

Guidance 021 Establishing and Extending Clean Equipment Hold Times

result in microbiological risk (e.g. if equipment is not water wet and if the clean equipment is held in a controlled clean environment).

Because of the above two risks, It requires that equipment be protected from the environment and not stored water wet for the API and Drug Product .

Since equipment is cleaned to acceptable active ingredient residues as part of the cleaning process, degradant formation would be expected to be none or negligible, and of low risk.

Factors to Consider in Evaluating the Risks

The following factors should be considered to determine the level of risk for clean equipment hold times:

- 1) Considerations for the risk of contamination of clean equipment with non-viable particulates (e.g. dust) due to exposure to the environment.
 - Conditions of equipment storage, such as protection from an uncontrolled unclean environment. Protecting equipment such as with plastic sheaths or bags, closing lids, storing in clean areas, etc. are methods of minimizing negative effects of storage with respect to potential non-viable particulate contamination.
- 2) Considerations for evaluating the potential for microbiological risk
 - Storage of clean equipment without water present:
 - If the equipment is either completely dried (including dead legs that may be drained, blown or heated dry) after cleaning, and/or flushed with organic solvent as last rinse, then microbiological risk is considered low and justification may be made for not performing testing for microbes.
 - Use of organic solvents and/or conditions not conducive to microbiological survival/growth (e.g. high temperature, high or low pH, etc) during subsequent processing of an intermediate, crude API or drug product could be justification for low risk with respect to microbial contamination.

However endotoxins (resulting from killed gram negative bacteria) could still be a risk for APIs that may go into subsequent parenteral DP dosage forms. The risk from endotoxins in these cases should be evaluated.
 - Nature of the materials manufactured in the equipment.
 - Drug Products that are susceptible to and tested for microbial limits or endotoxins (e.g. parenterals), would be considered higher risk than non-sterile products.
 - For example, non-sterile drug product may have a limit of up to 100 CFU per gram of product, in which case the equipment would have to have extremely high levels of bioburden to transfer that level of bioburden to the next product.
- 3) Considerations for both types of risk (non-viable and microbiological):
 - The step in an API process (i.e. whether the material is an intermediate or a final API)
 - Intermediates that will undergo further purification are considered lower risk than final