Table 27-5 What Must be Checked During Investigation of Sterility-Test Failure to Determine Assignable Cause

Manufacturing Facility
Media fill validation records
Sterilization records
Environmental data
Bioburden data
HEPA filter certifications
Sanitization records
Filter integrity records
Equipment maintenance records
Manufacturing ticket review
Operator training records
Sterile certification of purchased sterile raw materials
Sterility-test facility
Sterilization records
Environmental data
HEPA filter certifications
Sanitization records
Operator training records
Sterility-test control data

This statement has caused some consternation among QC groups in the pharmaceutical industry because assurance of sterility is so difficult to prove with absolute certainty.

Investigations of sterility-test failures should consider every single factor related to the manufacture of the product and the testing of the product sample. Table 27-5 shows a representative list of factors to be investigated by QC both in the manufacturing areas and in the sterility-test laboratory to determine how a sterility-test failure could have occurred. Most of the time, there is no concrete conclusive evidence pinpointing where the contamination occurred and, thus, QC must make a decision based on philosophical positions and retrospective history of the manufacturing and sterility-test areas.

The FDA aseptic guidelines indicate that persuasive evidence of the origin of the contamination should be based on the following:

1. The identification of the organism in the sterility test (genetic typing may be useful or required.
2. The laboratory's record of tests over time
3. Monitoring of production area environments
4. Product presterilization bioburden
5. Production record review
6. Results of sterility retest.

Identification of the Organism in the Sterility Test

Not only the genus, but also the species of the isolated organism will provide invaluable information concerning the organism's habitat and its potential resistance to the product formulation and sterilization methods. If the organism is one normally found on people, then the investigation can focus on employee hygiene, washing and gowning techniques, and aseptic techniques. Identification of the organism can be compared to historic microbial databases for the manufacturing and testing areas to assess probabilities of where the organism originated. Obviously, if the organism identified had been isolated before in the production area, but never in the testing area, then the production area would be implicated as the source of the organism and the test would be judged as a true sterility-test failure. Identification of the organism allows the manufacturer to perform further testing to determine if the organism is sensitive to the product formulation, particularly if the product contains an antimicrobial preservative. If an organism that was isolated from a product that was terminally sterilized and whose resistance to terminal sterilization is *proven* to be below the microbial reduction produced by the sterilization cycle,