other parts) should be designed to minimize particle generation. This includes opening of packaging containing sterile items as the opening process likely generates particles.

7. Material handling—The ease of transferring materials in and out of an isolator largely determines whether a process can be performed within an isolator. The role of the "mousehole" is very important for continuous transfer during filling operations.
8. Bio-decontamination method integration—Bio-decontamination of isolators is automated, either standalone or integrated. Standalone systems consist of a sanitizing agent injection system, a fan for moving the air, tubing to connect to the ports on the isolator, and a desiccant system for controlling humidity. Integrated systems are installed in the isolator structure. Sanitizing agent injection and humidity control are performed by the bio-decontamination system while airflow control is performed by the air handling unit of the isolator.
9. Equipment in the chamber—Equipment within the isolator must be designed to be cleaned and bio-decontaminated. Connections from the equipment to external sites (e.g., power supply) must be as seamless as possible. Equipment interventions must be minimal so equipment needs to be durable. Equipment must be designed for easy access during operation. Adjustments to equipment must not require a high degree of manipulation. Typically, equipment is specially designed to fit and work easily within isolators. Making connections, changing parts, correcting failures, and other manipulations are designed to be performed with one gloved hand.
10. Airflow—Isolators are either closed or open. Closed isolators are fully sealed while open isolators have mousehole openings for continuous processing. Unidirectional airflow is required for correct operation of open isolators. Close isolators can have no airflow or airflow that is either unidirectional or even turbulent. Airflow definitely is required for optimal bio-decontamination to assure proper distribution of sanitizing agent, humidity, temperature, and sufficient aeration. Large isolators usually require full HVAC systems to assure optimal airflow and distribution.

While isolators have been implemented in the industry, progress has been slower than initially anticipated. There are several reasons for this slow growth and acceptance:

1. General regulatory and industry caution because of the relative novelty of isolator technology.
2. Regulatory agencies have insisted so far that isolators be located in classified environments (usually at least Class 100,000/EC Grade D). This discouraged investment by some in isolator technology because it was originally thought that classified environments would not be necessary.
3. Initial promotion that isolator technology could create a truly sterile environment and, thus, allow a much greater claim for sterility assurance proved not to be true. Isolators tend to have small leaks, particularly at the glove ports and gloves or half suits. The industry has learned the hard way that for aseptic processing, sterility assurance levels for isolators are not much greater than conventional Class 100/EC Grade A filling operations.
4. Validation of isolators has been more difficult than expected. For example, it is difficult to convince reviewers that contamination will not occur despite constant movement of materials in and out of the isolator, the occasional need to manipulate equipment, and the problem of pinhole leaks. The significantly increased time and resources required to validate and maintain isolators have discouraged many companies from investing in these systems.

VALIDATION OF BARRIER ISOLATION AND ASSOCIATED STERILIZATION SYSTEMS

Like any other process in the pharmaceutical industry, barrier isolation must be shown to reproducibly deliver the desired result. Because of their complexity, there are several parameters to consider in the design and validation of isolation systems (Table 23-2) (10). United States Pharmacopeia (USP) Chapter <1208> provides guidance for the design and validation of isolator systems for use in sterility testing. The guidelines in USP <1208> are summarized below, as well as common practices in the validation of sterility testing isolators. For a complete description of <1208> consult the most current USP revision.

The steps and considerations that are essential to the isolator validation and design are outlined below.