Variability in sterility test processes and the benefits of modular workstations

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Overview of sterility testing in today's process applications

This paper reviews some of the current operational practices that incorporate sterility testing and provides an insight into the role of hydrogen peroxide vapour bio-decontamination and continuous particle monitoring.

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The development of sterility test processes

As requirements for biological contamination control to reduce risks become more understood, the trend is away from 'open barrier' systems. Uni-directional flow (UDF-LAF) clean-air benches or biological safety cabinets still have some open exposure to gowned operators that are known to generate biological contamination. Also associated manual disinfection processes, that have variable efficacy and are highly operator dependent, require risk management with respect to potential for false positive sterility test results.

There is a trend in sterility testing towards barrier separation technology e.g. isolators and closed barrier workstations. These 'closed systems' provide a physical separation of operators to the sterility test process and this is a major step towards more effective biological decontamination risk management. Closed barriers also provide a chance to apply automated hydrogen peroxide vapour (HPV) biological contamination, which has validated 6-log sporicidal efficacy.

Providing biological contamination control with effective bio-decontamination of the sterility test work zone is just one part of risk management. The major challenge is entering test materials and product samples into an aseptic environment without compromise of the aseptic conditions or sterile products.

Sterility test processes also have to be flexible to cope with different sample types, closure types and batch sizes. Some samples taken from a sterility test process may have other chemical, toxic or biological (virus) contamination on the outside of test containers or within the agar monitoring plate. In this instance, cross-contamination control may also be required.

The need for flexibility in sterility test process operations

Product profiles are changing with more biological and aseptic-toxic products that need sterility testing.

There are increasing numbers of small batches of specialised products. The number of 'big block buster' small molecule chemical entities is falling and alternative large molecule products, using targeted delivery paths are being developed.

Therefore bulk sterility testing of one product type, in the past completed in large flexible-film half-suit isolators, is being replaced by more versatile systems. These use rapid transfer technology to achieve high throughput in barrier separation gloved isolators.

Hence the move is towards modular systems that facilitate just-in-time processing of sterile supplies and samples. This enables more continuous and rapid testing together with a high degree of biological contamination control and risk management.

Modular systems providing options in sterility test process operations

Modular sterility test systems provide the flexibility to handle different product sample types and varying scales of production capacity depending on the system configuration or material transfer method used.

Generally there are four types processing operations:

- Batch processing.
- Gassed isolator work zone with aseptic hold and rapid gassing transfers of all test materials and product samples.
- Gassed isolator work zone with aseptic hold and two types of material transfer: (1) Test material transfer with rapid gassing disinfection. (2) Spray and wipe disinfection transfer of products samples not suitable for gassing exposure.
- Gassed work zone designed for aseptic sterility testing and containment against operator exposure to biological or toxic samples (product or environmental monitoring samples).

Batch processing

Batch sterility test processing is a process where all sterility test materials and the separation barrier (isolator) are gassed together using hydrogen peroxide vapour in one bio-decontamination cycle. To achieve effective decontamination of the test materials, sterile supplies in sterile packaging are supported on point-of-contact support racks or hangers. Product samples may also be within the load pattern or enter after the gassing cycle via a closed aseptic transfer using a rapid transfer port container.

Batch processing in one sterility test process zone

Within batch processing, test samples are sterility tested. They can then be transferred out via a closed, rapid transfer port device or remain in the process zone until all tests are complete and the isolator opened for recovery and transfer to the incubator.

This process has challenged ergonomics as the gassed load takes up considerable space and restricts movement. This in turn affects test procedures during sterility testing of the batch.

Full separation barrier isolator and test material load gassing cycle times can be excessive, restricting starting time and adding to overall batch processing time. This is not an optimised process.

Gassed isolator work zone with aseptic hold and rapid gassing transfers of all test materials and product samples

In this system variant, a gassing transfer chamber is loaded with test materials and when the cycle is complete, these materials are transferred to an interconnected sterility test process isolator that has been previously gassed and typically held for a specified aseptic hold period. Here the aseptic conditions are maintained between re-gassing of the separation barrier work zone.

For an optimised process, the test material gassing chamber module is typically configured for rapid gassing (20-30 minute total cycle times).

Product samples may also be within the load pattern or enter after the gassing cycle via a closed aseptic transfer using a rapid transfer port container.

Gassed isolator work zone with aseptic hold and two types of material transfer disinfection process

Here a test material load is bio-decontaminated in a gassing transfer chamber. When the cycle is complete, these materials are transferred to an interconnected sterility test process isolator that has been previously gassed and typically held for an aseptic hold period.

The variant in transfer disinfection is for product samples that cannot be exposed to the hydrogen peroxide vapour gaseous disinfection process. In this case, the system has a type D transfer hatch that can be used to enter product test samples

into the sterility test zone (or via the gassed test material transfer zone) using a spray & wipe disinfection procedure.

The simple 'clean' shape of product vials or closures facilitate effective surface bio-decontamination by a manual process. This process provides the best risk balance e.g. difficult to manually disinfect test materials in packaging use the gassing disinfection transfer and only simple wipeable items enter via a manual disinfection process.

The transfer hatch does need periodic gassing with the interconnected process or transfer zone to manage risks of resident biological contamination.

Gassed work zone designed for aseptic sterility testing and containment against operator exposure to hazardous biological or toxic samples (product or environmental monitoring samples)

Sterility test isolators are usually designed for handling biologically active or toxic samples. They employ both aseptic processing and containment features.

The isolators of a containment design would include a capability for both gaseous disinfection and a chemical decontamination process. The containment boundary (up to the primary inlet and exhaust HEPA filters) would have no inaccessible mechanical spaces that were not possible to chemically decontaminate (wipe or spray down with a chemical agent that would neutralize or destroy toxic or biologically active components).

Sterility test materials in sterile outer packaging would ideally enter the sterility test process zone by a rapid gassing transfer process.

Test product samples and environment monitoring plate samples would have come from a contaminated process zone hence need containment in recovery, transfer and entry into the sterility test isolator zone. A rapid transfer port container with aseptic transfer between the production process zone and the contained sterility test zone would be used. Sealed transfer bags may also be used, that may be contaminated with the product on the inside but free of toxic contamination on the outside. In this case, a rapid gassing transfer disinfection process may be applied if the packaging material is validated to be impermeable to hydrogen peroxide vapour.

All waste material needs treating as toxic waste with a contained and secure exit from the sterility test process zone. Sterile bag-out and heat seal systems provide a good solution for handling toxic waste on route to incineration.

The separation barrier work zone should not be capable of opening until the necessary decontamination process is complete after processing (i.e. interlocked against opening). These isolators may be held in containment conditions with decontamination processes completed under closed conditions between sterility test batches.

Care has to be taken in environmental monitoring interventions in these types of aseptic-containment systems as again samples may be contaminated. Typically plate samples may be recovered and placed in sealed sterile plates and incubated in these bags to prevent exposure to workers.

Continuous particle monitoring in sterility testing

There is no regulatory requirement for continuous particle monitoring in sterility testing. However, considering quality risk management (with a focus on managing risk of false positives), continuous particle monitoring is now being applied to sterility test isolators.

Within sterility testing, when comparing to typical control conditions, there will be trends in particle generation (as packaging is removed) and recovery clean up rates. Real-time alarms can be set around these trends. If there is a deviation in control state, an alarm can alert operators to suspend the sterility test (not putting the product sample at risk) until the cause is identified the test environment is back under control.

Continuous particle monitoring can be used on a sterility test isolator system for handling aseptic-toxic samples. During sterility testing, the continuous particle monitor must be closed off and isolated to protect it from toxic or biologically active contamination. However after decontamination of the sterility test isolator, the continuous particle monitoring system can be reactivated. To complete the data profile in system validation and re-qualification broth runs, full and continuous particle monitoring are used to monitor the complete simulated process.

Summary

Having modular sterility test barrier separation designs can provide operational flexibility, enabling managed in-process transfers of different test sample types with varying batch process throughput.

Modular systems may include different routes or decontamination methods for entry of difficult-to-decontaminate sterile packaged test supplies. They may also include simple-to-decontaminate test sample closures. Both of these may be impacted by a gaseous disinfection. Such options provide significant process flexibility and assure process compatibilities can be managed.

The application of advanced monitoring in sterility testing, including continuous particle monitoring, contributes significantly to risk management through process operations.

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