

Guidance 109 Lyophilizer Loading and Unloading Recommendations

For any option to be used successfully, the concerns of contamination (microbiological and chemical cross-contamination) as well as potential product mix-up must be addressed. For the purposes of this discussion, the definition of same product includes different strengths of a product containing the same active ingredient.

Regulatory Guidance

The FDA, in its Guidance for Industry: Sterile Products Produced by Aseptic Processing – Current Good Manufacturing Practice requires that “... partially closed sterile product should be transferred only in critical areas. Facility design should ensure that the area between a filling line and the lyophilizer provide for Class 100 (ISO 5) protection. Transport and loading procedures should afford the same protection.”

The FDA set similar requirements in their earlier Guide for Inspection of Lyophilization of Parenterals. Here, they state “The transfer and handling, such as loading of the lyophilizer, should take place under primary barriers, such as the laminar flow hoods under which the vials were filled. Validation of this handling should also include the use of media fills.”

The EC also requires that “Prior to completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

No requirements are stated for unloading the dryers. Here, with internal stoppering, the stoppers have been fully seated within the protection of the closed dryer. No requirements are stated for separation (in time or space) of loading and unloading activities or between multiple dryers.

A search of FDA Warning Letters on the FDA website (from November 1996 to date) found one reference to lyophilization or freeze dryer loading and unloading. This letter contained an observation that “The partially stoppered vials are not kept in a class 100 environment during mobile cart transfer process to the lyophilizer”. This observation references 21CFR 211.42b.

Finally, products containing penicillin, cephalosporins, sex hormones, cytotoxic compounds or live biological agents are excluded from consideration and require more rigorous isolation through separate facilities or dedicated equipment.

Recommended Standards

It can be recommended that transferring to (the) lyophilizer and loading into and unloading from the lyophilizer shall be processed using aseptic technique in a Grade A environment with a Grade B background. The stoppered vials shall remain in a Grade B environment and shall be conveyed to the stopper/sealer under Grade B conditions.

Barriers to Contamination

Multiple barriers exist to protect the product from microbial ingress and chemical cross-contamination during product transfer and dryer loading and unloading. As stated by the regulatory authorities, transfer from the filling line and loading should take place in a very clean and controlled environment; Grade A with a Grade B background. Unloading requirements are not specified by the regulatory authorities.

The separation of adjacent operations can be improved through the use of barrier technologies around the transfer cart such as that provided by an isolator or a restricted access barrier system (RABS). The isolator is enclosed on all sides while the RABS is open only below the work surface. In both cases, an overpressure protects any openings against particulate ingress. It may also be possible to provide adequate protection with a hermetically sealed cart. A slot door (“pizza door”) is used on new dryers to limit exposure to a single shelf during loading and unloading and to minimize disruption of the airflow surrounding the transfer operations.