LOGFILE Feature 40/2021

Non-Sterile Drug Products: Microbial Risks

A Report from the 2021 PDA/FDA Joint Regulatory Conference

by Sabine Paris, PhD

The **PDA/FDA Joint Regulatory Conference**, which is now in its 30th year, took place as a virtual event from September 27 – September 29. The Conference focused on the role of effective quality systems in ensuring an ongoing state of control throughout the product lifecycle by vigilantly managing risks to manufacturing and quality.

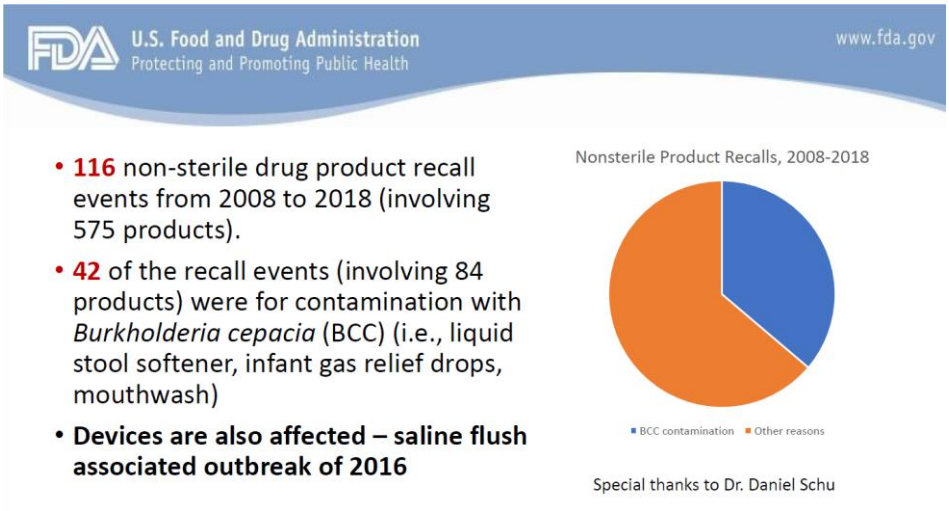
The session **Non-Sterile Drug Products: Microbial Risks** highlighted the risks posed by Burkholderia cepacia complex (BCC) and the crucial role of equipment in contamination.

"Non-sterile drug products are the most technical challenging drugs for the mircrobiologists!" Erika Pfeiler, CDER, drew this – perhaps unexpected – conclusion in her presentation The Complex: Science, Policy, and Case Studies of The Burkholderia Cepacia Complex in Aqueous Non-Sterile Drugs.

The presence of water is more predictive of microorganisms than the dosage form, because water has its own bioburden and it is necessary for microbial proliferation. Manufacturing controls for aqueous non-sterile products:

- Environmental monitoring – water monitoring
- Cleaning and cleaning validation – water system
- Controls of incoming components
- Additional step: bioburden reduction

Burkholderia cepacia complex (BCC) is problematic in manufacturing control. **"It is a kind of perfect storm for manufacturing,"** Erika Pfeiler said. BCC forms biofilms, can eat anything and is resistant to many preservatives. Product testing on BCC was not widely performed before 2015. From 2008 to 2018 there were 116 non-sterile drug product recall events in the U.S. 42 of the events were for contamination with BCC.



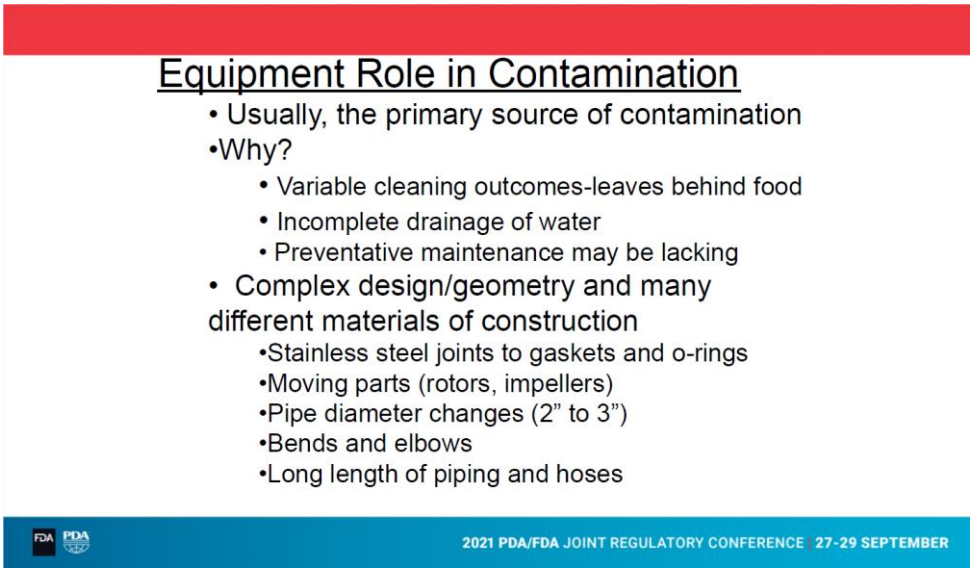
Observations made also in case studies:

- BCC infection can occur via multiple routes.
- BCC are capable of proliferating in the presence of preservatives.
- Water systems are a frequent culprit.

Authorities' reactions:

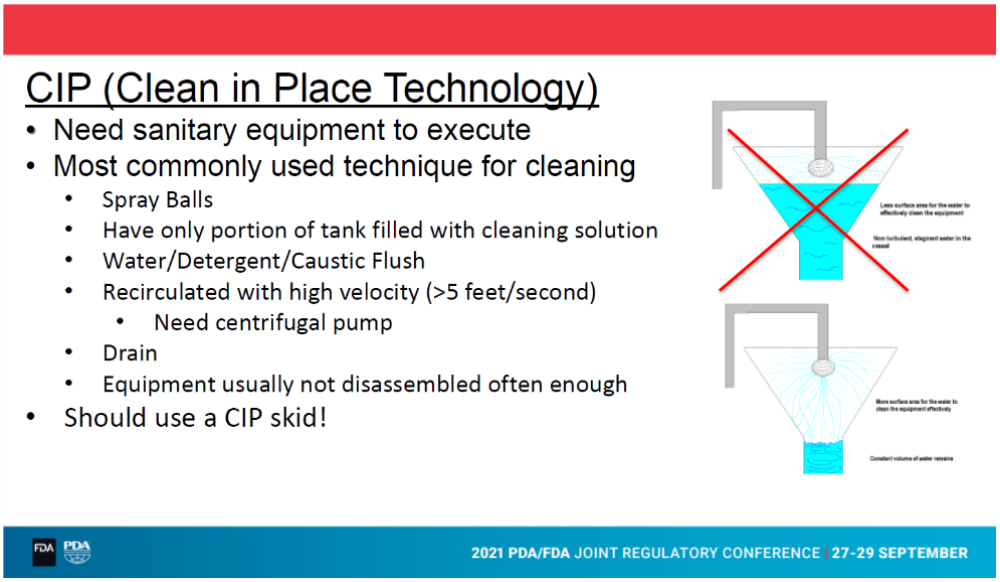
- FDA routinely asks applicants for new drugs for a BCC risk assessment and/or sprecification.
- USP Monograph <60> Microbiological Examination of Non-Sterile Products Tests for Burkholderia Cepacia Complex & FDA's Position on BCC – official as of 2019
- Microbiological Quality Considerations in Non-sterile Drug Manufacturing: Guidance for Industry – publication soon

Andrew Dick from KDC/One impressively described the role of equipment in contamination with many practical examples. **"Equipment is usually the primary source of contamination,"** he emphasized and also told us why.



"Out of sight, is out of mind", so a **sanitary design** is of utmost importance. The equipment should inter alia be easy to clean in place and to be accessible for inspection and maintenance.

When **spray balls** are used **as CIP technology**, it is crucial that you have only a portion of your tank filled with cleaning solution. Otherwise you would have only non-turbulent, stagnant water in the tank that cannot clean effectively.



"Nothing stays sanitary indefinitely!" – therefore, ongoing inspection, maintenance and monitoring are required. A constant oversight is necessary to reduce micro risks (e.g. cleaning and sanitization, maintenance, drainage of equipment).

"When there is food, water and time, propagation of microorganisms occurs. When the guard is let down, microorganisms will take advantage of the conditions."

Author

Sabine Paris, PhD
Senior GMP Expert / Chief Editor of the GMP Compliance Adviser
E-Mail: sabine.paris@gmp-publishing.com