VxP PHARMA
The Pharmaceutical Services Company

STERILE FILL AND FINISH

This crucial process entails many more risks than typical lyophilized drug manufacture.

by Raymond E Peck, CEO of VxP Pharma

For patients whose immune systems are already compromised, sterile drugs (also known as aseptic drugs) remain essential components of many treatment strategies. However, the manufacturing of sterile drugs requires an intensive process, involving steam autoclaves, dry heat ovens, and irradiation; all of which can impact the stability of the drugs' final forms.

In addition, many regulatory requirements limit the parameters of sterile drug manufacturing, both in the US and abroad. For example, the US Food and Drug Administration (FDA) requires that drug products, containers and closures must be sterilized separately, then brought together. These guidelines also mandate laboratory testing for sterility in the final products. The risks of non-compliance are significant: the FDA has recalled many sterile drugs over the past decade.
The completion of an effective, compliant aseptic fill and finish process requires attention to a number of interrelated parameters. This article provides a basic walkthrough of the core concerns.

In a sterile fill and finish cleanroom, aluminum stoppering equipment must be kept isolated from the sealing equipment.

ASEPTIC FILL AND FINISH MUST BE PERFORMED IN A CLEANROOM.

All processes involved in sterile fill and finish must be performed in a cleanroom, in which high-efficiency particulate air (HEPA) is circulated in a single direction. The cleanroom must be environmentally monitored on a constant basis throughout the manufacturing process. And in terms of workflow, the cleanroom must be laid out in a way that facilitates smooth flow of workers and product among the equipment.

For example, the cleanroom's organization should support the movement of personnel and sterilized components in one single direction, from the most sterile area toward the least. This type of layout will help minimize the risk of contamination, due to sterile goods inadvertently coming into contact with non-sterilized elements. Each workstation in the cleanroom should be equipped with pre-sterilized tools and machine parts, so technicians can quickly replace filling needles, stopper bowls, and other components as needed, without inhibiting the flow of personnel.

If the sealing process utilizes an aluminum seal, the sealing equipment must be kept isolated from the stoppering equipment, in order to reduce the risk of contamination by aluminum. Another solution to this issue is simple to utilize a plastic container system, which comes with much less risk of contamination. The stoppering equipment should also be located near the lyophilizer, in order to minimize the time from retrieval to stoppering.

ALL COMPONENTS OF THE STERILE FILL AND FINISH PROCESS MUST BE PREPARED CORRECTLY.

Every component and supply involved in the aseptic fill and finish process must be sterilized or sanitized before entering the cleanroom. This is typically achieved through the use of steam autoclaves, or via dry-heat ovens. This can be achieved either in a batch mode, which requires an oven, or in a continuous process, via a hot-air tunnel that leads directly from the bottle washer to the filling station.

Small parts such as needles, forceps and stoppering equipment must be washed before entering the autoclave, in order to remove any residual particle matter. The parts are then placed in the autoclave, which will destroy any remaining endotoxins. They may then be irradiated, which completed the sterilization process. The parts are now ready to enter the cleanroom.

Depending on the nature of the aseptic fill and finish process, filling may be performed by hand, by a semi-automated mono-block, or even by a high-speed filling line; though this final approach is rare outside of small-scale clinical manufacturing operations. In all cases, the filling lines must be designed to prevent operators from ever coming into direct contact with the aseptic drug itself, while still enabling them to see it through a transparent panel.

Approximately two weeks after the fill is completed, it's also standard procedure to perform a visual inspection of all packaging, in order to examine the drug products for the presence of any cloudiness, which might indicate contamination by microorganisms. This inspection must be performed manually, by trained inspectors; and even so, the risk of human error is significant. To offset this risk, many manufacturers have designed multiple inspections into their workflows.

Small parts such as needles and forceps must be sanitized before entering an aseptic fill and finish cleanroom.

THE LYOPHILIZATION PROCESS MUST BE ORGANIZED TO PREVENT CONTAMINATION.

Although every sterile fill and finish process requires delicate handling, the manufacture of a sterile lyophilized drug carries the additional risks and requirements associated with freeze-drying biological products. The lyophilization chamber itself must be designed and configured in a way that facilitates the transfer of the aseptic core with a minimal risk of contamination, which typically means that the loading and unloading processes are automated, rather than manual.

The initial step is to fill the product solution in an aseptic manner, with the stopper resting on the edge of each vial. In order to minimize exposure of the product, the partially stoppered vials are then automatically loaded into the lyophilizer, where they will be frozen. The drug is then subjected to the primary and secondary drying stages, after which the vials are immediately stoppered, typically by lowering the shelves within the dryer.

In non-aseptic cases, lyophilization process may be performed under vacuum or inert gas, in order to prevent contamination, with sterile nitrogen being used to provide slight pressure. However, these factors can negatively impact the quality of an aseptic lyophilized drug product. For this reason, many manufacturers of aseptic lyophilized drugs will refrain from freezing the shelves inside the lyophilizer, and will pump in sterile air in place of a vacuum or inert gas.

From the layout of the cleanroom, to the flow of personnel, to the preparation of equipment, to the lyophilization and stoppering processes themselves, the fill and finish of aseptic pharmaceuticals entails many more risks than traditional drug manufacture. At any stage of the process, a single moment of contact with a non-sterilized worker, tool or draft of air could render an entire batch of product unusable, and require the process to be restarted from the beginning.

However, with a carefully designed cleanroom, a well-trained staff of experts, and a workflow that minimizes the risk of human error, an aseptic fill and finish process can quickly be scaled up from the clinical to commercial stage, with minimal risk of inadvertent contamination. The difference truly boils down to a heightened attention to detail, addressing every material, component and stage involved in the process.

In addition to being a writer and speaker, Raymond E Peck is the Founder and CEO of VxP Pharma Services and VxP Biologics, both based in Indianapolis Indiana.