Sterilization of Blow-Fill-Seal Equipment for Aseptic Filling

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Nitrogen dioxide can sterilize and depyrogenate an aseptic fill area in a blow-fill-seal process.

Blow-fill-seal (BFS) technology—in which a polymeric container is formed, filled, and sealed in one continuous process—has been used for more than 40 years to aseptically package parenteral pharmaceutical products, such as ophthalmic solutions. Use of BFS technology is expected to increase for packaging biologics, such as vaccines and protein-based materials. BFS is an automated system that minimizes human contact. Typically, the product-contact path of the BFS process is sterilized with steam, and the entire process takes place in a cleanroom environment. Noxilizer, which supplies nitrogen dioxide (NO_2) sterilization systems, and BFS equipment supplier Weiler Engineering recently presented research on NO_2 sterilization and depyrogenation of the fill area in Weiler's ASEP-TECH BFS systems using a Noxilizer NOX FLEX Rapid Biodecontamination System (1). *Pharmaceutical Technology* spoke with David Opie, PhD, senior vice-president of R&D at Noxilizer, and Chuck Reed, director of sales and marketing at Weiler Engineering, about this novel sterilization and depyrogenation method.

Sterilization and depyrogenation

PharmTech: What are some of the concerns for sterilizing BFS equipment?

Opie (Noxilizer): Aseptic processing requires rigorous and careful manufacturing practices due to the potential adverse effect on the healthcare consumer. Regulatory agencies are placing greater focus on improved patient safety and are developing standards to ensure sterile, contamination-free products. In particular, regulatory standards increasingly state that pharmaceutical manufacturers should be aware of new procedures designed to reduce risk to the product through the use of enhanced technology. One such procedure is the reduction of pyrogens during the decontamination process.

Pyrogenic contamination comes from endotoxins, which are mainly lipopolysaccharide components of Gram-negative bacterial cell walls that can cause acute febrile reactions. These endotoxins are heat stable and may be present even when viable organisms are no longer detectable. Endotoxins are impossible to eliminate from filled containers; thus, procedures are generally directed at eliminating endotoxins during the preparation process.

Reed (Weiler). The entire BFS process takes place in a cleanroom environment, and the product-contact path is sterilized in place with steam. The fill area of a BFS system is much different from the fill area of a conventional aseptic filling system, because the product is filled as soon as the container is formed, which reduces the opportunity for contamination. The critical filling zone area of a BFS machine is the area comprising the fill system shroud, which typically encompasses the fill needles and electronic modular dosing system. This enclosed area has typically been manually sanitized prior to the start of a production batch, and during production is supplied by HEPA-filtered air. We wanted to provide additional assurance for our customers of the decontamination of the fill area. The NO_2 process offers a new procedure for depyrogenation and decontamination of the fill area in a BFS system to give that additional assurance.

Advantages of NO_2

PharmTech: What are the advantages of using NO_2 to sterilize the BFS-equipment fill area?

Opie (Noxilizer): The room-temperature process combines decontamination of exposed critical zone surfaces with the potential for depyrogenation of these surfaces. The Noxilizer process is a fast (less than one hour), automated process that yields more than a six-log reduction in biological indicator organisms and more than a three-log endotoxin reduction (1). The NO_2 process is a true gaseous process that has more uniform distribution than vapor processes. Another feature of the NOX FLEX system verified in this study was the remote operation of the decontamination process with up to 50 meters of conduit between the NOX FLEX unit and the ASEP-TECH system, which permits the location of the Noxilizer equipment outside of the cleanroom in which the BFS machine is installed.

Reed (Weiler): BFS technology is well suited for aseptic processing of biologics, such as vaccines and protein-based materials, which are particularly sensitive to residual sterilant in the filling environment. NO_2 has been demonstrated to

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have a fast aeration rate that results in low residual sterilant. In addition, the automated NO_2 system eliminates the human interaction required in the manual sanitization method. Finally, the integrated system is an efficient process that can be more easily validated than the manual process.

Cycle parameters

PharmTech: What are the critical parameters of the sterilization cycle?

Reed (Weiler): The cycle parameters were developed to coincide with the normal cycle time of the clean-in-place/sterilize-in-place process for sterilizing of the product path in the BFS machine. The BFS cycle parameters for the study were 30 mg of concentrated NO_2, 55% relative humidity, a 40-minute decontamination time and 30-minute aeration time (1).

Reference

1. C. Reed, et al., "Decontamination and depyrogenation of an Asep-Tech Blow/Fill/Seal system," poster presented at the PDA Annual Meeting (San Antonio, TX, 2014). **PT**