

and such microorganisms likely will be nutrient-depleted, the sterility test may require longer incubation times to allow microbial growth to occur.

No amount of retesting can overcome a valid initial positive sterility test result. FDA guidelines specifically stress that persuasive evidence must be found to show absence of laboratory error. If laboratory error is absent or inconclusive, then the manufacturer should err on the side of safety and reject a batch that has experienced an initial sterility test failure, regardless of the results of the retest. A finding of “no-growth” in the retest should be accorded less weight than other parts of the investigation. The identity of the organism causing the sterility test failure should be known to the species level.

Trend analyses of sterility testing results should be reviewed periodically. Manufacturers must react to any trend showing an increase in false positive results. Trends should be separated by product, container type, filling line, and type of aseptic process. Environmental monitoring data trends in the production area should also be monitored for any correlation to the failed sterility tests. Chapter 27 lists many other records and documents that must be evaluated during an investigation following a sterility test failure.

ASEPTIC PROCESSING ISOLATORS

FDA aseptic processing guidelines state that the following isolator systems require daily attention and preventative maintenance:

- Gloves
- Half suits
- Seams
- Gaskets
- Seals
- HEPA filters

A major weakness of isolators is glove integrity. Durable glove materials must be used and aggressive replacement frequency must be practiced. Glove integrity batch-by-batch or daily evaluation should be performed using both visual and mechanical integrity tests. Evidence of any leakage terminates the operation.

Airflow in the isolator must be either HEPA- or ultra low particulate air-filtered. FDA prefers rigid wall construction over flexible materials. The air pressure differential should range from 0.075 to 0.2 inches of water gauge. Where any opening exists, for example, the exit, Class 100 protection should exist. Class 100 environment should be present in the interior with the isolator background (where it is located) being at least Class 10,000, especially for applications with multiple transfers, mouseholes, and sanitizing transfer ports. Rapid transfer ports (RTPs) are considered effective as transfer systems, but still should be kept to a minimum in the isolator design. Ultraviolet light and localized, HEPA-filtered air can be used in transfer ports.

All surfaces within the isolator must be exposed to a chemical sterilant. Surface sterilization validation studies should include a thorough determination of the limitations of the sterilization cycle using biological indicators at various locations, especially “tough-to-reach” locations. The entire path of the sterilized liquid stream must be steam sterilized. An environmental monitoring program must be established where within the isolator, the air quality is evaluated periodically during actual operations. Even with isolator technology, the human factor still remains an integral component and concern, especially considering the fatigue factor and its effect on practicing inerrant aseptic technique.

Validation of barrier isolators is covered in more detail in Chapter 23.

ASEPTIC CONNECTIONS AND SAMPLING METHODS

A single pharmaceutical company will make anywhere from 25,000 to over 100,000 aseptic connections in a single year (4). Each connection or sample runs the risk of introducing contamination. In response, several vendors have made available new devices for making connections and taking samples more easily and quickly. Description of the various aseptic connectors and samplers is beyond the scope of this chapter, although some additional brief coverage can be found in Chapter 23. Major vendors such as Pall (Kleenpak™), Millipore (NovaSeptum®),