Table 21-1 Aseptic Process Operations and Support Systems That Should Be Part of a Qualification and/or Validation Study

- Cleaning and disinfection of tanks, mixing vessels, and transfer lines
- Raw material bioburden and pyroburden
- Raw material addition
- Compounding and mixing
- All product transfer steps
- Product filtration (sterilization step) including microbial retention, product compatibility, and filter extractables
- Sterilization of all filters (liquid and gas)
- Cleaning and sterilization of product contact surfaces, parts, vessels, lines, housings, all accessories
- Cleaning of all packaging components
- Cleaning and sanitization of clean room equipment, walls, floors, surfaces
- Operation of component handling and transport equipment, unscramblers, hoppers, bottle orienters, star wheels, component bowls and tracks, conveyors, turntables
- Operation of filling equipment, inert gas overlay systems, stopper inserters, cappers
- Operation of product removal systems, check weighers, volume detectors, leak detectors, inspection systems, vision systems
- Operation of labelers, sealers, cartoners, all packaging equipment
- Utilities generation and transport systems for air, water, cooling medium, vacuum, dust collection, nitrogen, plant and clean steam
- Monitoring systems, building automation, facility monitoring, distributed control systems, PLCs, LIMS data collection, all electronic record generation and storage systems
- Warehouse, cold storage, handling
- Disinfectant (sanitizing) and cleaning effectiveness
- Gown and glove sterilization
- Effectiveness of clean room HEPA filters
- Operation of clean room air handling systems
- Clean room airflow in and around exposed product and product contact surfaces in relation to the aseptic process and interventions
- Cleaning and disinfection of isolators or RABS interior
- Operator gowning
- Operator hygiene, aseptic techniques and practices

Abbreviations: PLC, programmable logic processor; LIMS, laboratory information management system; RABS, restricted access barrier system. *Source*: From Ref. 1.

BUILDINGS AND FACILITIES

Air classification is in accordance with both the FDA and EU guidelines, as seen in Table 21-2A and 21-2B, with surface quality standards given in Table 21-2C. Air particle counts must be measured not more than 1 foot away from the actual work site and should be measured during actual filling and closing operations. Air quality of powder filling operations must be certified under dynamic conditions (machinery running) without filling of actual powder. Air particle counts must be measured frequently during each shift, bracketing the beginning and end of the filling operation.

The air supplied to the Grade A/B or Class 100 clean room must have a velocity of 90–100 ft/min with a range of $\pm$ 20%. Airflow patterns must be determined using smoke tests and videotaping the smoke test results. Smoke tests verify the unidirectional flow of air. The

Table 21-2A Air Classifications According to FDA Aseptic Processing Guidelines

Clean area classification	Particles $\geq 0.5\mu m/ft^3$	Particles $\geq 0.5\mu m/m^3$	Air microbial action level (CFU/m^3)	Settle plate action level (CFU/4 hr)
100 ISO 5	100	3520	1 (Expect zero)	1 (Expect 0)
1000 ISO 6	1000	35,200	7	3
10,000 ISO 7	10,000	352,000	10	5
100,000 ISO 8	100,000	3,520,000	100	50