is well documented (7, 8). Beyond this, we must consider the enormous numbers of *B. cepacia* that have been shown to contaminate foodstuffs (9). Next to this threat the minimal potential exposure (even assuming the absolute worst-case situations) from non-sterile pharmaceutical products is vanishingly small. It would be far better protection to forbid CF patients from venturing outside or eating or especially from brushing their teeth—all of which will subject them to a huge challenge of “potentially pathogenic” organisms.

The second half of this “risk” discussion deals with four studies looking at the risk of performing lung transplant surgery on CF patients pre-colonized with *B. cepacia*. Based on these studies the procedure seems to be a very chancy situation, but the relevance of this to suntan lotion (or other non-sterile products) eludes me.

In an apparent effort to increase the scope of the proposed risk, the authors make the following astonishing and unsupported statement: “Only a subset of the human population is considered ‘healthy’.” Who is

doing this consideration remains in mystery, as are the criteria—to which the authors comment, “The specific characteristics of a healthy person are subjective and vary depending on the country and criteria used to make this judgment.” This seems to be really thin evidence upon which to be basing such a strong recommendation. Several specific populations are mentioned as particularly of concern:

- Elderly people
- Young people
- Those suffering from chronic illness
- Sometimes-healthy people.

However, it must be noted that no supporting documentation to support this assertion was cited despite this claim of broader susceptibility being made twice in the article. Based on a recent review of the literature it is, in fact, quite difficult to find evidence to support this assertion (however, see below in the discussion of alcohol-free mouthwash—those susceptible to pneumonia do seem to be at increased risk).

The phrase “clear and present danger” is usually reserved for something that is an established and immediate threat and seems to be somewhat of an exaggeration in this case.

II. Remove from Manufacturing Areas

This is another assertion the authors make, but one that is completely lacking even the semblance of scientific support in the article. It, quite literally, is presented as an established fact that the environmental monitoring program must have a list of “objectionables” and *B. cepacia* complex must be on this list. This would represent a policy change for the FDA and one that is not supported by the Code of Federal Regulations (CFR), previous guidance, or the scientific literature.

21 CFR 211 (Pharmaceutical Good Manufacturing Practice) uses the word “objectionable” three times:

- “21 CFR 211.84(d)(6). 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.”

- “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.”
- “21 CFR 211.165(b). There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.”

Note that nowhere in the CFR is the expectation to review the manufacturing environment for “objectionables.” Also note (as an aside) that “objectionables” are strictly tied to non-sterile products.

What about previous guidance? The most detailed description of the FDA expectations for the environmental conditions in manufacturing is presented in the Aseptic Processing Guide (10). Section X.A.1. explains: “In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (e.g., when a given batch is being manufactured) as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113).”

Section X.A.2 continues: “Environmental monitoring data will provide information on the quality of the manufacturing environment.”

So clearly the official position of FDA is that environmental monitoring data exist to allow for monitoring of the state of control of the facility, not as an indication of finished product quality. This is supported in published scientific articles.

Hussong and Madsen (11) discuss the use of quantitative environmental monitoring data, and from the perspective of facility monitoring tell us that “historically, however, the scope of OOS has gone beyond the ICH definition and has been applied to more than just product specifications. This historical misconception has led to an inappropriate use of environmental microbiology results as surrogate release criteria.”

Farrington (12) expands on this discussion, arguing that the relationship between environmental monitoring data and finished product quality is a popular, but unproven, belief.

If the FDA intends to make a policy change requiring “objectionable organism” evaluation of the environment, such a change should be done officially through public comment and amending 21 CFR 211. Most importantly, this change should be based on sound scientific principles rather than assumptions. This article did not provide any meaningful support for the establishment of a policy in this regard.

III. Remove from Products

This conclusion is the most heavily supported of the article. One argument presented runs as follows:

1. *B. cepacia* complex is hazardous to CF patients.
2. *B. cepacia* complex is hazardous to unhealthy patients.
3. Most of us are unhealthy.
4. We need to remove *B. cepacia* complex from all medications.

Note that this article provided no documentation to support points 2 and 3 (as described in the preceding text). Also note that this is actually an argument to require sterility of all pharmaceutical, over-the-counter (OTC), and personal products because the same argument can be made (if one is relieved of the requirement for proof) for scores of other microorganisms.

A more compelling argument presented was the following:

1. *B. cepacia* complex is hazardous to CF patients.
2. Under some conditions, CF patients might be exposed to contaminated product in a manner that might lead to infection.
3. Occasionally, CF patients so exposed may contract *B. cepacia* complex lung infection (the only proven risk).
4. Therefore all pharmaceutical, OTC, and personal products must have no *B. cepacia* complex organisms.

This argument was explained to me in conversation as the FDA “regulating to the most susceptible popula-

tion.” I have heard this philosophy expressed before as “everyone in the family must eat strained carrots because the baby can’t have steak.”

However, setting aside the questionable risk assessment inherent in this position (hazard avoidance at all costs is not risk assessment!), let’s look at the argument itself. As mentioned at the beginning of this response, there is no question about point #1. What about point #2?

Supporting evidence for point #2 was provided in the article:

1. Contaminated water system
2. FDA Guide to Inspections
3. Poor prognosis of lung transplant recipients previously colonized with *B. cepacia*
4. Contaminated mouthwash leading to patient pneumonia
5. “Voluntary” recalls following FDA findings:
 - Eyewash
 - Nasal spray
 - Mouthwash
 - Anticavity rinse
 - Skin cream
 - Baby and adult washcloths
 - Surgical prep cloth
 - Electrolyte solution
 - Radiopaque preparations

Clearly, items #1 and #2 are not relevant to establishing risk—they are statements that FDA is concerned about *B. cepacia* complex. As discussed previously, #3 is irrelevant to a discussion of risk associated with non-sterile pharmaceutical products and #5 describes firms “voluntarily” recalling products in response to FDA “suggestion”. It is precisely the basis of this FDA

“suggestion” that we are trying to determine. This leaves us with item #4.

The relevant text reads, “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.”

This is vague enough to be very difficult to comment upon, even with the curious conclusion to the statement (which might also be phrased “given the overwhelming challenge of environmental sources, contaminated product is not the first nor the most likely consideration”). However, there is a relevant case study in the literature that provides some data (13). In this situation, patients at risk for pneumonia (elderly and very young) led to 116 cases of *B. cenocepacia* (one of the organisms in the *Bacillus cepacia* complex, and the one that is most of concern to CF patients) pneumonia from 22 hospitals in widely separated geographic regions. The common thread among all these was use of an alcohol-free mouthwash that was shown to be contaminated by *B. cenocepacia*. The authors of this paper conclude: “This intrinsically contaminated AFM [alcohol-free mouthwash] led to a geographically dispersed outbreak of *B. cenocepacia*. AFM without therapeutic label claims is regulated by the US Food and Drug Administration as a cosmetic rather than a drug and is therefore subject to limited quality control requirements. Clinicians should be aware that AFM is not sterile. Its use in intubated and other patients with increased risk of aspiration should be avoided.”

This seems a reasonable and prudent course of action.

I looked for a scientific justification of the unwritten policy of viewing *B. cepacia* as a pathogenic organism whose presence alone justified recall of batches. As has been amply documented, this has been the *de facto* standard for years. Unfortunately, this proof is lacking. The discussion presented in this article states that *B. cepacia* is a pathogen because of recalls involving it and that these recalls involving Bcc prove its status as an objectionable organism. This circular argument is not what is to be hoped for in a rational risk analysis.

In conclusion, then, I appreciate the opportunity to read the opinions of FDA scientists whom I admire,

but have to point out not only does the article “*Burkholderia cepacia*: This Decision Is Overdue” employ questionable logic in risk assessment, it does not adequately support the arguments presented with relevant scientific data or case studies. If it is the intent of the agency to move towards requiring all pharmaceutical, OTC, and personal care products be sterile, this intent should be stated clearly to allow for discussion. If it is the intent to protect CF patients and those at risk for pneumonia from *B. cepacia*, then this should be done by cost-effective procedures in patient care. There are clearly some products that must be free of *B. cepacia* (inhalants, for example, and perhaps others based on demonstrated risk to the target population), but this article failed to provide convincing evidence or arguments that would lead to the conclusion that *B. cepacia* complex must be excluded from all product formats, or that we need to establish procedures for “objectionable organisms” in our manufacturing environment.

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