Table 13-4 Practical Realities of Environmental Monitoring

- Controlling the environment is not the same thing as monitoring the environment. Control exists at all times; monitoring is only a snapshot
- Can monitor too much where monitoring can be a source of contamination (the units themselves, more people in the clean room, disruption of laminar flow)
- There are many sources of error in EM sampling operations—media, recovery efficiency, incubation conditions, technicians contaminate plates or strips in their handling
- The enormous potential for variability in sampling, incubation, and other laboratory operations means that any CFU value could have a huge range associated with it. Air samplers, especially, are not quantitatively accurate
- Ordinary statistical methods cannot be applied to microbiological data with values typically 0 or 1 plus with all the variability in sampling and testing
- The source of microbial contamination is not from the air or facility, if properly maintained, but from people, of whom design engineers of facilities cannot control
- Microorganisms cannot survive in a clean room very long and cannot easily proliferate. Therefore, monitoring the environment at the end of a fill or shift does not mean that it will pick up the accumulation of microorganisms generated during that fill or shift
- Should not over-react should one plate or sample have a usually high number of CFUs. Looking more for trends, not single point data
- Anaerobes, molds, and yeast are common contaminants in aseptic processing areas and monitoring for their presence is essential

Source: From Refs. 15,16.

contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions. It also should be noted that time for microbial growth to occur increases the risk for elevated levels of pyrogens. Therefore, compounding and manufacturing processes should be carried out as expeditiously as possible, preferably planning completion of the process, including sterilization, within the maximum allowed time according to process validation studies. Aseptic processing guidelines require establishment of time

Table 13-5 FDA Warning Letter Statements Related to Environmental Monitoring (17).

- Monitoring is not conducted routinely nor concurrently with manufacturing. Sampling should be done daily during both shifts, both inside and outside of the LAF (laminar air flow) areas, and sample times should be varied to cover all parts of the production period. Sampling frequencies and locations must be defined
- Microbial air samples under laminar flow modules are collected only under static conditions
- Less than 10% of the microbial air samples were collected after noon, although production routinely continues until 3:00 p.m.
- Room air microbial samples are collected with the RCS (rotary centrifugal sampler) on a tripod at a height of 5 ft, which does not represent working level in these rooms. There is no trending of data
- There has been no daily monitoring of aseptic areas and LAF modules for nonviable particulates on a day-of-production basis
- High Efficiency Particulate Air (HEPA) filters have been certified with DOP (di-octyl phthalate) and a particle counter and not with a photometer
- Air velocities have been reported as an average and do not show the individual readings
- HEPA filters need to be DOP tested at least twice a year, not once a year as is currently being done
- Some of the validations of air quality in rooms were done only under static conditions without personnel. Also, no smoke pattern studies on the LAF have been performed to show effects of curtain movements on laminar air flows
- The firm has not set alert and action limits for most environmental samples; it needs to identify all organisms isolated from aseptic area until a database is established for normal flora found in the production environment (with frequency distribution) for use in evaluating sterility test results
- Failure to eliminate objectionable organisms from interior surfaces of transfer carts in which sterilized unsealed containers of drug product are exposed
- No validation studies have been conducted to assure the microbial settle plates are capable of supporting microbial growth after the stated 3-hr exposure time in Class 100 rooms
- The quality control unit did not assure that adequate systems and controls were in place to monitor the functioning, and to detect malfunctions, of the air handling systems used to control and assure aseptic conditions in aseptic manufacturing areas