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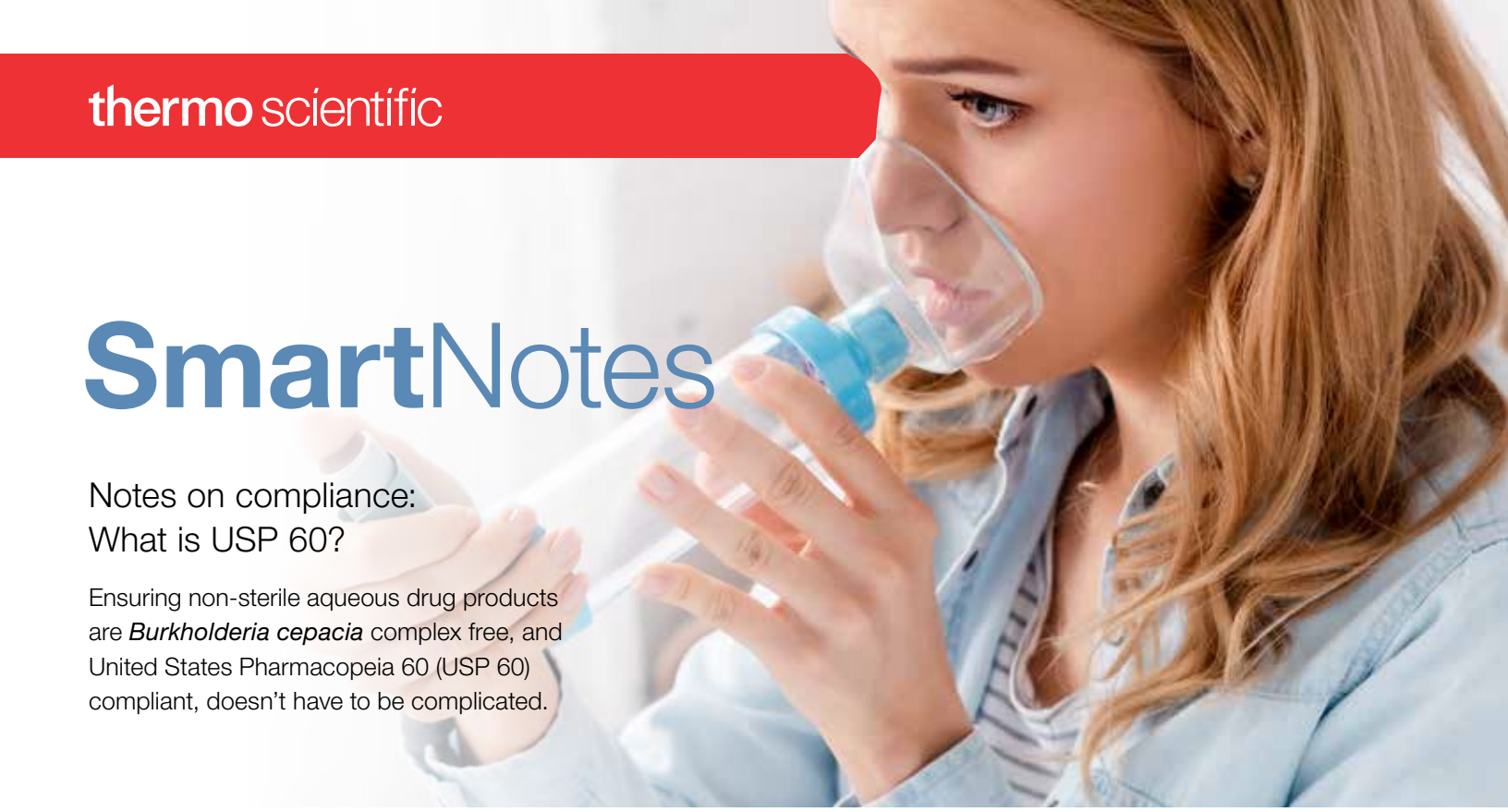

SmartNotes

Notes on compliance: What is USP 60?

Ensuring non-sterile aqueous drug products are *Burkholderia cepacia* complex free, and United States Pharmacopeia 60 (USP 60) compliant, doesn't have to be complicated.

By building a validated microbial limits database for non-sterile products and making some simple tweaks to common workflows, pharmaceutical laboratories can be assured they will not fall victim to contaminants with potentially fatal results for customers.

What is *Burkholderia cepacia* complex?

Burkholderia cepacia complex (Bcc) is among the top three microorganisms on the FDA's objectional list and has caused the recall of multiple non-sterile products.

Bcc refers to a 21-species strong group of water-borne opportunistic pathogens that can grow in preserved aqueous oral liquids or topical products. They have a broad metabolic capability, meaning they can survive in a wide range of environments and are quick to adapt to their surroundings.

They are found in a huge range of both natural and man-made environments, but in pharma, they most commonly grow in purified water and water for injection systems.

Bcc bacteria are resistant to commonly used antibiotics and can remain viable under harsh conditions due to their tenacity to overcome antimicrobial preservative systems and antiseptics.

Crucially, they pose a very real threat to the health of immunocompromised and other vulnerable people. While many people will experience asymptomatic infections, in others the bacteria may lead to serious or even fatal complications, including pneumonia.

The risk factors include:

- Being very young or very old
- People with cancer
- Pregnant women
- People on manual ventilation
- People with chronic illnesses, including cystic fibrosis

However, Bcc is dangerous for everyone and can be found in many everyday commercial products, including:

- Skin cream
- Eye wash
- Nasal spray
- Ultrasound gel
- Surgical prep solution
- Electrolyte solutions
- Wash cloths
- Mouth wash

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What is USP 60?

USP 60, which came into effect on December 1, 2019, followed a 2017 FDA advisory to drug manufacturers on the risk of non-sterile water-based products becoming contaminated with Bcc.[1]

In 2004, for example, an over-the-counter nasal spray was voluntarily recalled by manufacturers when it was found the product contained the bacteria. Later that year, Bcc was identified in a number of nosocomial infections among intensive care patients who had been exposed to sublingual probes.[2]

The following year, the Centers for Disease Control (CDC) was notified of several clusters of Bcc-induced pneumonia across multiple states. All were linked to a contaminated mouthwash.[3]

The advisory reminded drug manufacturers to establish robust, scientifically sound procedures to prevent the contamination of non-sterile drug products.

USP 60: Microbiological Examination of Non-sterile Products - Tests for Burkholderia cepacia Complex cemented that advice by providing the first compendial method for detection in pharmaceutical components and finished products.

The consequences of non-compliance are dire. Quite aside from the risk to human health and the huge potential for reputational and brand damage, releasing Bcc-contaminated pharmaceutical products into the market can lead to a facility being shut down.

Non-compliance, then, is not an option.

Implementing USP 60

Building new processes from the bottom up is never easy, regardless of the department's previous compliance experience.

At Thermo Fisher Scientific, we have been working with our laboratory partners to help them to implement new standard operating procedures (SOPs) that ensure effective, efficient, ongoing compliance.

The USP 60 regulation addresses the finished product. SOPs, however, should cover each step of the manufacturing process. If testing reveals contamination in the end product, laboratories need to understand the point of entry – the alternative is disposing of entire batches.

Using microbial limit testing (MLT), teams can carry out a validation of components and create a baseline dataset.

Starting with purified water samples and ingredients that are most susceptible to Bcc growth even under harsh conditions, the team can perform MLT at every step of the manufacturing pathway to understand how the bacteria react within the process.

Not only will this information prove invaluable in informing any future investigations, but it will also build acceptable microbial ranges to share with suppliers.

When building workflows, it is worth noting that while there are multiple species of Bcc, laboratories do need not test them all. The biochemical reactions involved in detecting ***B. cepacia, B. cenocepacia***, and ***B. mutivorans*** relate to all species, meaning a single test can confirm the absence of all 21 species.

Another important consideration relates to the interpretation of positive results. The possible presence of Bcc is indicated by the growth of greenish-brown colonies with yellow halos, or white colonies with a pink or red zone on ***Burkholderia cepacia*** Selective Agar (BCSA).[4]

To indicate Bcc, the growth should occur within 48 hours, and the colour change within 48 to 72 hours. It means that unlike in many similar workflows, this process contains two vital observation steps. Both should be built into processes.

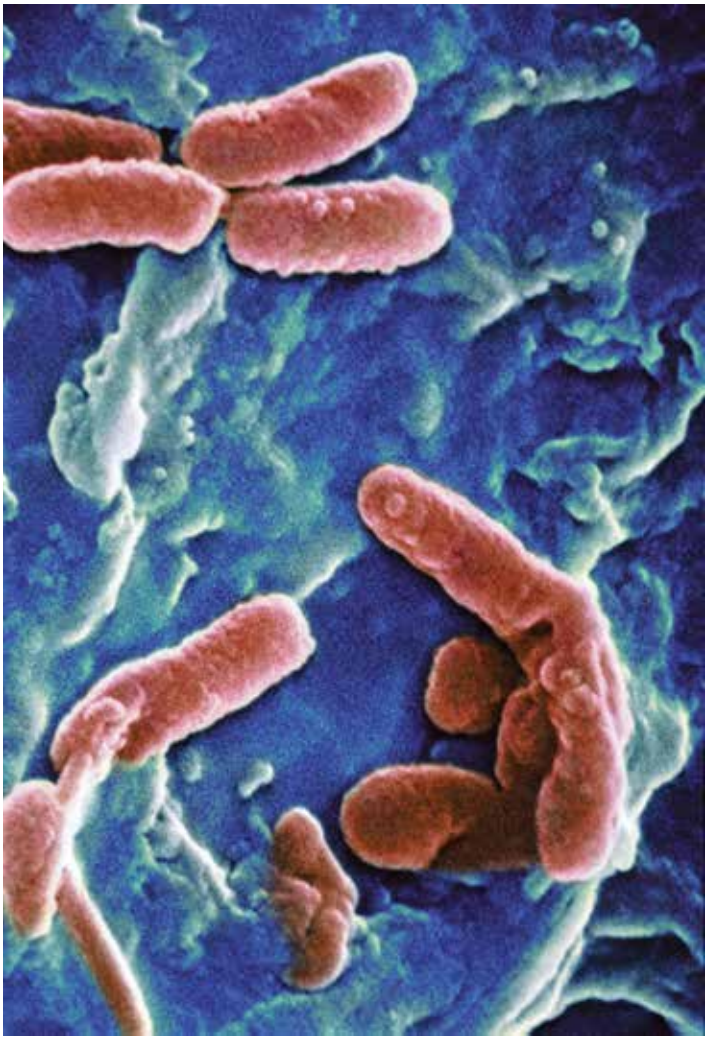
Complete for compliance

We understand the challenges of building compliance processes from scratch – particularly when they relate to a pathogen such as Bcc, which is present in so many environments and is so easy to miss.

USP 60 represents an important step forward in patient safety, and both pharma and contract laboratories are both morally and duty bound to comply.

Thermo Fisher is the only microbiology partner offering a complete end-to-end solution to ensure the absence of Bcc according to USP 60 requirements for all non-sterile pharmaceuticals.

Our workflow approach can deliver simplicity, confidence, and agility as industry adapts to this new, vital requirement and settles into using its scientifically robust, reliable, and efficient SOPs.

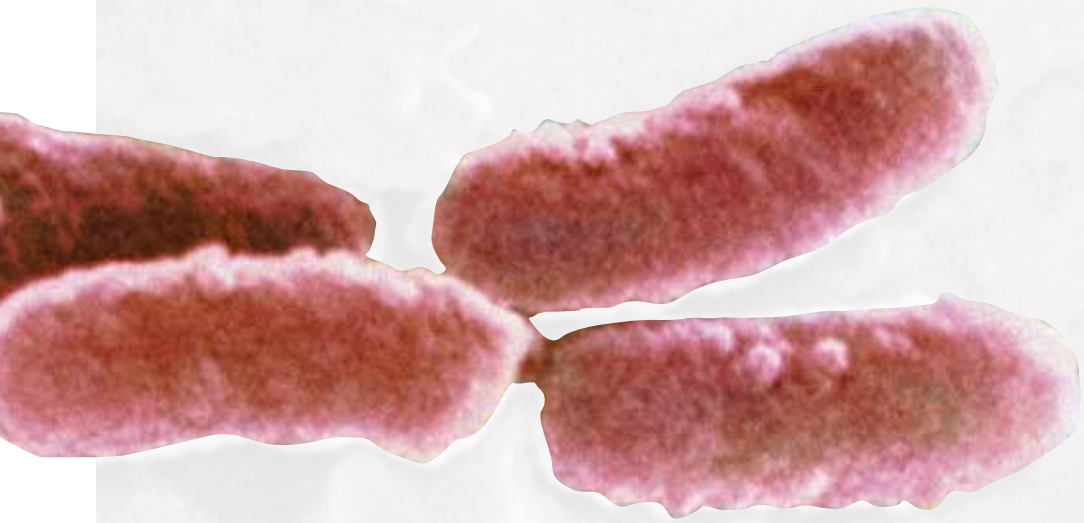


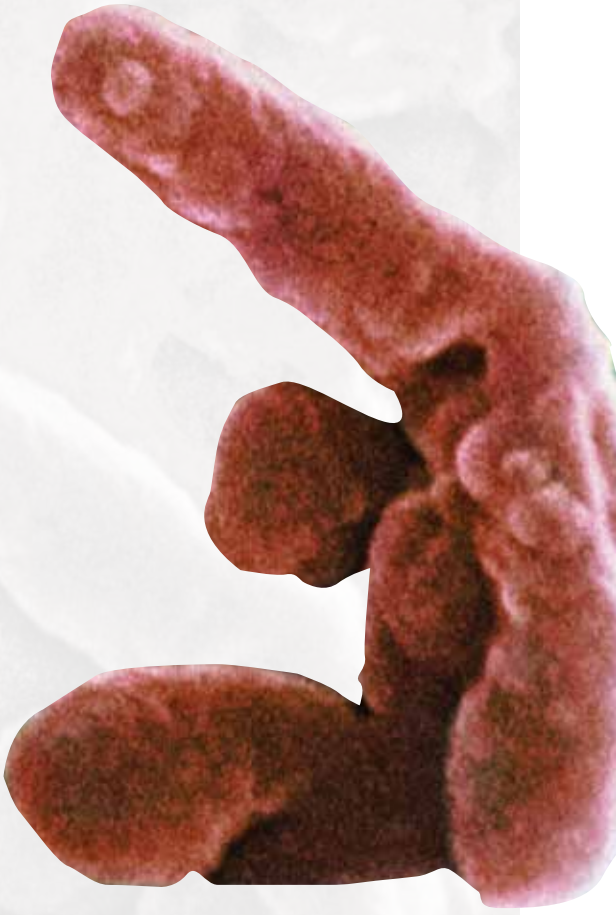
Thermo Scientific™ complete Bcc complex workflow

- Dehydrated Culture Media and Supplements
    - o R452642 Burkholderia cepacia Selective Agar (USP 60) 500g for 10 liters of medium
    - o Burkholderia cepacia Selective Supplement USP 60
        - SR0247E 0.5 vials for 1 liter of medium
        - SR0099E 12 vials for 1 liter of medium
        - SR0185E 0.4 vials for 1 liter of medium
        - SR0186E 0.8 vials for 1 liter of medium

Note: antibiotics are added separately when making in-house batches with dehydrated culture media (DCM) and will require calculations based on batch size.

- Prepared Culture Media
    - o R110244 Burkholderia Cepacia Selective Agar (60 mm plate for water filters)
    - o R110245 Burkholderia Cepacia Selective Agar
- Thermo Scientific™ Quanti-Cult Plus™ Quality Control Organisms
    - o Guaranteed to return <100 colony forming units per 0.1ml
    - o Ease of use – simply rehydrate, mix and incubate, then inoculate
    - o 100 tests per kit
    - o Strains derived from ATCC® cultures
- Growth promotion and suitability testing organisms
    - o R4715221 *Burkholderia cenocepacia* ATCC® BAA-245™
    - o R4715222 *Burkholderia multivorans* ATCC® BAA-247™
    - o R4715220 *Burkholderia cepacia* ATCC® 25416™
    - o R4715210 *Pseudomonas aeruginosa* ATCC® 9027™
    - o R4717016 *Staphylococcus aureus* ATCC® 6538™





References

[1] https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile

[2] https://www.cdc.gov/hai/organisms/bcepacia.html

[3] https://www.cdc.gov/hai/organisms/bcepacia.html

[4] https://www.fda.gov/media/88801/download

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