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The sterility test

Abstract

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The sterility test is perhaps one of the most critical tests performed by the microbiologist and yet very little of the methodology has changed since its inception. The one area that has changed is the environment in which the test is undertaken.

Traditionally, sterility testing has been performed within a laminar hood (GMP Grade A), which is sited within a cleanroom (GMP Grade B).[1,2] Due to the advances in isolator technology, there has been a shift by organisations to use these units for performing sterility testing. Isolators are units that encompass only the area that must be controlled, which restricts access and provides complete separation of people and product to maintain an organism-free environment.[3,4]

For many years, the pharmaceutical industry has recognised that personnel are the dominant risk relative to microbial contamination in aseptically produced sterile products.[5] Indeed, gloveboxes were used in sterile manufacturing before the introduction of cleanroom technology.[6] It was evident back then, that there was an understanding of the risk from human-borne contamination where no physical separation between the operator and production existed.

The switch from sterility testing within a cleanroom to an isolator is not a simple, quick or an inexpensive process. Despite this, there are advantages to using isolators over cleanrooms for sterility testing, as well as benefits to the organisation and, more importantly, improvements to patient care.

Costs and design

Cleanrooms have the advantage of offering considerable space for operators and equipment compared with isolator technology. The downside is the costs for civil and mechanical operations.7 Depending on the size of the classified area, cleanrooms can be expensive to build. Start-up costs for isolator systems are high; however, they can be significantly less expensive than conventional cleanrooms for most microbiological laboratories.

Isolator systems offer cost savings and performance enhancement, making this technology an attractive alternative to the construction of a cleanroom. Sterility testing within an isolator reduces the frequency of false positive results and environmental excursions.[7]

Operating costs are lower for isolators due to the smaller workspace footprint, lower utility costs, reduced (or eliminated) gowning, reduced training and cleaning costs and lower classification for the room.[7,8] The estimated saving using isolators over cleanrooms is approximately £15,000 per

year, plus the latest designs in sterility testing isolators provide compact and ergonomic space saving solutions.[7]

The salient point of all isolator designs is the complete separation of internal and external environments. This feature alone affords vastly superior performance relative to manned cleanrooms in excluding personnel; it is a lot more effective and ergonomic to contain either the operation or source of contamination rather than wrap the person up.[7]

Sterility testing isolators operate under positive pressure, which protects the sample and provides a measurable pressure differential between the enclosed environment and the operator.[2] Most isolators are fitted with HEPA filters with interlocked transfer devices for products to be passed into the isolator and the varying styles (rigid, flexible or half-suit) provide ease of use for the operator.

The quality of rooms containing isolators is of minor consideration since properly designed isolators should not allow the exchange of contaminants with the surrounding environment.[7] That said, an isolator is expected to be located within a room in which the only activity performed is sterility testing. The size and shape of the room in which the isolator is located is important, as access to all sides is required for routine work and maintenance.[7,8]

Validation of a cleanroom is well understood and as such is easier than validation of an isolator. However, it is important that sterility testing within a cleanroom requires a validated process for decontamination of the product's external surface, e.g. glass vials and plastic containers. This can sometimes be difficult for a contract service laboratory that will be testing a range of product types. Isolator validation can take months to complete due to the various load patterns and sanitisation cycles, which require the use of biological indicators, necessary to establish acceptable sterility assurance levels.[2,4,7,9]

The fundamental limitation of sterility testing within a cleanroom is that the sterility assurance level (SAL) is lower than the sterilisation processes that it is used to monitor. During the test, micro-organisms are in close proximity to the test samples and the culture medium, since testing must be performed by people and people are a prolific source of micro-organisms. Thus, the closer the operator is to the testing area, the greater the risk of microbial contamination.[10] Even under optimal conditions, a gowned, motionless human may generate 100,000 particles per ft^3/min within a cleanroom, while a walking operator may generate 10,000,000 per ft^3/min.[11]

Test sample packaging, media containers, and testing consumables can also be sources of contamination. Through stringent techniques, the impact of these and other sources of micro-organisms can be minimised, but not eliminated.[8] Labs take extensive precautions to protect the integrity of the cleanroom sterility testing process. Test sample packaging is removed and exteriors disinfected before entering the cleanroom. No sterilisation occurs therefore some micro-organisms may remain on a surface and end up in the laminar hood during the test.

Several days elapse from the time culture media is sterilised until its use – for growth promotion checks. During this time, the exterior of the media containers may pick up microbial contamination, even if stored in a cleanroom. Media containers must be disinfected. Furthermore, the hood's work surface is disinfected before each sterility test, as is the entire cleanroom.

In contrast, isolators can be loaded with the consumables and samples the evening before testing, sanitised overnight and be ready for testing the following day, effectively increasing efficiency of the sterility testing process.8 An advantage of an isolator is that it can be decontaminated to a higher sterility assurance level (SAL) than for a cleanroom.

Sanitisation and maintenance

Disinfection within the cleanroom, prior to sterility testing, will not preclude airborne contamination, including the very person performing the decontamination. Cleaning and disinfection of a cleanroom is a manual, time-consuming process and requires a thorough training programme to work effectively.[12]

Isolators and their contents are typically decontaminated to an SAL of 10^{-6} with vaporised hydrogen peroxide. Even though they are designed to prevent the ingress of contamination, they still require regular cleaning and disinfection to maintain EC GMP Grade A classification.[13] Procedures used to pass product into isolators highlight the potential for starting materials to be contaminated. Research has found that 60% of consumables are contaminated with bacteria and 40% of consumables are contaminated with bacterial spores.[14]

Isolators are subjected to a validated reproducible decontamination process with no operator requirement, apart from setting up the unit. The relative ease of decontamination compared with cleanrooms makes a good case for isolators' superior sterility assurance potential. An isolator system needs to be decontaminated only when in production, unlike cleanrooms, which must be maintained at all times.

Cleanrooms require an annual shutdown for maintenance. Sanitisation and monitoring to re-commission can add to the downtime.[8] Due to costs and space, most facilities performing sterility testing within a cleanroom will have only the one room. Therefore, any fault or unscheduled maintenance will cause significant disruption to the testing operation.

Conversely, organisations using isolator technology tend to have a second or more usually two isolators linked together via a pass-through hatch, which can be used as one large unit or two separate isolator units. This allows the availability of a 'backup isolator'. Two isolators connected also have the advantage of increasing testing capacity.

Isolators can be used as retrofits to an existing cleanroom facility. The existing infrastructure of the cleanroom and its classification can remain largely unchanged.[11] Other advantages of isolators over cleanroom technology are expansion and portability. To add another isolator is relatively simple compared with expanding a cleanroom, and the isolator can be easily relocated.[8]

Sterility testing using isolator technology improves sample throughput, reduces consumable costs, reduces the frequency of microbial isolates due to environmental excursions and lowers the probability of false positives. Regulations favour the systems that are best at reducing risk and increasing patient safety, and sterility testing within an isolator is a good example of this.

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