

Guidance 022 Evaluating Non-Cleaned Equipment Hold Times for Cleaning Validation of APIs and Drug Products

Consideration of the hold time of equipment after manufacturing use and before cleaning is important because it may impact the equipment cleaning.

The following considerations should be evaluated in a documented and approved risk analysis:

1. Drying of product on the surface.
 - a. Certain organic compounds, APIs, waxes, or polymeric formulations may harden on drying or standing, making it more difficult to remove. Example is polymethylacrylates as coating polymers.
 - b. In some cases, it is possible that after drying of the residue during normal manufacturing, further increase in hold time will have no effect on the difficulty of cleaning to remove product residue. For example, this may be the case when processing conditions are significantly more severe than idle hold time conditions (e.g. drying a product in a Rosenmund Filter for 3 days at 70 degrees C versus idle hold time of the empty non-cleaned filter at room temperature).
2. Increased Adhesion of material to surface (e.g. hygroscopic). If exposed to humid conditions, materials may become sticky and more difficult to remove. Example is corn starch.
3. Potential for Degradation compounds. Degradants may have different solubility, toxicity, and cleanability characteristics than the original compound. These may be easier or more difficult to clean and should be evaluated on a case by case basis.
4. History of failures. A product or equipment piece with a history of cleaning problems may be an indication that dirty equipment hold times are a factor that should be considered. This must be evaluated as part of the cleaning failure investigation.
5. The nature of the equipment surface such as aluminum, steel, hastelloy, plastic or rubber may be affected by the duration of the contact. Staining may result.
6. The solubility of the residue in cleaning agent. In some cases, the solubility of the residue in the cleaning agent is so great, non-clean equipment hold time does not affect the difficulty of cleaning.
7. Microbiological accumulation or proliferation. Organisms may grow exponentially if wet residues or stagnant water is left in equipment. Microbiological considerations should be evaluated when water rinsing is used. A microbiological assessment of residual product over time on the non-cleaned equipment should be considered. Conditions of temperature, exposure, time, and product history should be evaluated with respect to the ability of microorganisms to proliferate. The ability of the cleaning process to reduce microorganisms would also be a factor, along with the subsequent dosage form of the next product to be produced in the equipment.
8. If data are available to support dirty equipment hold times as non-critical These may include: