

## Hyde Manufacturing COGS Reduction Series—Sanitization vs. Sterilization

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In this edition of the COGS reduction series we will evaluate how simple thermal disinfection can be used instead of complex autoclave cycles to disinfect and control the bioburden of processing equipment. The terms disinfection and sanitization are used interchangeably here, however, the international standards all reference the term disinfection.

The introduction of new manufacturing

processes or changes to existing processes frequently results in increases to autoclave utilization. As a result, manufacturing firms are faced with the expense of purchasing or upgrading an autoclave. Rather than incur high capital and validation costs associated with additional autoclave capacity, firms can actually reduce their cost of goods by applying the principles of lean manufacturing as they seek continuous

process improvements.

Factors which drive the need for additional autoclave capacity include:

1. Current autoclave utilization is high (>80%), and flexibility for “just in time” loads is needed.
2. Most items used in product processing or utilities testing are autoclaved.
3. Policy or practice dictates that these items be sterilized.
4. Requalification activities require periodic empty chamber and load testing.

To reduce COGS, we must consider and understand the production process, how autoclaved equipment is to be used, the rationale for autoclaving certain items, and what other types of bioburden control steps are used in the process.

There is a technology that can not only impact the amount of autoclaving needed but can also aid in the cleaning of equipment. Most firms already own and use this technology, but don't leverage their asset

*Continued on page 2*



### Wall of autoclaves circa 1948

The autoclave was invented at Louis Pasteur's laboratory in 1879 by Charles Chamberland who developed it for sterilizing culture media. The term derives from Greek *auto* (self) and Latin *clavis* (key) for the chambers ability to 'self-lock' as a result of pressurization.

## HYDE HIGHLIGHTS

Recent Hyde Publications include the following:

Ruggedness of Visible-Residue Limits for Cleaning (Part II) by Richard Forsyth, Senior Consultant, published in *Pharmaceutical Technology*, March 2011

Top Ten Changes in FDA's Process Validation Guidance, by Peter K. Watler, Ph.D, CTO, published in *BioProcess International*, June 2011

Join senior Hyde leaders Richard Jushchysyn, John Hyde and Peter Watler at the GMP by The Sea Conference, Tampa, Florida, August 8th -10th, 2011 where they will present the latest industry thinking on Supply Chain and CMOs for Manufacturing Scale Up, Tech Transfer and GMP issues for Facilities.

*Continued from page 1*

or have set it up correctly. The technology we're referring to is the final hot WFI rinse cycle of a common parts washer as a thermal disinfection and sanitization step.

Descriptions and requirements for thermal disinfection processes can be found in ISO 15883 and in HTM01-01 and HTM2030 standards for processing medical devices for use in healthcare establishments. ISO defines the disinfection process as a reduction of the number of viable microorganisms on a product to a level previously specified as appropriate for its intended further handling or use. Chemical or thermal processing are the two methods for achieving disinfection. In this article, we will focus on thermal processing because pharmaceutical facilities already have systems in place capable of thermal disinfection.

The principles of thermal disinfection are very similar to the time-temperature relationship used for sterilization. The difference is the conditions in which the process takes place. As stated in ISO 15883, thermal disinfection can be achieved by exposure to hot water, steam, or a combination of the two. Most parts washers employ a final equipment rinse with WFI at approximately 80°C.

The effectiveness of a moist heat disinfection process can be defined by the  $A_0$  method. The  $A_0$  value of a moist heat disinfection process is the equivalent time in seconds, at a temperature of 80°C, deliv-

ered to the product with reference to microorganisms possessing a  $z$  value of 10°C. This is analogous to the  $F_0$  method employed for sterilization cycles.  $A_0$  is calculated as:

$$A_0 = \sum 10^{[(T-80)/z]} \times \Delta t$$

where

$A_0$  is the  $A$  value when  $z$  is 10°C;  
 $t$  is the chosen time interval, in seconds;  
 $T$  is the temperature in the load, in °C.

In calculating  $A_0$  values, a lower temperature limit for the integration is set at 65°C since at temperatures below 65°C, the  $z$  value and  $D$  value of thermophilic organisms may change dramatically, and below 55°C there are a number of organisms which will actively replicate. In this manner, thermal disinfection validation can be conducted with thermal mapping, clean hold studies, and equipment handling processes, all of which are typically performed as part of existing cleaning validation studies.

So how can thermal disinfection reduce manufacturing COGS? By identifying which equipment can be disinfected for bioburden control via thermal disinfection rather than sterilization in an autoclave, firms can typically reduce autoclave equipment loads by 30 to 40 percent. Equipment used for buffer preparation, process waste containers, chemical dispensing, and aseptic transfers are excellent candidates for thermal disinfection.

Thus, implementing thermal disinfection processing and validation can lower COGS by eliminating the capital purchases of additional or larger autoclaves, by lowering autoclave utility usage, and by reducing recurring costs for qualifying and re-qualifying autoclave load cycles. Realizing these significant COGS reductions, however, requires that a manufacturer develop a clear understanding of process risks, use this risk assessment to determine which equipment can be sanitized, and, most importantly, build a solid understanding of the justification and rationale for the thermal disinfection of processing equipment.

#### References.

ISO 15883-1:2006 Washer-disinfectors — Part 1: General requirements, terms and definitions and tests  
HTM 01-01: Decontamination of reusable medical devices

## Experts Ask Experts

### Dear Cleaning Expert:

What are the most appropriate analytical studies to demonstrate cleaning cycle effectiveness for purification equipment in a multiproduct biopharmaceutical plant? Is it appropriate to use an assay standardized with our product and to set limits based on a maximum acceptable carryover calculation?

### Dear Production Expert

Using a product assay standardized with your product would give erroneous results since, unlike small molecule products, protein products are likely hydrolyzed and denatured by the harsh caustic and acid cleaning agents. The intent of the 1/1000th limit is that a patient does not get an additional

fraction of an active therapeutic dose. Using the product assay would be erroneous, as the denatured protein in the cleaning sample is not a therapeutic dose. In addition, using a standardized, product-specific assay will further confound acceptance criteria since your cleaning assessment sample (degraded protein, likely peptides) and the standard (unadulterated product protein) are different molecules and will have different assay standardization curves. In cases like this, we suggest performing a product fragmentation study using specific methods like ELISA or HPLC to compare the impact of cleaning agents on the intact product over time against comparative samples analyzed via a non-specific analytical method such as TOC.