

# Decontamination and depyrogenation in aseptic filling operations

Sterilisation equipment developer Noxilizer and aseptic liquid processing technology provider Weiler Engineering have worked together to put the 'c' in cGMP through improvements in decontamination and depyrogenation process technology

**No one ever got fired for buying IBM;** this 1970s adage succinctly captures the conservatism of the biopharmaceutical industry. That is not to say that conservatism and caution are not required when patient safety is at risk – but how much of this is driven by the fear, uncertainty and doubt of incumbent suppliers defending existing technology?

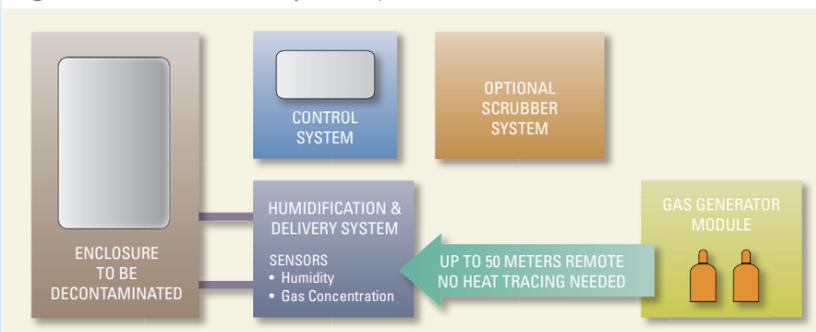
The 'c' in cGMP is for 'current' and indicates that the GMPs are not static and should move with the times. To quote the FDA: "The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement", and 'systems and equipment that may have been 'top-of-the-line' to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards'.

Thus, rather than promoting conservatism, the FDA is encouraging innovation – inciting suppliers to raise the bar and put the 'c' in cGMP, while of course meeting and exceeding the regulatory requirements and assuring patient safety.

So it was in this vein that US-based industry innovators Noxilizer and Weiler Engineering got together to develop a novel and improved method for decontamination of the critical zone of Weiler's ASEP-TECH Blow-Fill-Seal (BFS) aseptic filling machine.

In the BFS system, a container is moulded from plastic resin, aseptically filled and hermetically sealed in one continuous, integrated and automated process. The BFS process provides flexibility in container design, high volume product output, low operational costs and a high assurance of product sterility.

**Figure 1** The Noxilizer NOX FLEX system components



Packaging liquid pharmaceuticals with BFS technology provides the highest level of sterility assurance available for aseptic filling. The critical filling zone of a BFS machine is the area comprising the fill system shroud, which typically encompasses the fill needles and electronic modular dosing system. This shroud area has traditionally been steam sterilised or manually sanitised prior to the start of the production batch.

Weiler saw the opportunity to increase the safety margin over these traditional methods with the integration of Noxilizer's room temperature nitrogen dioxide (NO<sub>2</sub>) decontamination system, which has been demonstrated not only to kill micro-organisms, but also to effectively reduce endotoxin levels.

Endotoxins, or pyrogens, are mainly lipopolysaccharide components of Gram-negative bacterial cell walls, which can cause acute febrile reactions (i.e. fever). These endotoxins are heat stable and may be present even when viable organisms are no longer detectable. In layman's terms, they are residues of dead micro-organisms that may induce fever and are therefore

dangerous to already sick patients receiving a drug through parenteral administration. Endotoxins are impossible to eliminate from filled containers; thus procedures are generally directed at eliminating endotoxins during preparation processes.

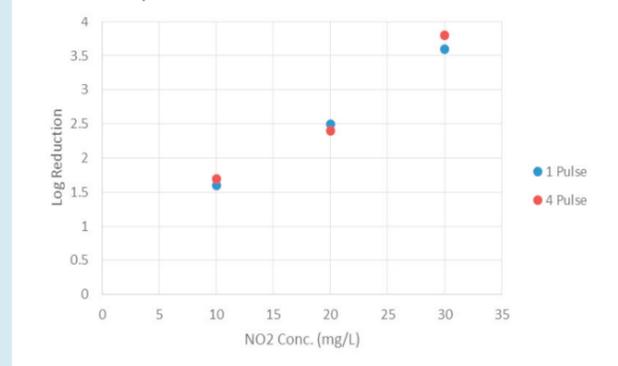
Weiler and Noxilizer worked for more than a year to integrate Noxilizer's NOX FLEX system into the ASEP-TECH BFS machine, efficiently completing decontamination and depyrogenation in a single, rapid, room temperature process.

Study results from the first demonstrated decontamination and depyrogenation of the critical zone of an aseptic filling system using NO<sub>2</sub> were presented at the 2014 PDA Annual Meeting in San Antonio, Texas. The Noxilizer process is a fast (less than one hour), automated process that yields more than a 6 log reduction in biological indicator organisms (*Geobacillus stearothermophilus*) and more than a 3 log endotoxin reduction (see Figure 2).

Another feature of the NOX FLEX system verified in this study was the remote operation of the decontamination process with up to 50 metres of conduit between the NOX FLEX unit and the ASEP-TECH system. This unique capability permits the location of the Noxilizer equipment outside the cleanroom in which the filling machine is installed.

As a result of the successful collaboration with Noxilizer, Weiler Engineering is now able to offer the NO<sub>2</sub> process with NOX FLEX Rapid Biodecontamination units for its ASEP-TECH Blow/Fill/Seal Systems through an exclusive global supply agreement (for BFS systems). Noxilizer's NOX FLEX provides a single-step decontamination and depyrogenation

**Figure 2** Endotoxin Log Reduction versus NO<sub>2</sub> concentration showing linear dose response



The Noxilizer process is a fast, automated process that yields more than a 6 log reduction in biological indicator organisms and more than a 3 log endotoxin reduction

process in a patent-pending application that is expected to broaden the use of ASEP-TECH BFS systems worldwide.

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**Key features of the ASEP-TECH blow/fill/seal system STERI-Shroud with NOX FLEX decontamination and depyrogenation**

- Completely automated process, requiring no human intervention in the filling zone
- Provides non-aqueous decontamination and depyrogenation of the critical filling zone
- Better than 3-log endotoxin reduction in an easily validated process
- Low residuals for high efficacy with sensitive biological products
- Rapid cycle for efficient equipment clearance when running multiple products
- Cycle coincides with the normal CIP/SIP process for cleaning and sterilising of the product path



**"Weiler and Noxilizer worked for more than a year to integrate Noxilizer's NOX FLEX system into the ASEP-TECH BFS machine"**