U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Lyophilization of Parenteral (7/93)

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s).

INTRODUCTION

Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes; freezing, primary drying (sublimation), and secondary drying (desorption).

The advantages of lyophilization include:

Ease of processing a liquid, which simplifies aseptic handling

Enhanced stability of a dry powder

Removal of water without excessive heating of the product

Enhanced product stability in a dry state

Rapid and easy dissolution of reconstituted product

Disadvantages of lyophilization include:

Increased handling and processing time

Need for sterile diluent upon reconstitution

Cost and complexity of equipment

The lyophilization process generally includes the following steps:

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22 micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers.

There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products. Additionally, inspections have disclosed potency, sterility and stability problems associated with the manufacture and control of lyophilized products. In order to provide guidance and information to investigators, some industry procedures and deficiencies associated with lyophilized products are identified in this Inspection Guide.

It is recognized that there is complex technology associated with the manufacture and control of a lyophilized pharmaceutical dosage form. Some of the important aspects of these operations include: the formulation of solutions; filling of vials and validation of the filling operation; sterilization and engineering aspects of the lyophilizer; scale-up and validation of the lyophilization cycle; and testing of the end product. This discussion will address some of the problems associated with the manufacture and control of a lyophilized dosage form.

PRODUCT TYPE/FORMULATION

Products are manufactured in the lyophilized form due to their instability when in solution. Many of the antibiotics, such as some of the semi-synthetic penicillins, cephalosporins, and also some of the salts of erythromycin, doxycycline and chloramphenicol are made by the lyophilization process. Because they are antibiotics, low bioburden of these formulations would be expected at the time of batching. However, some of the other dosage forms that are lyophilized, such as hydrocortisone sodium succinate, methylprednisolone sodium succinate and many of the biotechnology derived products, have no antibacterial effect when in solution.

For these types of products, bioburden should be minimal and the bioburden should be determined prior to sterilization of these bulk solutions prior to filling. Obviously, the batching or compounding of these bulk solutions should be controlled in order to prevent any potential increase in microbiological levels that may occur up to the time that the bulk solutions are filtered (sterilized). The concern with any microbiological level is the possible increase in endotoxins that may develop. Good practice for the compounding of lyophilized products would also include batching in a controlled environment and in sealed tanks, particularly if the solution is to be held for any length of time prior to sterilization.

In some cases, manufacturers have performed bioburden testing on bulk solutions after prefiltration and prior to final filtration. While the testing of such solutions may be meaningful in determining the bioburden for sterilization, it does not provide any information regarding the potential formation or presence of endotoxins. While the testing of 0.1 ml samples by LAL methods of bulk solution for endotoxins is of value, testing of at least 100 ml size samples prior to prefiltration, particularly for the presence of gram negative organisms, would be of greater value in evaluating the process. For example, the presence of Pseudomonas sp. in the bioburden of a bulk solution has been identified as an objectionable condition.

FILLING

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.

Validation of filling operations should include media fills and the sampling of critical surfaces and air during active filling (dynamic conditions).

Because of the active involvement of people in filling and aseptic manipulations, an environmental program should also include an evaluation of microbiological levels on people working in aseptic processing areas. One method of evaluation of the training of operators working in aseptic processing facilities includes the surface monitoring of gloves and/or gowns on a daily basis. Manufacturers are actively sampling the surfaces of personnel working in aseptic processing areas. A reference which provides for this type of monitoring is the USP XXII discussion of the Interpretation of Sterility Test Results. It states under the heading of "Interpretation of Quality Control Tests" that review consideration should be paid to environmental control data, including...microbial monitoring, records of operators, gowns, gloves, and garbing practices. In those situations in which manufacturers have failed to perform some type of personnel monitoring, or monitoring has shown unacceptable levels of contamination, regulatory situations have resulted.

Typically, vials to be lyophilized are partially stoppered by machine. However, some filling lines have been noted which utilize an operator to place each stopper on top of the vial by hand. At this time, it would seem that it would be difficult for a manufacturer to justify a hand-stoppering operation, even if sterile forceps are employed, in any type of operation other than filling a clinical batch or very small number of units. Significant regulatory situations have resulted when some manufacturers have hand-stoppered vials. Again, the concern is the immediate avenue of contamination offered by the operator. It is well recognized that people are the major source of contamination in an aseptic processing filling operation. The longer a person works in an aseptic operation, the more microorganisms will be shed and the greater the probability of contamination.

Once filled and partially stoppered, vials are transported and loaded into the lyophilizer. 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 media fills.

Regarding the filling of sterile media, there are some manufacturers who carry out a partial lyophilization cycle and freeze the media. While this could seem to greater mimic the process, the freezing of media could reduce microbial levels of some contaminants. Since the purpose of the media fill is to evaluate and justify the aseptic capabilities of the process, the people and the system, the possible reduction of microbiological levels after aseptic manipulation by freezing would not be warranted. The purpose of a media fill is not to determine the lethality of freezing and its effect on any microbial contaminants that might be present.

In an effort to identify the particular sections of filling and aseptic manipulation that might introduce contamination, several manufacturers have resorted to expanded media fills. That is, they have filled approximately 9000 vials during a media fill and segmented the fill into three stages. One stage has included filling of 3000 vials and stoppering on line; another stage included filling 3000 vials, transportation to the lyophilizer and then stoppering; a third stage included the filling of 3000 vials, loading in the lyophilizer, and exposure to a portion of the nitrogen flush and then stoppering. Since lyophilizer sterilization and sterilization of the nitrogen system used to backfill require separate validation, media fills should primarily validate the filling, transportation and loading aseptic operations.

The question of the number of units needed for media fills when the capacity of the process is less than 3000 units is frequently asked, particularly for clinical products. Again, the purpose of the media fill is to assure that product can be aseptically processed without contamination under operating conditions. It would seem, therefore, that the maximum number of units of media filled be equivalent to the maximum batch size if it is less than 3000 units.

After filling, dosage units are transported to the lyophilizer by metal trays. Usually, the bottom of the trays are removed after the dosage units are loaded into the lyophilizer. Thus, the dosage units lie directly on the lyophilizer shelf. There have been some situations in which manufacturers have loaded the dosage units on metal trays which were not removed. Unfortunately, at one manufacturer, the trays warped which caused a moisture problem in some dosage units in a batch.

In the transport of vials to the lyophilizer, since they are not sealed, there is concern for the potential for contamination. During inspections and in the review of new facilities, the failure to provide laminar flow coverage or a primary barrier for the transport and loading areas of a lyophilizer has been regarded as an objectionable condition. One manufacturer as a means of correction developed a laminar flow cart to transport the vials from the filling line to the lyophilizer. Other 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 order to correct this type of problem, another manufacturer installed a vertical laminar flow hood between the filling line and lyophilizer. Initially, high velocities with inadequate return caused a contamination problem in a media fill. It was speculated that new air currents resulted in rebound contamination off the floor. Fortunately, media fills and smoke studies provided enough meaningful information that the problem could be corrected prior to the manufacture of product. Typically, the lyophilization process includes the stoppering of vials in the chamber.

Another major concern with the filling operation is assurance of fill volumes. Obviously, a low fill would represent a subpotency in the vial. Unlike a powder or liquid fill, a low fill would not be readily apparent after lyophilization particularly for a biopharmaceutical drug product where the active ingredient may be only a milligram. Because of the clinical significance, sub-potency in a vial potentially can be a very serious situation.

For example, in the inspection of a lyophilization filling operation, it was noted that the firm was having a filling problem. The gate on the filling line was not coordinated with the filling syringes, and splashing and partial filling was occurring. It was also observed that some of the partially filled vials were loaded into the lyophilizer. This resulted in rejection of the batch.

On occasion, it has been seen that production operators monitoring fill volumes record these fill volumes only after adjustments are made. Therefore, good practice and a good quality assurance program would include the frequent monitoring of the volume of fill, such as every 15 minutes. Good practice would also include provisions for the isolation of particular sections of filling operations when low or high fills are encountered.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.