

Aseptic Processing Minimizing Risk Through Technology

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In comparison with other production processes, aseptic processing presents unique challenges for pharmaceutical manufacturers and regulatory agencies. One of these challenges is the inability to monitor the output of the process to ensure the sterility of every manufactured unit. Aseptic processing also is a high-risk activity. Failures, if undetected, can produce serious health consequences in patients receiving the medication. Advances in manufacturing technology and the application of risk assessment can minimize patient risk by providing robust process control and high levels of sterility assurance.

For most pharmaceutical products, chemical and microbiological tests and assays are used to evaluate raw and in-process materials, the manufacturing environment, the validated manufacturing process, and the finished product. These tests and assays can confirm the suitability of the materials, show that the manufacturing processes functioned as intended, and demonstrate that the finished product possesses its predetermined quality attributes. In the case of aseptic processing, however, no finished product test is available to confirm the sterility of each manufactured unit.

The *USP* sterility test is of limited value in detecting the presence of a few contaminated units in a lot of aseptically produced product. When 20 samples are tested, the sensitivity of the test is such that nonsterility would be detected at a 95% confidence level only when 14% or more of the batch is contaminated. If 0.1% of the units in a batch were contaminated, the sterility test would detect that contamination with a probability of only 2%. A contamination rate of 1 in 5000 would be detected only 1% of the time. This means that process control and monitoring must be the primary mechanisms through which the sterility of aseptically produced products is ensured.

The US Food and Drug Administration addressed risk analysis under its "CGMPs for the Twenty-First Century" initiative, which ran from

August 2002 to September 2004. The purpose of this two-year program was to align the level of regulatory scrutiny with risk and to encourage the industry to adopt risk-management approaches.

The primary risk associated with conventional aseptic processing in staffed clean rooms is microbial contamination introduced by gownned personnel during normal operations and particularly during "interventions," *i.e.*, activities performed to correct problems that require breaching the critical zone in which product, product-contact surfaces, and containers and closures are exposed. No reasonable amount of environmental monitoring is likely to detect every viable microorganism that might be released into the aseptic processing environment, and sterility testing is not sensitive enough to ensure the sterility of every unit of finished product.

Using risk management to evaluate, redesign, and control the manufacturing process can minimize the risks associated with aseptic processing. Real control of risk, however, can only be achieved by removing people from the aseptic processing environment, which can be achieved most effectively by using new technologies that do not rely on gownned personnel and do not expose sterilized product, containers, or closures to the aseptic manufacturing environment. Such technologies include isolators and barrier systems, blow-fill-seal and form-fill-seal machines, and dosed-vial filling systems. These systems, which exclude personnel from the critical aseptic manufacturing environments, are designed with automated sterilization, monitoring, and control features that detect and react to abnormal conditions that could compromise product sterility.

This *Aseptic Processing Supplement to Pharmaceutical Technology* contains articles describing new technologies such as dosed-vial filling and improvements to existing techniques such as isolators and gownning systems aimed at minimizing risk. The supplement also provides a vision for the future of aseptic processing. *Enjoy.* **PT**