The MF method offers at least four advantages over the use of the DT method. They are as follows:

1. Greater sensitivity.
2. The antimicrobial agent and other antimicrobial solutes in the product sample can be eliminated by rinsing prior to transferring the filter into test tubes of media, thereby minimizing the incidence of false negative test results.
3. The entire contents of containers can be tested, providing a real advantage in the sterility testing of large-volume parenterals and increasing the ability to detect contamination of product lots containing very few contaminated units.
4. Low-level contamination can be concentrated on the membrane by filtering large volumes of product. This results in faster reporting of test results since MF requires only seven- day incubation (for most terminally sterilized products).
5. Organisms present in an oleaginous product can be separated from the product during filtration and cultured in a more desirable aqueous medium.

Interpretation of Results

No visible evidence of microbial growth in a culture medium test tube, after subjecting the sample and medium to the correct procedures and conditions of the USP and EP sterility test, may be interpreted that the sample representing the lot is absent of intrinsic contamination. Such interpretation must be made by those having appropriate formal training in microbiology and having knowledge of several basic areas involved in quality control sterility tests:

- Industrial sterilization methods and their limitations
- Aseptic processing
- Statistical concepts involved in sampling lots for representative articles
- Environmental control procedures used in the test facility.

If microbial growth is found, or if the sterility test is judged to be invalid because of inadequate environmental conditions, the sterility test may be repeated. However, this introduces a controversial and somewhat complicated subject.

STERILITY RETESTING

Sterility retests have been allowed by the USP since sterility testing became a USP requirement (XI edition, 1936). Specific definitions of first and second stage sterility re-testing were introduced in USP XX (1980). While sterility retesting is allowed per the CFR, retesting is no longer allowed per USP as of the eight supplement released in May 1998. The FDA has repeatedly reaffirmed that it supports the USP position provided that industry shows due diligence in their investigations of initial sterility-test failures. Sterility retesting and investigation of initial sterility-test failures should be done with the highest degree of diligence and responsibility on the part of high-level management of the parenteral industry.

FDA GUIDELINES ON STERILITY TESTING

The September, 2004 FDA Guideline on Sterile Drug Products Produced by Aseptic Processing contains a fair amount of direction regarding conductance, evaluation, limitations, interpretation, and retesting requirements of the USP sterility test (2). This was highlighted in Chapter 21, p. 322, but for the sake of completeness, some redundancy will be covered here. The testing laboratory environment should employ facilities and controls comparable to those used for the filling and closing operations (e.g., Class 100 air conditions for critical operations where a sterile product is exposed to the environment). The limitations of the USP Sterility Test cause the FDA considerable concern with respect to sampling plans and any positive test result that may occur. In investigation of sterility-test failures—positive test results, the guidelines state that

> When persuasive evidence showing laboratory error is absent, or when available evidence is inconclusive, firms should err on the side of safety and batches should be rejected as not conforming to sterility requirements.