

**Table 14-1** Examples of 483 Observations Related to Manufacturing Facilities for Sterile Product Production

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- Capping area not under auspices of a controlled environment
  - Loading vials into freeze-dryers not under auspices of a controlled environment
  - Evidence of cracks, deterioration of walls, ceilings, floors; debris in clean rooms
  - Lack of proper certification of HEPA filters
  - Lack of smoke test data and video during operations
  - Lack of environmental monitoring data during operations and at specific locations related to actual filling areas
  - Inadequate sanitization validation
  - Lack of documentation regarding facility maintenance (e.g., cleaning, differential pressure checks, gas filter integrity, improper storage of equipment)
  - Inadequate air monitoring (environmental plates, air velocities, air pressure differentials, reactions to out-of-specification limits)
  - Facility changes made without change control procedures followed
  - Failure to establish a system for maintaining equipment to control aseptic conditions
  - Failure to follow appropriate written procedures designed to prevent microbial contamination of drug products in designated facilities
  - Deficiencies in the cleaning validation of equipment and facilities and lack of evidence of effectiveness of sanitization procedures
  - Inadequate controls to prevent cross-contamination of products within the manufacturing facility
  - Inadequate facility design, e.g., porous drywall-like material not easily cleaned
  - Rust-like substances seen in several locations in different rooms
  - Failure to replace faulty HEPA filters
  - No air flow pattern testing in aseptic areas
  - Lack of classified environments after vial stoppering
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*Abbreviation:* HEPA, high efficiency particulate air.

GMPs for large-volume injectables (CFR sect. 212) were never formally legalized but several statements in section 212 were adopted and commonly practiced by the parenteral industry at large. Here is one example:

Section 212.42: Walls, floors, ceilings, fixtures, and partitions in controlled environment area shall (a) have a smooth, cleanable finish that is impervious to water and to cleaning and sanitizing solutions and (b) be constructed of materials that resist chipping, flaking, oxidizing, or other deterioration.

To achieve these specific criteria, the materials of construction specially made and much more expensive than materials used to construct “normal buildings,” even nonsterile pharmaceutical manufacturing facilities.

### **FUNCTIONAL AREAS IN A STERILE PRODUCT MANUFACTURING FACILITY**

To achieve the goal of a manufactured sterile product of exceptionally high quality, many functional production areas are involved:

- Warehousing or procurement
- Compounding (or formulation)
- Materials (containers, closures, equipment)
- Preparation
- Filtration
- Sterile receiving
- Aseptic filling
- Stoppering
- Lyophilization (if warranted)
- Packaging
- Labeling
- Quarantine.

Each of these areas has standard design criteria for the acceptable maximum limit of airborne particles greater than or equal to 0.5  $\mu\text{m}$  either per cubic foot (United States classes)