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Optimizing Elastomeric Stopper Performance for Lyophilization Processes

One of the most important concerns of a parenteral drug manufacturer regarding primary packaging systems is ensuring integrity of the final drug product. Primary packaging components used for sensitive applications like fill and finish of biopharmaceuticals and, in particular, of lyophilized drug products have many requirements. In addition to the functional aspects to ensure container closure integrity (CCI), manufacturers need to protect the drug formulation from degradation during storage. Maintaining CCI is a high priority for companies manufacturing valuable drug formulations. This issue of *The Source* addresses opportunities to optimize stopper performance and handling in drug product lyophilization.

Lyophilizing sensitive protein drug formulations maintains the stability of the active pharmaceutical ingredient over time. Small and moisture-sensitive lyophilizates could be at risk of collapse if exposed to humidity. Replacing ambient air in the vial headspace with chemically inert gases like nitrogen or even storing the lyophilizates under vacuum helps to minimize chemical alterations such as oxidation of the protein preparations.

Container closure systems need to keep the lyophilizates dry and protected from gas ingress. Any incomplete stoppering after the lyophilization process might lead to the occurrence of raised stoppers. One typical

West can help select the appropriate stopper formulation to reduce the transfer of retained moisture to the lyophilized cake.

situation is known as the “stopper pop-up effect.” The pharmaceutical industry aims to reduce the percentage of stopper pop-ups in order to maintain CCI and minimize the rejection rate. Recent amendments in regulatory requirements address the necessity of stoppering and capping in a defined cleanroom environment.* CCI is a function of several parameters: elastomer formulation, vial and stopper configurations and their compatibility, component processing and assembly procedure.

Elastomeric closures are perfectly suited for sealing. An elastomer formulation has specific physical characteristics such as hardness and compression set, which can influence the stopper sealing performance. The combination of a vial with a stopper needs to be well chosen to avoid improper vial-to-stopper compatibility. In addition, the shape of a stopper may influence its machinability as a “two-leg” lyophilization stopper can be inserted more evenly due to its symmetry. On the other hand, a stopper with an igloo design is more stable and avoids the twinning effect during transport and storage of the stoppers.

Closure processing can be adjusted to the requirements of lyophilization procedures. Lyophilization stoppers are typically washed, siliconized, steam-sterilized and dried. The recommended washing process is a gentle agitation followed by a rinse cycle with water for injection (WFI). Since the steam-sterilization process adds moisture to the closure, additional drying time must be added to the autoclave cycle. If the drying conditions for the stopper are not ideal, residual moisture could transfer to the lyophilized drug product over time, which could

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West FluroTec® on the top of elastomeric stoppers can eliminate sticking of stoppers to shelves in lyophilization chambers.

cause degradation. Drying performance is also influenced by parameters such as characteristics of the elastomeric formulation, shape of the closure, drying chamber size and its load in the drying process. Because heat has a cumulative effect on elastomeric closures, steam sterilization and drying temperatures as well as the duration of these treatments are related to the stoppers' physical properties and performance. Thus, elastomeric components should be evaluated for functional characteristics before and after processing to assess the potential effect of the treatments.

Please contact West for additional information about West's closure storage and processing recommendations.

Experience has shown that additional adjustments of the lyophilization equipment and assembly process could improve the stoppering process significantly. One critical step in this context is to ensure the stopper is seated perfectly after lyophilization and before the aluminium seal is crimped. After finishing the freeze-drying cycles, stoppers are fully inserted by lowering the shelves of the lyophilization chamber onto the vials. An airtight seal can be achieved if the elastomer is slightly compressed and held in contact with the inner vial neck and its rim. Adjustable settings help to ensure a successful fit of stopper to vial in order to maintain CCI. Some practices that help to ensure proper CCI are mentioned here, but the list is certainly not complete:

- Cleaning the lyo chamber shelves with purified water helps keep the stainless steel shelf surface smooth and salt free.
- Stoppering the vials while vacuum is applied
- Holding the pressure inside the chamber while releasing the shelves may contribute to keeping the stoppers seated.
- Keeping the transportation of stoppered vials on the conveyer belt as short as possible reduces the time between stoppering and final crimping, which is vital to ensure CCI.

* Reference: EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products (corrected version) 25 November 2008. This guideline became effective 01 March 2009; provisions on capping of vials were recently implemented on 01 March 2010.

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