Evaluating Non-Cleaned Equipment Hold Times for Cleaning Validation Medicinal Products

Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion:
The recommendations to evaluate if the time between equipment use and cleaning needs to be established and controlled are described for Active Pharmaceutical Ingredients (APIs) and Drug Products. When they are determined to be critical, recommendations on how to establish and extend existing hold times are also
described.

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

Information used to determine if a study is necessary, and if so the amount of sampling, sampling approach (e.g. grouping of products and equipment) and number of replicate runs for a potential validation study are described.

The non-cleaned equipment hold time period is defined from the "end of manufacturing" to the start of cleaning. The end of manufacturing is when the individual equipment piece is emptied of the material contained within (e.g. when no additional product is removed for further processing).

The beginning of cleaning is defined when a cleaning activity is initiated on the equipment. Examples include pre-rinsing initiation or post campaign flush, placing an item into solution for soaking, or a CIP cycle is started.

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. (1,2). For drug products the intervals must be demonstrated in at least one cycle of use and cleaning, and it must be documented in the validation.

Non-cleaned equipment hold times for APIs are not required to be validated. A recent international guide has stated that risk approaches are acceptable in differentiating efforts in cleaning of equipment based on intended use.

Factors in the Consideration of Establishing Hold Times
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

