Inspections, Compliance, Enforcement, and Criminal Investigations

Lyophilization of Parenterals

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DEPT. OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION *ORA/ORO/DEIO/IB*

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ITG SUBJECT: LYOPHILIZATION OF PARENTERALS

Recent inspections have disclosed potency and sterility 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 ITG.

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; 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 and methylprednisolone sodium succinate 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 stored prior to sterilization.

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. Because different stoppering equipment is required, stoppers are sometimes placed on vials by operators rather than by machine. Obviously, there is a much greater chance of contamination in this type of operation because of the involvement of people. Validation of these types of filling operations should include media fills and the sampling of critical surfaces and air during active filling (dynamic conditions).

Once vials are partially stoppered, they are transported to the lyophilizer. Any transfer and handling, such as loading of the lyophilizer, should take place under primary barriers, such as laminar flow hoods under which the vials were filled. Validation of this handling should also include the use of filled vials of media.

A 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. Because many of the types of products are antibiotics, subpotency in a vial can present a potentially very serious situation. Good practice and a good quality assurance program would include the frequent monitoring of the volume of fill such as every 15 minutes. Also, there should be provisions to isolate particular sections of the filling operations when low or high fills are encountered.

Lyophilizer Sterilization

The sterilization of the lyophilizer is one of the most frequently encountered problems. Some of the older lyophilizers cannot tolerate steam under pressure and sterilization is marginal at best. These lyophilizers can only have their inside surfaces wiped with a chemical agent that may be a sterilant. Unfortunately, piping such as that for the administration of inert gas (usually nitrogen) and sterile air for backfill or vacuum break are often inaccessible to such surface "sterilization" or treatment. It would seem very difficult for a manufacturer to be able to demonstrate satisfactory validation of sterilization of a lyophilizer by chemical "treatment."

Another method of sterilization that has been practiced is the use of gaseous ethylene oxide. As with any ethylene oxide treatment, humidification is necessary. Providing a method for introducing the sterile moisture with uniformity may be difficult.

A generally recognized acceptable method of sterilizing the lyophilizer is through the use of moist steam under pressure. Sterilization procedures should parallel that of an autoclave and a typical system should include:

1. Two independent temperature sensing systems. One would be used to control and record temperatures of the cycle as with sterilizers, and the other would be in the cold spot of the chamber.
2. Provisions for sterilizing the inert gas or air supply lines.
3. Provisions for sterilizing and assuring the integrity of vent filters or filters used to sterilize the inert gas and air.

Provisions for sterilizing the shelf support rods unless they are only exposed to the inside of the chamber after stoppering. Generally, lyophilizers should be sterilized after each cycle because of the potential for contamination of the shelf support rods.

Finished Product Testing

Typical finished product testing that should be reviewed includes dose uniformity testing, sterility testing, and any required stability testing of aged batches of reconstituted solutions.

1. Dose Uniformity

   When the lyophilized product does not include an excipient or other additive and only represents the active ingredient, weight variation can be employed as the means to test for dose uniformity. However, when excipients or other additives are present, weight variation may be applied provided there is correlation with the sample weight and potency results.

2. Sterility Testing

   Although products may be labeled for reconstitution with Bacteriostatic Water for Injection, Sterile Water for Injection (WFI) should be used to reconstitute products. Because of the potential toxicities associated with Bacteriostatic Water for Injection, many hospitals only utilize WFI. Bacteriostatic Water for Injection may kill some of the vegetative cells if present as contaminants.

3. Stability

   Generally lyophilized products have short expiration dates. Stability data should be reviewed and the justification of the expiration date should be based on batches with the higher moisture content. Additionally, stability data should include provisions for the assay of aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labeling. Additionally, this stability testing should include least concentrated as well as the most concentrated reconstituted solutions.

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