4. Stopper sealability: Machine-sealing parameters must be identified to ensure proper sealing of the vial with the stopper and thereby providing adequate container closure integrity to maintain sterility of the product. This is typically achieved by establishing the required machine mechanical pressure conditions to achieve a cosmetic and well-seated cap. The pressure operational parameters should be confirmed by integrity test results.

Manufacture of Sterile Solution for Lyophilization

1. Process/equipment machineability studies: Evaluation of the required change parts for the proposed process equipment throughout specific manufacturing stages should be performed. The recommended mechanical operational parameters for each piece of equipment should be defined during the execution of this study.
2. Sterilized stoppers staging/holding time: Sterilized stoppers must be packed in suitable bags and/or containers and transferred into the aseptic staging or marshaling area. Normally, it is convenient for the operation to have them stored temporarily in the aseptic clean room until its final use. Integrity of stopper bag during the holding time must be demonstrated through microbiology studies to monitor the sterility state of stoppers throughout this time.
3. Cleaning/sanitization/fogging agents' interference studies: Clean rooms and other manufacturing areas must be cleaned and sanitized using qualified agents in order to maintain proper environmental conditions. The manufacturing isolators are sterilized using sterilants such as vaporized hydrogen peroxide (VHP). It is common to use a fogging agent for control of spores. Chemical and physical effect of the residual agents on the quality of the product should be assessed to define the tolerable levels and or develop appropriate decontamination procedures during specific manufacturing process.
4. Processing times and bulk solution holding times: The performance of the bulk formulation solution process is normally defined and monitored by establishing time requirements for materials' addition into the formulation vessel/reactor. Once a solution with predetermined quality attributes is obtained, bulk solution holding times are established. The following processing time categories are normally defined:

    a. Excipient ingredients' mixing time: The specific mixing time for total dissolution of each excipient ingredient is monitored and established. A mixing time range should be established.
    b. Active pharmaceutical ingredient (API) mixing time: The specific mixing time needed for total dissolution of the active pharmaceutical ingredient is monitored and established.
    c. Formulation time: This is the elapsed time since the addition of the first ingredient into the formulation vessel until the formulation process is completed (normally end of mixing after final batch volume is made up).