

## PARTICLE MONITORING REQUIREMENTS FOR FREEZE-DRYERS

### Introduction

Freeze-drying is used to produce the majority of today's dried pharmaceuticals, i.e. those compounds that require reconstitution with water prior to use. Freeze-drying or lyophilization refers to the only manner in which water can be removed from organic substances without damage to the cell structure and subsequent loss of volatile components. The process requires freezing the product, separating out the water as ice crystals, and then under vacuum, introducing controlled heat causing the ice to sublime, releasing the water as a vapor. The final product is left completely dry with minimal change to the product structure, cell matrix or chemical composition.

The process under which products are manufactured using the lyophilization requires a standard aseptic manufacturing filling operation, sterilization of the vials, classic filling in either open or isolator fill lines and subsequent stoppering of the final product. It is at this final stage where a freeze-dried product diverts from the classic model; the stopper is only partially closed allowing air to exit the stopper. The stoppered vials are then transferred to the lyophilizer where the freeze-drying process is run; once the cycle is complete the final closure of the stopper is performed within the machine. The product is then removed from the Lyophilizer and packaged.

### Freeze Dryer Environment



It is therefore apparent that the environment where the freeze dryer is located needs to be within a sterile area, also, due to the non-closure of the final stopper prior to freeze drying, additional controls to prevent contamination should be in place. Once the freeze dry process is completed and the vial closed the product can be packaged as per normal. In their Guide to Inspectors the FDA identify that “The filling of vials that are to be lyophilized has some problems that are somewhat unique. The stopper is placed on top of the vial and is ultimately seated in the Lyophilizer. As a result the contents of the vial are

subject to contamination until they are actually sealed”.<sup>i</sup>

Once filled and partially stoppered, the vial transfer and handling, such as loading of the lyophilizer, should take place under laminar flow hoods, the same classification as which the vials were filled. In the transport of vials to the lyophilizer, there is concern for the potential for contamination. It is therefore essential, especially in new facilities, to ensure that laminar flow or primary barrier protection is surrounding the loading areas of a lyophilizer.

An additional problem is that of potential leakage through the lyophilizer door seal. For units that have only a single load/unload door, leakage is not a major problem from a sterility concern, as the door opens into sterile areas. However, leakage from a door seal from non-sterile areas may present a problem. For those systems that unload into a non-sterile area it is recommended that this area be a clean area, although this may be a class C/D environment.

### Particle Counting Requirements

As the loading areas for freeze-dryers are to be maintained as ‘Sterile’ Class A environments, the particle monitoring should also reflect the critical nature of this area. The required monitoring for critical areas is defined in both the FDA and EU GMP guidelines on aseptic manufacturing, as being continuous and within the zone immediately surrounding the product whenever the product or open container is exposed to the



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environment. The original text from the FDA was ‘continuous and within 12 inches of the critical area’<sup>ii</sup> the change to ‘immediate zone surrounding’ was adopted by the World Health Organisation<sup>iii</sup>. The monitoring locations should therefore be as close as practically possible to the exposed product or partially stoppered vials. The location of the sample point at the door of the lyophilizer will depend on the type being used. A standard swing door would have the sample point on the wall opposite the hinges of the door, the door therefore not contributing to the particulates nor shielding the sensors from potential events. A ceiling mounted probe would be installed inline with the entrance to

the open doorway and at a suitable height, in the immediate zone within the airflow above the product.

Where a significant distance exists between the end of the filling line and partial stoppering, and the loading door of the lyophilizer the product should be maintained within a Class A environment and monitored at intervals throughout this distance. A means of meeting this requirement resulted in a laminar flow cart to transport the vials from the filling line to the Lyophilizer. Manufacturers building new facilities have located the filling line close to the lyophilizer and have provided a primary barrier extending from the filling line to the lyophilizer. In retrospective installations it is possible to install a vertical laminar flow hood between the filling line and lyophilizer.

For applications where portable monitoring is performed and a dedicated monitoring location is not available the revised EU GMP rules on portable monitoring apply<sup>iv</sup>, the sample volume should not be less than 1m<sup>3</sup> for Grade A and B areas.

### **Data Interpretation**

From the above requirements the particle counts must therefore comply with Class A environments for the loading of the lyophilizer. The setting of alert and action levels for non-viable particle count values needs due consideration, the maximum concentration of particle for this area is 3500 m<sup>-3</sup> @ 0.5 µm and 1 m<sup>-3</sup> @ 5.0 µm<sup>v</sup>. Alert settings are typically set at 30-50% of this level and action settings are 75-100%; these are fairly general thresholds and experience will identify where the Upper Control Limit (UCL) is for the operational state.

The operational aspects of loading and unloading lyophilizers is historically manual, a change to automated systems is being adopted in new facilities. However, existing facilities may exceed alert and action boundaries due to operator actions. Due to the nature of operations with lyophilizers and the potential for contamination to arise from multiple sources (operators, secondary unload areas, leaking seals, compressed gas lines, steam cycles etc) additional caution is advised when reviewing data.

Where the alert is of a known source standard procedures should be followed; that is allow the particle level to stabilize to normal baseline levels and continue operations, entering into the batch log the reason for the count level. If the occurrence is due to operator intervention additional micro samples from the proximity and operator can be taken to support continuation of the process.

If an action limit is exceeded it is routine to either discard the batch or subject it to additional stability and micro contamination testing.

In both cases a review of the viable monitoring data will support the discard or release of the product.

Lyophilization is a critical process step in the manufacture of aseptic products and should be maintained within a sterile environment. The particulate monitoring and classification of this environment follows predefined procedures these sterile areas.

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<sup>i</sup> FDA Guide to inspections of lyophilization of parenterals, note this document is for FDA inspector guidance and does not bind the FDA to its interpretation.

<sup>ii</sup> FDA guidelines on sterile drug products produced by aseptic processing, CDER 1987

<sup>iii</sup> World Health Organization, WHO Technical Report Series, No 902,2002 Annex 6, Good manufacturing practices for sterile pharmaceutical products, page 80

<sup>iv</sup> EC Guide to Good Manufacturing Practice, Annex 1, September 2003

<sup>v</sup> EC Guide to Good Manufacturing Practice, Annex 1, September 2003

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