Dirty Hold Time—Why Validate?

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“Cleaning Compliance Forum” discusses scientific principles, strategies, and approaches associated with cleaning that are useful to practitioners in compliance and validation. We intend this column to be a valuable resource for daily work applications. Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Jenna Carlson at carlson.jenna@gene.com.

KEY POINTS

The following key points are discussed:

• Dirty hold is defined as the time between end of use of the equipment and the start of equipment cleaning.
• The condition and length of time equipment may sit idle prior to cleaning and the condition under which this storage will occur must be established and validated.
• Actual dirty hold times from cleaning validation trials may be useful to establish the validated dirty hold time.
• Dirty hold time should be established based on the routine hold time during normal manufacturing that a piece of equipment will be held before cleaning is possible.
• Special situations where the dirty hold time is exceeded should be treated individually, and full testing through a cleaning assessment should be performed when returning this equipment to service.

INTRODUCTION

Dirty hold time is an important but often overlooked aspect of cleaning validation. The dirty hold time for a cleaning process must be validated, clearly documented, and supported by data. This article discusses the regulatory requirements and expectations around dirty hold time validation. In addition, it discusses how to plan, establish, and validate the appropriate dirty hold time.

WHAT IS DIRTY HOLD TIME AND WHY IS IT IMPORTANT?

Dirty hold time is defined as the time between the end of use of the equipment and the start of equipment cleaning. The purpose of validating the dirty hold time is to provide evidence that the length of time equipment may sit idle prior

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to cleaning and the condition under which this storage occurs will not challenge the ability of the cleaning process to remove process or microbial residues. The drying of residues onto equipment surfaces may make them harder to remove and thus challenge the ability of the cleaning process to be successful. Also, allowing process residues, media, or solutions to remain in equipment for a long period of time or exposed to the environment may allow microbial proliferation to occur. This also would challenge the ability of the cleaning cycle to successfully remove microbial contamination.

When preliminary or gross cleaning is performed after equipment use and then a primary or return to service cleaning is performed before the equipment is used again, the dirty hold time is the time between the end of equipment use and start of the preliminary or gross cleaning. When preliminary cleaning is utilized, microbial proliferation control and absence of process residue change that could effect subsequent cleaning must be demonstrated for this preliminary cleaning state.

REGULATORY EXPECTATIONS
Regulatory agencies have acknowledged the importance of dirty hold time in their published guidance documents for many years. Relevant comments from specific international guidance documents are provided as follows.

Eudralex Volume 4 Annex 15 states, “The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined” (1).

Health Canada states, “Time-frames for the storage of unclean equipment, prior to commencement of cleaning, as well as time frames and conditions for the storage of cleaned equipment should be established” (2).

The World Health Organization (WHO) states, “The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures” (3).

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) states, “The period and when appropriate, conditions of storage of equipment before cleaning and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation” (4).

The US Food and Drug Administration’s Guide to Inspections Validation of Cleaning Process states, “Always check for the presence of an often critical element in the documentation of the cleaning processes; identifying and controlling the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process” (5).

The references cited above demonstrate that regulatory agencies are well aware of dirty hold time considerations. The condition and length of time equipment may sit idle prior to cleaning and the condition under which this storage will occur must be established and validated if equipment is routinely not cleaned immediately after use.

FDA Warning Letter
Inadequate validation of dirty hold times is a common health agency inspection observation. Companies should be prepared to discuss their validation approach in regard to dirty hold times during inspections or submission reviews. One of the most common questions around cleaning is “what is your validated dirty hold time?”

A recent warning letter published by FDA in February 23, 2010 to Tri-Med Laboratories, Inc. stated the following: can we reference this?

“Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product [21 C.F.R. § 211.67(a)]. For example, you have not provided any evidence to support your firm’s (b)(4) dirty hold time for equipment (e.g., mixing tanks) used in production.”

A company needs to ensure that the validated dirty hold time is reasonable. There is a regulatory expectation that cleaning occurs within a reasonable time frame not just within a validated hold time. For example, just because a company was able to validate a 70-day dirty hold time before cleaning does not mean that the company should routinely hold equipment dirty for 70 days. Cleaning of equipment should occur within a reasonable timeframe in order to ensure that microbial proliferation
does not occur during storage.

YOU ALREADY HAVE A DIRTY HOLD TIME
Manufacturing sites may not have consciously validated a dirty hold time, but do have their three-lot cleaning validation trials. Manufacturing data from these runs should be compiled to assess whether a dirty hold time can be immediately established. Manual records that indicate timing for end of manufacturing and start of cleaning steps can be used to determine the actual dirty hold time for completely lots. Electronic manufacturing systems also provide these times. These compilations can be reviewed to determine the dirty hold time. Laboratory data from cleaning process development may also be helpful in supporting the dirty hold time determination. While these data may not have been specifically intended to determine a dirty hold time, they may be useful in starting to establish a dirty hold time.

DIRTY HOLD NOT VALIDATED OR IS TOO SHORT
A common challenge in industry today is getting time on the equipment to perform dirty hold time validation. Manufacturing will always want the longest time possible to encompass all types of potential system breakdowns. However, no one (i.e., scheduling, manufacturing, and management) wants to have equipment sitting idle while dirty hold times studies are performed for these worst-case scenarios. The following two questions are fundamental to help determine a target dirty hold time to be validated:
• What is the routine hold time during normal manufacturing? This is the typical duration for this piece of equipment after use and before cleaning.
• If the clean-in-place (CIP) skid is in use or has a minor breakdown, what would be the expected dirty hold time? This is a reasonable maximum dirty hold time that could occur.

Using these two durations provides a practical duration of dirty hold time to be validated. Special situations where the dirty hold time is exceeded beyond these time frames should be treated individually, and full testing through cleaning assessment should be performed when returning this equipment to service after exceeding the dirty hold time validation.

If dirty hold time needs to be validated for multiple products, the grouping of these products may need to be considered. Things to take into consideration when grouping include potency and dosage of product, toxicity, concentration or amount of process residue, chemical and physical properties of process residues (e.g., solubility, viscosity), processing time (e.g., process step and campaign length), and results from laboratory challenge studies. Products in groups must be manufactured on the same equipment categories and must be cleaned by the same cleaning process for common dirty hold times to be valid.

CONCLUSIONS
Dirty hold time is an important parameter within a company’s cleaning program. It is a regulatory expectation that condition and length of time equipment may sit idle prior to cleaning, and the condition under which this storage will occur must be established and validated. When validating dirty hold time, product grouping may be performed to reduce the overall amount of testing required. In the event that validated dirty hold time is exceeded, a cleaning assessment should be performed when returning this equipment to service.

REFERENCES

ABOUT THE AUTHOR
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