Key factors in the choice and development of a cleaning strategy

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ABSTRACT: Many aspects need to be considered in setting up a cleaning procedure. This is certainly a multidisciplinary issue that involves various company areas: from "Regulations" to Engineering, from Quality Control lab to Production department. Contributions of all these areas together can lead to a robust and reproducible cleaning process.

KEYWORDS: Cleaning, COP, cleaning equipment.

INTRODUCTION

Cleaning is an essential practice for any pharmaceutical activity: it is impossible to manufacture drugs in dirty conditions, even if dirt is not evident. Defining differences between a sterilization and a cleaning treatment is important in order to understand in depth the main problems and peculiarities when defining a cleaning strategy. To sterilize means to destroy or inactivate microorganisms: we know the target and we can define it in terms of a number (UCF/unit) and resistance (D, z). The definition of sterile product/item (PNSU – Probability of Non-Sterile Unit or SAL – Sterility Assurance Level), is probabilistic but is universally accepted. The kinetics of ordinary sterilization processes are well understood and as a result so is the determination of the lethal dose to be administered.

On the other hand, for a cleaning process, the "enemy" is not defined and in any case can vary on a case-by-case basis: residue of previously processed product, diluents, solvents, various chemicals, lubricants, generic dirt, m.o., etc. There is no absolute definition of cleanliness. The kinetics of the cleaning procedure is unknown. Consequently, also the definition of "cleaning dose" to be provided is undetermined.

In these conditions, even regulatory bodies struggle. Essentially, they allow manufacturers considerable flexibility in establishing their own cleaning specifications. The FDA, for example, does not define methods describing how a cleaning process should be validated. FDA inspectors have to assess the rationale used to set the cleaning limits, making sure that their basis are scientifically justifiable and grounded on adequate knowledge of the materials involved.

Brief glossary

Cleaning equipment - system, device or even simple tool used for cleaning.

Equipment - fixed or movable system or equipment or even tool to be cleaned.

m.o - microorganism(s)

CIP - Cleaning in place, i.e., cleaning performed without removing the item from its usual location.

COP - Cleaning out of place, i.e., cleaning performed on the item removed from its usual location.

FDA - Food and Drugs Administration

PDA - Parenteral Drugs Association

PDA Technical Report no. 29 suggests a Cleaning Spectrum, which includes cleaning program development criteria, equipment characteristics, formulation/product characteristics and production/process characteristics (see Table 1).

Automated cleaning	Manual cleaning
In-place cleaning	Out-of-place cleaning
Dedicated equipment	Non-dedicated equipment
Indirect product contact surfaces	Product contact surfaces
Low risk site	High risk site
Minor equipment	Major equipment
Low risk drugs	High risk drugs
Highly characterized	Poorly characterized
Liquid formulations	Solid formulations
Easy to clean product	Difficult to clean product
Materials with a smooth, non-porous surface	Porous materials
Single product facility	Multiple product facility
Non-campaigned production	Campaigned production

Table 1 Cleaning Spectrum - PDA Technical Report no. 29

All above listed factors directly influence the cleaning capacity of the considered process; their importance and criticality however, can have different impact depending on the case study. This Cleaning Spectrum can be useful to assess the most challenging factors affecting the process and it can allow the manufacturer to set a scale of priorities, outlining the cleaning rationale.

Therefore, there are many aspects to be considered when approaching the issue of cleaning. First of all, one has to consider where to perform cleaning activity: in-place (CIP) or out-of-place (COP).

1 MAIN ASPECTS THAT DISTINGUISH/CONDITION A CLEANING PROCESS

1.1 Cleaning location: CIP vs. COP

CIP is performed on equipment in its usual location and configuration. The process can be manual or automated and is used for large components and equipment: fermentation reactors, fluid bed dryers, etc.

COP is performed on generally smaller machine parts, which are carried to a dedicated area or room. Usually, these are parts of small devices, which can be easily disassembled and are difficult to clean. Transport itself entails particular attention to identify the item and its components (in fact it usually entails disassembly operations) and precautions for cross-contamination during transport, final drying, and storage after cleaning. COP of easily transportable objects is often performed with fully automatic machines. When it comes to treating various objects not clearly similar a careful sorting into families is required to obtain uniform results. If all the precautions are followed, the procedure can be highly effective and repeatable.

1.2 Automatic vs. manual cleaning

Manual cleaning is considered quite common, but challenges regarding inefficiency, inconsistency and difficulties to trace and document the process are often reported. The risk of cross-contamination increases if cleaning is performed with manual or semi-automatic equipment due to the margin of error of the operator who is responsible for the activity.

Automatic systems typically do not involve human intervention, except for selecting a cycle and starting and/or shutting down the equipment at the end of activity.

For cleaning validation, as with validation of other processes, at the end of the process you should provide scientific data showing that the system works as expected with an outcome that consistently meets predetermined requirements. The use of automation provides data reliability, process uniformity and robustness for cycles and parameters control and monitoring. Consequently, the standardization and reproducibility of procedures might facilitate the process validation.

Another point to be considered, especially focusing on validation is the overall effectiveness of the process. Does it have to be scrubbed by hand to achieve an effective cleaning? For the most challenging loads, it is suggested the use of innovative dedicated washing racks with spray nozzles. These devices, designed for automatic washers, are engineered to cover all load surfaces and customized for cleaning peculiarities, thus simplifying validation even for

worst cases (see section 3.4).

In addition, an automatic cleaning system can offer several advantages regarding the reduction of total process time, optimization of material flows, traceability and documentation, increased throughput and reduction of overall energy consumption and operating costs.

1.3 Critical vs. non-critical sites

Risk is a function of:

- the identification of a danger
- the possibility to detect a danger
- the exposure to the identified danger.

The locations where a residue might create a high level of contamination are considered high-risk sites. Typically, a needle used in filling systems. Critical sites where the accumulation of contaminant is greater or cleaning is more difficult (due to the limited accessibility of the region or due to the type of material) require special attention, receiving dedicated "acceptable levels" of residue limits (see Fig. 1).

Fig. 1 Part of an encapsulation system: considerable criticality due to the assembly of the parts into a single body, which cannot be disassembled for the treatment.

In the example above, the parts were used on capsules production contaminated with a strongly colored gelatine very difficult to remove especially on internal parts and junctions. The problem was solved with the combined use of steam and compressed air during the cleaning process. Fedegari has developed a specific and customized cleaning approach based on the bubbling effect inside the dish (focused on mechanical action). Two bars with nozzles fixed on the bottom of the chamber were used for the injection of deionized-water, steam and compressed air.

1.4 Sterile vs. non-sterile production

As discussed before, the cleaning activity can be performed as a preliminary step. If a system/piece of equipment/tool is used to manufacture sterile drugs, sterilization must be scheduled after cleaning. In this case, to reach a bioburden reduction already during cleaning steps is “preparatory” for the subsequent lowering to a SAL of 10^{-6}.

At the same time, by eliminating dirt, the microorganism is deprived both of a growth medium and of a “protection” from the biocidal agent. Residues of organic material can often cause the failure of a microbial burden inactivation treatment.

Addressing an ever increasing need for flexibility and cost-effectiveness in pharma manufacturing, Fedegari, for example, has developed a washer-sterilizer. It is capable of operating in different modes to optimize processes where both cleaning and/or sterilization are needed. This machine brings features and performances typical of a steam sterilizer into a jet washer, using steam for improving washing/degreasing performances and vacuum for drying. Thus, representing a more environmental-friendly machine with lower energy consumption than traditional alternatives.

1.5 Equipment considerations: dedicated vs. non-dedicated production systems

Dedicated production systems sharply reduce both cross-contamination and cleaning problems but entail large investments. They are used for the treatment of a single product or, in rare instances, for a range of products. Dedicated systems are required for:

- Products that are difficult to remove: tar-like, rubber-like, etc.
- Elements that are difficult to clean: filters, convoluted structures with small lumens
- High-risk/high-activity products

Cleaning procedures should minimize the residual limits of high-risk/high-activity drugs that might contaminate production batches.

When the same equipment is used for different product formulations, preventing the risk of

carryover becomes a priority. In such cases, systems for preventing cross-contaminations must be adopted and maintained rigorously. Moreover, for non-dedicated production system the design of the washing racks (e.g. part cleaning unit), must be modified according to the load.

1.6 Preventing malfunction through adequate cleaning strategy

CFR (Code of Federal Regulation) 21 part 211.67, “Current good manufacturing practice for finished pharmaceuticals”, on the subject of Equipment Cleaning and maintenance, states:

> *(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*

First, the cleaning process might assure the safety and quality of the manufactured drugs. However, a cleaning strategy should take into consideration the most suitable process development avoiding damages and contamination to the treated parts and to the cleaning equipment.

Accordingly, temperature, pressure, flows and chemical agent aggressiveness applied during the process must be tailored and validated according to type of load and production.

For example, Fedegari has recently developed a series of industrial washers using the experience with steam to reduce the need for detergents and chemical agents but maintaining the cleaning effectiveness. An adequate cleaning strategy is studied by the R&D department for each case to assure a correct balancing between process parameters (e.g. pressure, temperature) and cleaning target.

1.7 Aspects of microbial proliferation

Items subjected to cleaning must be stored dry, in order to avoid the risk of microbiological growth. High humidity, cracks, crevices and highly corrugated surfaces that might not be perfectly dry at the end of the drying phase are major threats representing ideal culture media for microorganism proliferation.

During the development of a cleaning strategy, the pharmaceutical company must set the timing between item cleaning and reuse (CLEAN HOLD TIME) and between equipment end of use and cleaning start (DIRT HOLD TIME). This procedure is applied to optimize the result of cleaning and reduce the risk of microbiological proliferation.

2 SETTING UP THE CLEANING PROCEDURE

Cleaning must remove different types of dirt, including residues of previously processed products (active ingredients, excipients, solvents, etc.), detergents, sanitizers used as process adjuvants and microbiological contamination in general.

Besides “solid dirt” and “liquid dirt”, there are also intermediate cases, such as emulsions, dispersions, suspension, gels, creams, ointments, etc.

To summarize, a cleaning procedure must take into account:

- the type(s) of dirt to be removed
- the equipment/items to be cleaned (quantity of objects to be treated, uniformity, type, shape, size, geometry, convolutions, construction material, any welds, fragility)
- management of the process waste
- the expected result.

The type of dirt influences the choice of the cleaning agent. However, the agent must be not only effective in removing residues, but also compatible with the materials, easily removable, non-toxic, non-volatile, non-flammable, and possibly low-foaming. Removal of dirt can be conditioned by the nature of the active ingredient, by the excipients and/or by degradation products. The choice of the cleaning agent must be based on a scientific rationale.

There are various types of cleaning agent (which can be combined or used individually):

- water of various purity (the lower the conductivity of the water, the lower the

risk of seeing halos which appear on the treated object due to salt deposits), cold or warm

- organic solvents
- acid or basic detergents
- organic/inorganic complexing agents
- dispersants, surfactants, wetting agents
- sanitizers of various kinds
- pressurized water vapor or superheated water.

2.1 The "chemistry" of the product as a guide for the choice of process/detergent

Today, the "Green Policies" of companies are leading to the search for cleaning systems that have a reduced use of chemical agents and, consequently, a lower environmental impact. While water soluble products might require the use of water alone as "detergent", other lipophilic products represent a great challenge if one wishes to reduce or eliminate the use of chemical agents. For example, corticosteroids, which form a "gripping" film on the steel surface on which they are deposited, can be a challenge (see Fig. 2). Chemical agents are the classic solution in this specific case; steam, which softens this film, followed by treatment with water at approximately 100 °C, is a valid alternative. The use of superheated water, in the specific case, also eliminates the deposited dirt.

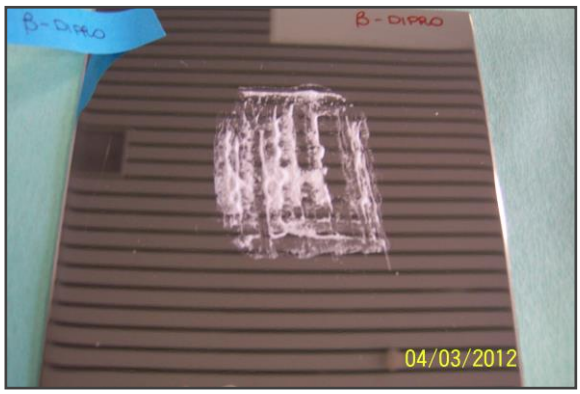

Fig. 2 Dirty coupon with Diprostene - Fine-tuning of a machine part cleaning process at the R&D department of Fedegari

However, it should be stressed that the good outcome of a cleaning process often depends on the customization of the cleaning equipment. For example, if the water jets are not adequately directed to strike the dirty surfaces, the result might not be optimum.

Sometimes the use or not of high temperatures in the various steps of the process can hinder the achievement of the goal instead of aiding it. Knowing the chemical structure of the product to be removed will help us to avoid mistakes. A few examples:

Dirt	**Solubility**	**Removal**	**Changes due to heat**
Sugars	Soluble in water	Simple	Caramelization, harder to clean
Protein	Insoluble in water Soluble in alkali Scarcely soluble in acids	Difficult	Denaturation, harder to clean

Therefore, in the case of sugars and proteins preference is given to cleaning processes that do not use high temperatures.

2.2 Major vs. Minor equipment/parts

This definition might not be clear since it is not related to a cleaning challenge. "Minor" equipment or tools can constitute a high risk if considering the need to assure effective cleaning for each single item. Typically, the cleaning of a "major" equipment is individual and subject of specific SOP (Standard Operating Procedure), whereas minor tools can be grouped, especially if the cleaning operation is performed with automatic machines.

2.3 Surfaces

Surface type and finish can affect the ability to clean the material. Depending on the level of roughness (Ra), the surface will represent a better or worse "hiding place" for contaminants, including biological ones. For example, an electro-polished steel surface has a distinctly lower degree of roughness than "raw" steel resulting in an easier cleaning process.

Scratches and cracks of the material are difficult

to clean. Particularly porous materials, such as filters, which are very delicate, require particular precautions.

2.4 Equipment design & performance

The complexity of machines/machine parts, of tools intended for cleaning, the convoluted shape of some structures, the presence of recesses, can make it difficult to achieve the intended cleaning target.

Typically, cleaning validation relates to the surfaces in contact with the product, but it is difficult to exclude migrations of contaminant toward regions that theoretically entail no contact, especially if they are segregated and where accumulations can occur (e.g., gaskets and their seats).

This leads to the need for a cleaning apparatus that is dedicated to the item/items and can ensure that the cleaning medium reaches every surface to be treated. Its customization is often the keystone of a good cleaning outcome; therefore, not only the process, but also the dedicated equipment, are developed around the item to be cleaned.

Operating pressures, process fluids, type and adequate inclination of the nozzles from which the cleaning medium exits, suitable receptacles for the parts to be cleaned (in the case, for example, of a parts cleaning unit) are some of the key elements of the definition of a cleaning machine and of the consequent process.

An interesting case to illustrate the use of a custom designed accessory for improving cleaning results can be seen below (Fig. 3). This steel wheel, with complex internal channels and holes to be washed is an example of challenging load in which the result of the process is inevitably tied to an accurate study of the cleaning apparatus.

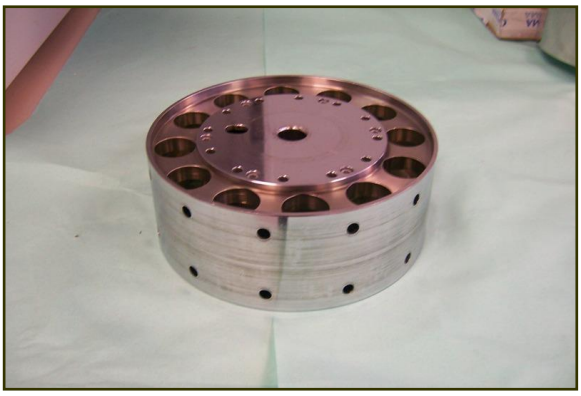

Fig. 3 Steel wheel from which Carbapenem is to be removed

Given the structural complexity of the load, a “distribution spider” (Fig. 4), with small holes along the steel arms has been developed to allow the injection of the cleaning medium in the channels. The device is used also to feed the air through the machine part in the subsequent drying step. This dedicated solution turned out to be essential for effectively cleaning the internal parts of the wheel.

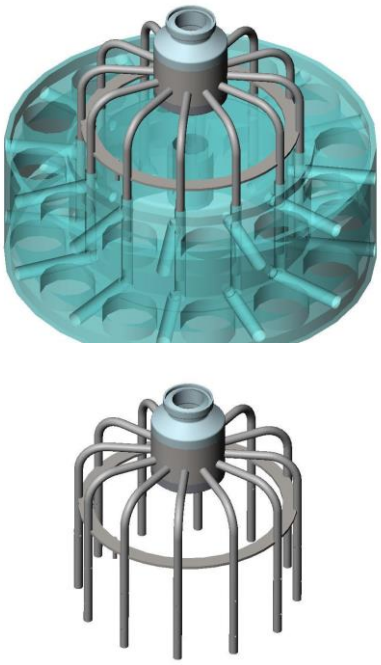

Fig. 4 In gray, system for injection of the cleaning medium within the channels of the steel wheel. The system is also useful for conveying compressed air during load drying phases.

2.5 Process waste

Today, the environmental aspect of every process is a pivotal point in its provision. This way, a cleaning practice must also consider process waste. If the product to be removed is harmful, the waste produced by each cleaning step have to be conveyed in a dedicated tank in order to perform its inactivation in a later phase.

If instead there are no problems in this regard, the free waste can become a means for assessing cleaning effectiveness: a small amount drawn and analyzed with on-line monitoring systems can give an idea of the level of removal of the active ingredient and/or of the detergent used.

3 REFERENCES

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