Consumables Used

For candidate WHO standards 5 mL or 3 mL, type I neutral glass, DIN ampoules are used for freeze-drying, fitted with 13-mm igloo-style halobutyl closures. In addition to DIN ampoules, various vials are also used, ranging from 5 to 20 mL with crimped, tear-off, aluminum caps and 14- to 20-mm diameter halobutyl cruciform-style closures. A screw capped 5-mL vial is also used with cruciform 14-mm diameter halobutyl closure and a plastic overcap that can be color coded.

Processing Environment

The environment in which materials are processed is tightly controlled in terms of temperature and microbial contamination. All reusable equipment parts such as vessels, needles, and pump heads are washed and then autoclaved before use, and disposable material such as tubing is autoclaved before use and disposed of after use. The microbial contamination of the environment is monitored on a weekly basis to ensure that low bioburden conditions are maintained. This is achieved through the placing of settle plates and of swab samples throughout the processing areas. There are defined alert and action limits for the number of colonies detected in each area. All products for dispensing are also tested as bulk material, post filling and post freeze-drying. The testing includes methods for bacterial contaminants and for moulds and yeasts.

Pilot Scale Work (see sect. "Process Design and Troubleshooting")

In most cases, small-scale trials are carried out well in advance of the large-scale batch to determine the best processing conditions; this is not always necessary where past experience can be used, but in all cases the results of the pilot studies and any previous batches of the same formulation are reviewed and recorded well in advance of processing the definitive batch to allow time for any potential problems to be identified and addressed. Previous lyophilization experience, obtained with different dryers and cycles, should only be used with caution.

Preparation

All critical consumables are quarantined on receipt until checked and released, if acceptable, for use in the processing. All glass consumables are cleaned in a nondetergent system. Normally dilute acetic acid is used for glassware and alcohol for cleaning of rubber/plastics. Closures are washed in a commercial stopper-washing machine and siliconized. Freeze-drying stoppers for use with vials are subjected to a drying process to remove absorbed moisture. Prior to use, all filling vessels, tubing, and needles are autoclaved after cleaning.

Dispensing

Prior to processing, the bulk material is stored, if required, at the appropriate temperature using controlled, calibrated, and monitored storage facilities. Dispensing is carried out under controlled, monitored conditions, as demanded by the material, typically 2°C to 8°C, with gentle stirring. The dispensing machine is adjusted and verified to give the nominal fill weight required.

After dispensing, ampoules and vials are automatically fitted with the closure by the filling machine to the part-stoppered depth and are packed into stainless steel tins with removable bases. They are then stored at the same temperature as required by the bulk product until the entire batch has been filled.