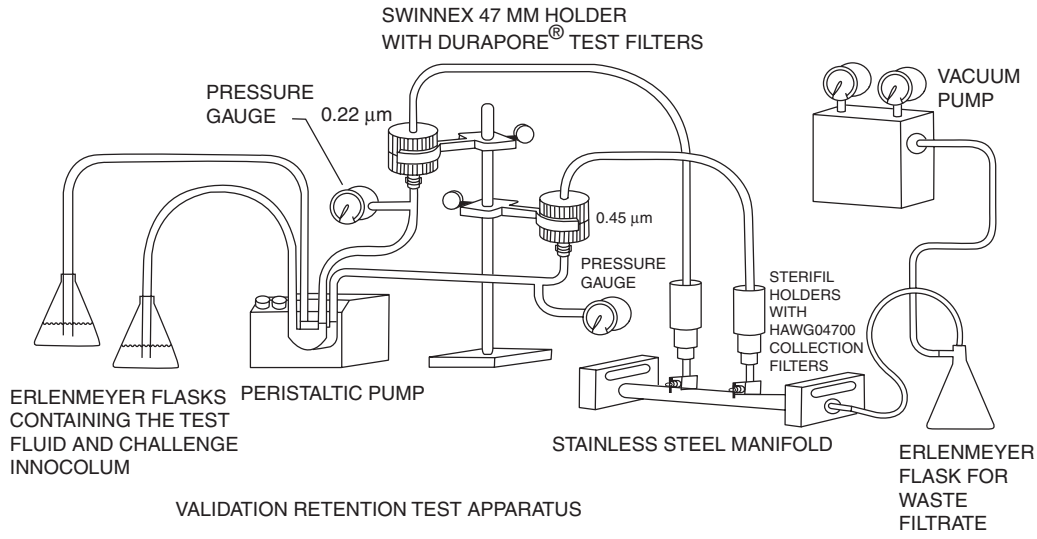

Figure 18-4 Filter validation retention test apparatus. *Source*: From Ref. 3.

Product-Filter Compatibility

Tests must be performed to demonstrate that (1) the product does not adversely affect the retention properties of the filter, as is accomplished in most cases with the bacterial retention studies discussed above, and (2) does not cause the filter to leach materials into the product. Compatibility and extractable studies are performed by the filter manufacturer, although like bacterial retention studies, the product manufacturer is ultimately responsible for the validity of the data. The filter manufacturer will provide information on the flush volume required to yield negative oxidizable substances and provide the data on the level of extractables obtained with different solvent exposures. Potential filter extractables include oligomers, mold release agents, antioxidants, wetting agents, manufacturing debris, plasticizers, membrane backing, cartridge body, and 0-ring material.

There are a few examples, almost all involving protein drug products, where the protein will bind to the filter material with most studies involving in-line membrane filters, not large surface area filters used in commercial manufacturing (4–6). Typically, an insignificant amount of drug will adsorb on the filter surface and occupy all the binding sites. One purpose of a preflush step prior to filtration is to occupy available binding sites as well as remove potential extractables. Polyethersulfone (PES) and PVDF filters are low protein-binding filters.

Other data provided by the filter manufacturer in performing qualification studies on the filter to be used with the finished product include:

- Limits for flow rate, temperature, and pressure
- Ensure that the filter meets the nonfiber releasing criteria from 21CFR 210.3b(6)
- Procedures for filter sterilization
- The filter bubble point or diffusion rate for the in-process integrity tests
- Correlation of the integrity test value and the amount of *B. diminuta* retained
- Written instructions and specifications for the filter integrity test.

IN-PROCESS FILTER INTEGRITY TESTING

Prior to actual filtration of the product, the filter should be flushed either with product or with water for injection to reduce potential extractables and downstream particles. The filter is then subjected to a filter integrity test (prefiltration filter integrity test) and after the solution is filtered, the filter is again subjected to a second filter integrity test (postfiltration filter integrity test). This integrity test usually is performed either as the *bubble-point test* or as the *diffusion or forward flow* test. The bubble point test is commonly used on smaller filters. As the surface area of filters becomes large, diffusion of air through the water-filled pores tends to