14 Sterile manufacturing facilities

The manufacturing facility—its floors, walls, ceilings, and all associated equipment and utilities—must be designed, constructed, and operated properly for the production of a sterile product with the excellent quality level required for safety and effectiveness. Materials of construction for sterile product production facilities must be "smooth, cleanable, and impervious to moisture and other damage." All facilities, equipment, and fixtures must be flush fitted to meet the need for smooth and cleanable surfaces. All connections or junctions between ceilings, walls, and floors cannot be 90° angles, but coved for easy cleaning. There is no place for gaps, cracks, recesses, or other defects that can be harbors for microbial contamination to build up.

What might not seem obvious to the average person is the special design of openings for air entrances and returns, doors, windows, light fixtures, and communication systems (speakers, telephones, intercoms) to meet the "smooth, cleanable, and impervious to moisture and other damage" requirements. All of these kinds of essential building items need to have flush fittings and appropriate sealed systems that do not contribute to particle or microbial contamination. Air systems, lighting, and communication systems need to be designed to be accessible from areas that are not part of the clean room. Doors must be designed to be opened and closed easily with minimal disturbance to the normal airflow patterns in the clean room. Of course, rooms are to be built such that air flow moves toward rooms of lesser cleanliness and this is accomplished via room air pressure differentials with air from higher classifications (e.g., Grade A or ISO 5) moving toward rooms with lower classifications (e.g., Grade C or ISO 7). Doors should be self-closing and in rooms where there are two doors (e.g., change room), doors must be interlocked so that only one door at a time can be open. Emergency doors must have workable alarm systems such that if any emergency door is ajar or opened, typically leading to an unclassified environment, personnel are alerted immediately. If such a door is ever opened, purposefully or not, during production, batches risk being rejected because of uncertainty of the classified environment being jeopardized.

Further, the processes used must meet current good manufacturing practices (cGMP) standards. Since the majority of small-volume injectables and topical ophthalmic products are aseptically processed (the finished product not terminally sterilized), adherence to strict cGMP standards with respect to sterility assurance is essential.

The cGMP regulations have several statements regarding facility requirements, but two particularly apply to sterile production facilities:

> Section 211.42: There must be separate or defined areas of operation to prevent contamination, and that for aseptic processing there be, as appropriate, an air supply filtered through HEPA filters under positive pressure, and systems for monitoring the environment and maintaining equipment used to control aseptic conditions.
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> Section 211.46: Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature be provided where appropriate, and that air filtration systems including prefilters and particulate matter air filters, be used when appropriate on air supplies to production areas.

Table 14-1 lists examples of GMP compliance problems (FDA 483 observations) where the above two GMP reference statements were cited as evidence of lack of compliance. It is interesting that most facility problems are a result of poor design to begin with, poor maintenance and repair, and/or concerns about potential facility contributions to lack of sterility assurance of products manufactured in the facility.