Cleaning Validation

19Sep2013
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Outline:

- Definition of Cleaning Validation
- Why do we need cleaning validation
- Scope of a cleaning validation program at the Swiftwater Site
- The Science of cleaning validation
  - Understand your Soils
  - Understand your Equipment
Definition of Cleaning Validation

The purpose of cleaning validation is to establish documented evidence with a high degree of assurance that the cleaning process will consistently yield results that meet predetermined specifications and quality characteristics.

The action of proving in accordance to principles of GMP that the cleaning procedure actually leads to expected results.

Validation helps to know the process capability and create an avenue for process improvement.

Definition of Cleaning Validation (Cliff Notes)

Removing:

- all components of the previous product (antigen, Hg, Al, egg proteins, etc)
- Bioburden
- Endotoxin
- Detergents

Down to levels that are “safe”

- have no impact on the next product or the patient with a large safety factor built in

Prior to using the equipment for the next product.
Why do we need Cleaning Validation?

- FDA Guide to cGMP for Finished Pharmaceuticals: 21 CFR 210 & 21 CFR 211
- Health Canada: Cleaning Validation Guidelines
- EU Guide to GMP

BUT – more than the reason “because we have to,” we need cleaning validation to ensure that our products remain safe and effective for our patients.

Scope of Cleaning Validation Program

- The cleaning must be validated for all “product contact parts” used for
  - The production of phase III clinical batches
  - The production of process validation/consistency validation batches
  - The production of all Licensed products
Product Contact Equipment

vs

Equipment that is Contacted by Product

Biologically Active Material – BAM – live or inactivated vaccines (intermediates, bulk and final product) that have a potential to engender an immune response.

BAM Contact Surfaces –

Condition 1: Equipment surfaces that are in direct contact with biologically active material (BAM) during manufacturing activities. During the production and cleaning processes, these surfaces are soiled with BAM, product components (e.g., buffers, media, etc.) and cleaning agents. The cleaning must be validated to show removal of soils.

Condition 2: Equipment surfaces that are not contacted by BAM by design but may contact BAM in practice (due to splashing or spillage) will be individually assessed to determine the risk involved should the surfaces not be sufficiently cleaned and/or sterilized before contact is made.
Non-Biologically Active Material – NON-BAM – Components used in the production process that do not have the potential to engender an immune response (buffer, media, stoppers, silicone, etc)

Non-BAM Contact Surfaces –
   Condition 1: Equipment surfaces used for preparing and/or transferring reagents, medias, buffers, components (e.g., stoppers) etc. that are incorporated into the product. During the production and cleaning processes, these surfaces are soiled with product components and/or cleaning agents but are not soiled with BAM. The cleaning must be validated to show removal of these soils.

   Condition 2: Equipment surfaces that are not contacted by reagents, medias, buffers, components by design but may contact reagents, medias, buffers, components in practice (due to splashing or spillage) will be individually assessed to determine the risk involved should the surfaces not be sufficiently cleaned and/or sterilized before contact is made.

The Manufacturing Process from a Cleaning Validation Perspective
The closer you get to the patient, the more stringent your cleaning validation criteria become

Processing Stage 1 - those phases of a manufacturing process that precede the purification steps. Stage 1 process equipment includes the preparation of raw materials, the fermentation or culture process and primary filtration steps.

Processing Stage 2 - those phases of a manufacturing process involving product purification and conjugation up to but not including final formulation

Processing Stage 3 - those phases of a manufacturing process involving final formulation and filling
Cleaning Systems

Clean-in-Place (CIP): The process of cleaning a piece of equipment, piping, or device without taking it out of line; cleaning performed without the need to relocate the equipment being cleaned (may be manual or automated.)

Clean-Out-of-Place (COP): The process of cleaning a piece of equipment, piping, or device after it has been taken out of line (may be manual or automated.)

- **Sonicator** – Utilizes ultrasonic energy to clean small parts
- **Vial Rinser** – Utilizes hot WFI to clean vials
- **Cabinet Washer** – alternately described as a glass or bottle washer - is a compartment type pressure washer with doors that is designed to utilize racks, spray nozzles, cleaning solutions and air to clean and dry the interior and exterior of items placed within its chamber.
- **Manual Cleaning** - Manual cleaning is performed by trained personnel who follow detailed procedures pertaining to preparation and use of cleaning solutions, disassembling, scrubbing using non-abrasive and non-shedding brushes or pads, soaking, rinsing and drying.

Clean In Place Skid (CIP)
Sonicators
Sonicators

Vial Washer
Parts Washer

Manual Clean
Manual Clean
First:

Know and Understand the Soils you Must Clean
Virus

Raw Meat and Prions
Formalin

Sucrose

Sodium Citrate

Triton X-100

Aluminum

Mercury

Allantoic Fluid

Figure 1. A diagrammatic representation of the extra-embryonic membranes and fluid compartments for the chick embryo around a third of the way through incubation. Note that the size of these structures, and their development relative to each other, have been modified to clarify types of cells present in each of the membranes.
• Gram-positive bacteria
• Gram-negative bacteria are pathogenic, meaning they can cause disease in a host organism. This pathogenic capability is usually associated with certain components of Gram-negative cell walls, in particular the lipopolysaccharide (also known as LPS or endotoxin).
Your Soils may Change with Heat/pH/Time
Your Soils may Change with Drying

Your Soils May Change After Exposure to the Cleaning Detergent

Resulting Vaccine - Split Virus

Resulting Material after cleaning with cleaning detergents or disinfectants (to be demonstrated through degradation studies)
Second:

Know and Understand the Equipment you Must Clean