The importance of sterility testing in biopharmaceutical manufacturing

Robust sterility testing protocols are essential to protect patients, medicine supply chains and manufacturers' bottom lines. But how do companies build successful sterility processes?

"Sterility testing may be based on producing a simple presence/absence result, but that is just the tip of the iceberg"

What can pharmaceutical laboratories do to mitigate the risk of contamination during the manufacturing process?

Sterility testing is a crucial part of pharmaceutical manufacturing and the consequences of non-compliance can be fatal. It is, however, a time and resource-hungry process, needing to be carried out under aseptic conditions by specialised staff according to detailed protocols.

Finished product samples must undergo a 14-day incubation period before being cleared for release onto the market. Anything less than a 100 percent pass rate can relegate an entire batch, preventing it from reaching the people who depend on it.

The key to helping pharmaceutical laboratories reduce the risk of avoidable test failures and smoothing the road from component intake to product release, is robust and validated protocols.

Why is sterility so important to human and business health?

Patient safety is of the utmost importance in drug development, but parenteral drug products bypass many of the body's natural defences. As such, they carry an increased risk of infection.

In 2012, for example, a multi-state outbreak in the US of fungal meningitis and other infections was linked to preservative-free methylprednisolone acetate (MPA) steroid injections distributed by the New England Compounding Center in Framingham, Massachusetts.

The Centers for Disease Control and Prevention (CDC) were notified of more than

750 linked cases in 20 states. Tragically, 64 people died.

Cases like this demonstrate why parenteral products are so strictly regulated by the health and regulatory authorities, including the US, European and Japanese pharmacopeias.

When it comes to sterility the stakes are high, both in terms of protecting human health and keeping supply lines open. Between 2004 and 2011, more than 75 percent of US Food and Drug Administration (FDA) recalls involved sterile products. Of these, 80 percent were linked to a "lack of sterility assurance".

Sterility testing failure, then, is not an option for organisations that are committed to protecting both human and business health.

Why do laboratories need to comply with USP <71>?

US Pharmacopoeia (USP) <71> Sterility Tests relates to the sterility of all parenteral medicines and has been harmonised with its regulatory counterparts in Europe and Japan.

It requires drug manufacturers to ensure their end products are completely free from objectionable organisms, such as *Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa, Aspergillus brasiliensis, Eschericia coli, Clostridium sporogenes* and *Bacillus subtilis*.

To comply with the simple presence/absence requirement, samples must be incubated in both fluid thioglycolate medium (FTM) and soya bean casein digest medium (SCDM) or tryptic soy broth (TSB) for 14 days, to check for the turbidity that may indicate the growth of colonies.

It is a statistical test that demands a 100 percent pass rate. In batch sizes of less than 100 containers, laboratories must test 10 percent or four containers, whichever is the largest figure. When the batch size is larger than 500 containers, the requirement is to test two percent or 20 containers, whichever figure equates to the fewest.

It means that manufacturers can never be completely sure that the whole batch is objectionable organism free, even if the tests are all negative. Conversely, one positive test will result in the whole batch being held back, sometimes for months, or even destroyed.

With budgets built to reflect the typical batch release lead time of 20 to 28 days, each day of delay is considerably expensive. More importantly, it can restrict people's access to the medications they need to get on with their lives.

To avoid this, laboratories must do everything in their power to comply with USP <71> – and that includes ensuring standard operating procedures (SOPs) do not contribute to the problem. Building robust processes is the first step to eradicating avoidable sterility testing failure. »

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How do laboratories build the process?

Sterility testing may be based on producing a simple presence/absence result, but that is just the tip of the iceberg.

Pharmaceutical laboratories first need to build and validate scientifically robust, product-specific protocols they can rely on. It is a challenging process, but it is essential if laboratories want to be sure their methods do not introduce risk.

Teams first need to carry out suitability or growth promotion tests and validation or bacteriostasis and fungistasis testing to select the right tools for their SOP.

During suitability testing, laboratories must first find a medium that supports the growth of viable objectionable organisms within the product. It is a process of trial and error that requires access to media, the indicated organisms and a high level of technician knowledge and expertise.

Next, that medium itself must be incubated and assessed for sterility.

Laboratories must also perform validation, to ensure the test sample will not inhibit the growth of the microorganisms in the selected media. The aim is to ensure the active

ingredients of the product are neutralised to allow the microorganisms to grow, rather than inhibiting their growth.

The way these tests are performed will depend on the method of the final sterility testing, which will tend to be membrane filtration for liquid pharmaceuticals or direct transfer for medical devices.

To reduce the risk of contamination during sterility testing, the procedure should be carried out in a closed system under aseptic conditions. Most organisations interpret this as using an International Organization for Standardization (ISO)-regulated laminar airflow cabinet within an ISO-regulated clean room or an isolator in a controlled environment.

Samples must be prepared as per the detailed protocol and incubated for 14 days. If a sample appears to indicate the presence of pathogens within that period, incubation must continue for the full two weeks before teams can take steps to quantify the results or identify the microorganism.

If growth is confirmed, a re-test is only permitted if an investigation finds cause to invalidate the results.

Robust sterility testing protocols are essential to protecting patient safety and keeping manufacturing on time and budget.

To build effective strategies, pharmaceutical laboratories need skilled staff, high manufacturing standards and access to a wide range of media, rinses and QC microorganisms.

EXPERT VIEW

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Meeting environmental monitoring needs

Environmental monitoring: what are the key hurdles?

Maintaining a facility that consistently releases quality products according to strict regulations is difficult. Pharmaceutical facilities can work with thousands of plates in a single day, each one of which has the potential to introduce contamination to the manufacturing process.

As demand for pharmaceutical products continues to rise, the industry is looking at ways to reduce costs.

What are the top three sterility risks?

1. Movement – Every step of aseptic processing, from raw material intake to microbiological testing, introduces multiple opportunities for microbes to enter finished goods
2. Personnel – Manufacturing and laboratory personnel are essential, however they also introduce particulates and microbes to environments
3. Water – Microbes proliferate in the very water that is required in the production of products. Water systems must be tested to determine microbiological bioburden load.

How can these risks be reduced?

By acquiring the largest lot sizes with the longest expiry date, facilities can mitigate risk and cut the number of batch tests required, reducing resource use without compromising on quality.

Full traceability of plates is also essential. QC teams need to know, without a shadow of a doubt, where the samples have been collected, as well as where and when potential contamination could have occurred.

Individually barcoded plates drive efficiencies by providing teams with the data they need to manage processes, investigate and rectify any breaches.

What is Thermo Fisher Scientific doing to help?

Working with QC partners we find practical ways to reduce risk and boost efficiency.

Our specially designed packaging eliminates cardboard and its contamination risk, it also features handles for easy transportation.

Our triple-wrapped, irradiated Thermo Scientific™ Trinity Plates confirm the integrity of the wrapping material and seal during vaporised hydrogen peroxide (VHP) exposure.

We have developed color-coded plates, meaning technicians can quickly find the media they are looking for.

These may sound like small changes, but every second saved in staff time, and microorganism kept out of the facility, drives down the cost.

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For further information, visit:
www.thermofisher.com/environmental-monitoring-plates

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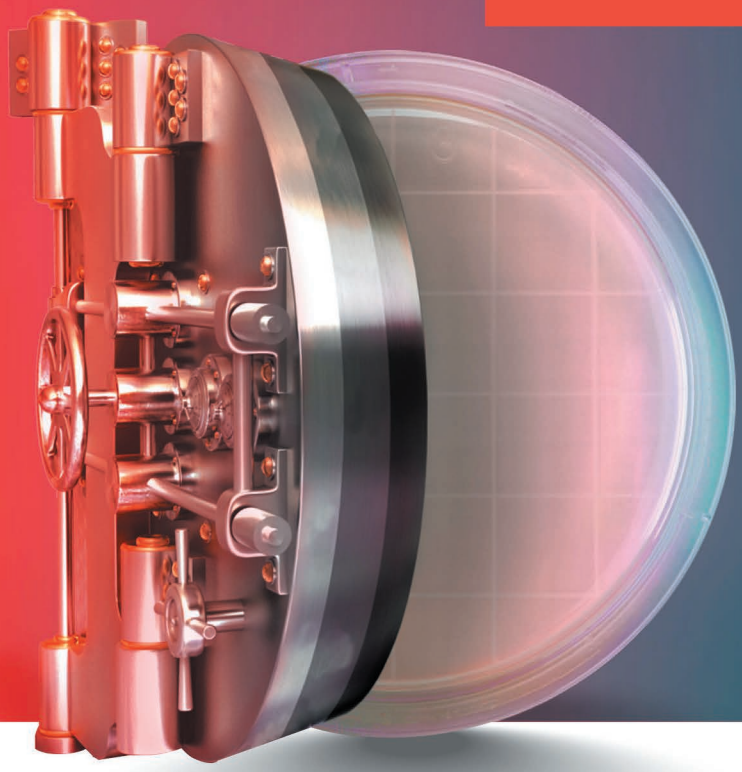

Environmental monitoring

Make it better

Thermo Scientific™ Triple Wrap Plates - Sealed, Sterile, Secure

Designed to support the most sterile environments, the Thermo Scientific Triple Wrap Plates feature the latest in quality-assurance technology.

Confidence in results

Unique VHP indicator confirms integrity of the see-through triple wrapping, which is designed to keep media in optimal condition.

Innovative technology

Available with 2D barcoding for sampling accuracy with full traceability, while sanitized polypropylene storage boxes ensure sterility every time.

High volume that lasts

Not only do our plates have improved shelf-life and room temperature storage, they're also available in high volume single lots.

Learn more at **thermofisher.com/environmental-monitoring-plates**