

Cleanroom manufacturing practices and voluntary compliance

Rationale for non-compliance with voluntary environmental control standards requires understanding 'best practice' recommendations by industry experts

By Gregg Mosley, Communications Vice President, IEST



In reviewing the current standards and recommended practices for cleanrooms and controlled environments it is difficult to imagine the simple beginnings for the concept. Although many professionals worked on test methods and controlling microbial bioburden and particulate contamination, the original idea of

a modern cleanroom was quite different. In the late 1950s, engineer Willis Whitfield, on staff at Sandia National Laboratories in Livermore, CA, conceived a simple idea: "To keep a room very clean, let air be the janitor." His first tested design—using cleansed, monotemperature, laminar airflow—produced room contamination levels 1,000 times cleaner than any previously obtained. Patents for the cleanroom idea were issued to Whitfield in 1962.

Timing for Whitfield's concept appears perfect as immediate applications were made in three separate areas. Electronics manufacturers saw the application as a tremendous cost savings to reduce product failures. Health care facilities implemented the design to reduce infections in operating room theaters. And the U.S. government operations at NASA applied the cleanroom concept to control particulate and microbial bioburden contamination of extraterrestrial vehicles in the space program. The latter application was combined with sterilization of materials and components to minimize the prospect of accidental contamination of space and other extraterrestrial bodies in the solar system by projectiles from earth.

Manufacturing sterilized medical products

The combination of controlled environmental and sterilization practices developed at NASA has had a primary impact on manufacturing of sterile medical products. The outcome of the NASA projects demonstrated that sterilization was a function of the pre-existing product bioburden. Therefore, control of the environments for manufacturing and packaging of medical products has a direct impact on one's ability to produce these sterile products. Many of the scientists involved in the NASA systems moved on to careers in government or industry

directly related to production of sterile medical products. Recent ISO sterilization standards 17665-1 (2006) for moist heat; 11137-1, -2, and -3 (2006) for radiation; and 11135-1 for ethylene oxide (2007) identify the importance of quantifying and characterizing product bioburden as part of sterilization validation. For aseptically manufactured sterile products, components must be sterilized first, then the product should be final packaged in a controlled environment to ensure aseptic conditions are maintained for processing of the lot. These sterilization standards are not required by the U.S. Food and Drug Administration (FDA), though they are often considered best practice. However, for products marketed in the European Union (EU), the standards are required in the Medical Device Directives (MDD).

Current recommended practices and ISO standards for cleanrooms are developed under the leadership of the Institute for Environmental Science and Technology (IEST). Status of these standards and recommended practices was reviewed in the July issue of *CleanRooms*. IEST is the secretariat for ISO Technical Committee 209 (ISO/TC 209), Cleanrooms and associated controlled environments, and represents the United States as administrator of the U.S. Technical Advisory Groups (TAG) to ISO/TC 209 and 142.

Industry perspectives on critical environments

A corporate determination of whether to comply with the ISO 14644 and 14698 series of standards for cleanrooms often appears to depend on whether the effects imparted by the critical environment are direct and immediate or not. For instance, manufacturers of electronic components verify the performance of components immediately and generally at a 100 percent inspection level. These quality control inspections may be repeated when multiples of components are assembled as subsystems. An increase in the number of rejects is detected immediately and correlates directly to the financial bottom line. Numerous quality inspections, set up early in the production sequence, minimize the potential loss of materials and employee time compared to inspections that are less frequent and further downstream.

In health care facilities, applying best practice for operating rooms

and other potential sources of nosocomial infections minimizes both the probability of patient lawsuits and successful prosecution. In addition, best control practices as well as lawsuit history affect insurance premiums at health care locations.

Similarly, manufacturers of pharmaceutical products that are aseptically filled see direct correlation. When such products fail required tests for sterility, the finished products lots may be rejected. In these situations, product cannot be reworked and the financial impact is immediate. Rework is not possible because tests are destructive; hence, statistically based sampling plans rather than 100 percent inspections are used. However, for these manufacturers, loss of the product is only the beginning of the financial loss. Medical product manufacturers operate as a regulated industry under the auspices of the FDA, similar national regulatory agencies, and/or the ISO notified bodies. Therefore, quality system problems often require internal investigations where effort is expended by staff at higher administrative levels to investigate and review all related data, training, and system controls. This is necessary to determine whether a general degradation of control can be identified somewhere in the quality system as the root cause. An identified root cause must be resolved, a corrective action implemented, and the effects monitored over time to determine whether the correction was successful. Requirements for these activities are covered in 21 CFR Part 820, Subpart J or ISO 13485: 2003, 8.5.2.

For products that are terminally sterilized, the effects of the critical environment used for manufacturing are not as clear as the examples given. Environmental particulates and microbes may have no impact on the ultimate quality of manufactured medical products. If products are cleaned, decontaminated, passivated, or rinsed prior to final packaging, most contaminating microbes may be removed or inactivated. For some products, the contribution of microbes by the manufacturing environment may be relatively insignificant compared to the levels on incoming components.

Sterilization validation

Terminally sterilized products may use an

approach to sterilization based on bioburden, which is the microbial load naturally occurring on the product. Another approach referred to as “overkill” uses substitute microbes (biological indicators) with a known very high resistance to the sterilization method. Finally, a combination approach using information from both microbial groups is referred to as the “bioburden/BI approach.” Validation methods using radiation sterilization are bioburden based, so the impact of bioburden numbers and resistance is critical. Manufacturers using radiation take more notice of product bioburden changes and the manufacturing environment that may be a contributor. However, moist heat and ethylene oxide sterilization most often employ the overkill method. In this approach, bioburden has a lesser significance so long as the numbers remain below some maximum defined level and the types of microbes have a known low resistance to the sterilization method. Some manufacturers using these sterilization methods appear less concerned with the manufacturing environment and potential impact on the product. Often their rationale is that the overkill approach to sterilization will compensate for excursions in product bioburden, possibly imparted by the controlled manufacturing environment.

As it relates to reliance on an overkill sterilization method, bioburden must still be monitored and known so far as numbers and resistance to the process. Objective evidence must be available comparing bioburden levels for product and the manufacturing environment to show whether or not a correlation exists. Without historical data maintained in a baseline monitoring program, one cannot determine what levels of environmental contamination do or do not create a problem for the finished product. If the environment could have an impact on the product quality attributes, then a defensible monitoring program is a requirement. A scientifically based, pragmatic approach to controlled environmental monitoring should ensure consumer safety and reduce manufacturer cost and risk.

Regulatory perspectives

The regulatory requirements are not so forgiving, though. The same investigations and

corrective actions apply for terminally sterilized products as for aseptic pharmaceuticals. In addition, FDA and ISO regulations cite the need for monitoring and control of the manufacturing environment. The FDA Quality System regulation addresses issues related to manufacturing environmental controls in sections 21 CFR §820.3, §820.70, and §820.75 discussing processes, process controls, and validations. Sections §820.181 and §820.184 cover documentation requirements for process and device records. ISO 13485: 2003 cites similar needs in clauses: 4.2.4 control of records, 6.3 infrastructure, 6.4 work environment, 7.5 production controls and validation, and 8.2.3 monitoring and measurement of processes.

In addition, changes in quality system regulations such as those specified in ISO 13485: 2003 require that risk assessment (including the impact of environmental controls) must be performed. The risk assessment task can be reduced by comparing devices typically manufactured in similarly controlled environments. When a company chooses not to follow voluntary ISO standards guidelines, the supporting rationale should be documented and re-evaluated when risk assessment changes.

Conclusion

The desire by manufacturers to comply with voluntary cleanroom standards often directly correlates to finances. However, it is important to understand how regulatory agencies perceive compliance to quality systems regulations and these voluntary cleanroom standards because they have been developed by a consensus of experts. Rationale for why they do not or need not comply is essential if they choose another testing series and compliance is often easier to accomplish. ☐

Gregg A. Mosley is founder and president of Biotest Laboratories, Inc. (Minneapolis, MN). Mosley serves IEST as chair of the editorial board for the peer-reviewed *Journal of the IEST* and as the executive committee communications vice president. He has more than 30 years of experience as a microbiologist, chemist, and biochemist in various academic and industry positions. He is co-chair of both the AAMI Biological Indicators and the Industrial Moist Heat Sterilization Committees. Email: gmosley@biotestlabs.com.