The above examples of problems with distillation units used to produce WFI point to problems with maintenance of the equipment or improper operation of the system. The system likely has not been properly validated or that the initial validation is no longer valid. If you see these types of problems you should look very closely at the system design, any changes that have been made to the system, the validation report, and the routine test data to determine if the system is operating in a state of control.

Since microbiological test results from a water system are not usually obtained until after the drug product is manufactured, results exceeding limits should be reviewed with regard to the drug product formulated from such water. Consideration with regard to the further processing or release of such a product will be dependent on the specific contaminant, the process, and the end use of the product. Such situations are usually evaluated on a case-by-case basis. It is a good practice for such situations to include an investigation report with the logic for release/rejection discussed in the firm's report. End-product microbiological testing, while providing some information, should not be relied on as the sole justification for the release of the drug product. The limitations of microbiological sampling and testing should be recognized.

Manufacturers should also have maintenance records or logs for equipment, such as the still. These logs should also be reviewed so that problems with the system and equipment can be evaluated.

In addition to reviewing test results, summary data, investigation reports and other data, and the print of the system should be reviewed while conducting the actual physical inspection. As pointed out, an accurate description and print of the system is needed in order to demonstrate that the system is validated.

AIR

Chapter 13 discussed standards (limits) for particles and microorganisms for the primary classifications of clean areas in sterile product manufacture. Table 15-3 is an abbreviated summary of air particle standards comparing U.S. and European classifications and clean room designations assigned by the International Society of Pharmaceutical Engineers. The numbers are based on the maximum allowed number of airborne particles/m^3 of 0.5 μm or larger size and, for Europe, 5.0 μm or larger size. The classifications used in pharmaceutical practice normally range from Class 100,000 (Grade D) for materials support areas to Class 100 (Grade A) for aseptic areas. To achieve Class 100 conditions, high-efficiency particulate air (HEPA) filters (Fig. 15-5) are required for the incoming air, with the effluent air sweeping the downstream environment at a uniform velocity, normally 90–100 ft/min ± 20%, along parallel lines [laminar airflow (LAF)]. HEPA filters are made of densely compacted fiberglass fibers, randomly arranged, that trap particles and other pollutants. HEPA filters are defined as 99.99% or more efficient in removing from the air 0.3-μm particles generated by vaporization of the hydrocarbon Emory 3004. Other characteristics of HEPA filters are given in Table 15-4.

Air Cleaning

Since air is one of the greatest potential sources of contaminants in clean rooms, special attention must be given to air being drawn into clean rooms by the heating, ventilating, and air-conditioning system. This may be done by a series of treatments that will vary somewhat from one installation to another.

Table 15-3 Comparison of Air Cleanliness Classifications

U.S. classification	European grade	ISO room designation	ISPE classification	Particles/m^3 ≥ 0.5/5.0 μm
100	A	5	Critical	3,500/0
100	B[a]	6	Clean	3,500/0
10,000	C	7	Controlled	350,200/2,000
100,000	D	8	Pharmaceutical	3,520,000/20,000

[a]Class B is the same as Class A at rest, but during operation, Class B has a limit of 350,200/2,000 particles/m^3 ≥ 0.5/5.0 μm. Class C has the same limits as Class D during operation.