Table 21-3 Examples of 483 Observations Related To Media Fill Processes and Related Documentation

- Inadequate investigation of media fill failure.
- Inadequate training of employees after media fill failure.
- Media fills did not follow SOP.
- Media fill aborted due to high particulate counts, but inadequate investigation into reasons for high counts.
- Media fill did not start at point after product had been sterilized.
- Defective vials discarded prior to incubation and not counted as failures.
- Number of units filled too small.
- Media fills did not simulate what was documented in batch records.
- Certain environmental data not collected during fill.

TIME LIMITATIONS

Aseptic processing guidelines require that maximum hold times be established through reproducible studies for:

- Filtration processes
- How long a non-sterilized bulk solution can be held prior to filtration
- How long a sterilized solution can be held prior to filling
- How long sterilized equipment can be held prior to using them
- How long sterilized containers and closures can be held prior to using them

PROCESS VALIDATION AND EQUIPMENT QUALIFICATION

There are three main aspects to aseptic process validation and equipment qualification for aseptic processing—process simulation testing (media fills), filtration efficiency, and sterilization of equipment and materials.

Process Simulations (Media Fills)

The FDA aseptic processing guidelines and the EU guidelines for sterile drug manufacturing contain a large number of specific guidances for the sterile drug industry to abide by. FDA inspections have increasingly focused on media fill studies that truly simulate the production process. Table 21-3 lists some examples of 483 observations issued by FDA inspectors related to media fill operations and documentation.

Because so many factors affect the assurance of sterility of an aseptic process operation, the use of sterile culture media has become the best determinant to validate the fact that all these factors are in place. Basically, culture media replaces the product that is prepared, filtered, and filled into the final container. Since culture media will support microbial growth, the presence of microorganisms due to any breach of asepsis in the manufacturing area, components and equipment used, the entire process, and personnel involved will show up as positive growth in culture media filled and stoppered into final containers. There are many factors that must be considered in designing a valid simulation of the actual process (Table 21-4).

The *media fill* or *process simulation test* involves preparation and sterilization (often by filtration) of sterile trypticase soy broth and filling this broth into sterile containers under conditions simulating as closely as possible those characteristics of a filling process for a product.[2] The key is designing these studies that simulate all factors that occur during the normal production of a lot. The entire lot, normally at least 4750 units, is incubated at temperatures verified to support microbial growth, usually rotating 20–25°C storage and 30–35°C storage, for at least 14 days and examined for the appearance of growth of microorganisms. It must be verified that the media used is capable of supporting microbial growth. If growth occurs, contamination has entered the container(s) during the processing. To pass the test at 95% confidence, not more than 0.1% of the challenged units may show growth, although the current expectation of regulatory agencies is "approaching zero." This evaluation also has been used as a measure of the proficiency of an individual or team of operators. This test is a very stringent evaluation of the

[2] For sterile powder filling, sterile lactose is used to simulate the filling process followed by dissolving with trypticase soy broth under aseptic conditions prior to incubation.