Summary - Evaluating Non-Cleaned Equipment Hold Times For Cleaning Validation of APIs and Drug Products

This guidance outlines considerations and risks associated with hold times between equipment use and cleaning.

The non-cleaned equipment hold time period is defined from the "end of manufacturing" to the start of cleaning. The beginning of cleaning is defined when a cleaning activity is initiated on the equipment. Maximum allowable time intervals for periods between API equipment use and cleaning (non-cleaned or "dirty" hold time) are required to be specified unless there is an approved documented rationale or data demonstrating the time interval is non-critical. Non-cleaned equipment hold times for APIs are not required to be validated.

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

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).

Lab recovery study data for the product residues may have been generated when residues are dried on representative sample surfaces (coupons). These data may also support non-cleaned equipment hold time rationales or data demonstrating that they are not critical. This may be more applicable for APIs, where only a single component is typically removed during cleaning (versus active and excipient mixtures in Drug Product).

Many GMP sites currently requires one validation run for drug product equipment to validate hold times between equipment use and cleaning. The rationale for one run of data is that this is considered current industry standard based on recent external benchmarking data. Reproducibility will have been demonstrated in the replicates of the validation study. Some GMP sites have validated with 3 runs to assess variability. Other sites have validated with 1 run.

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