

A Brief Review On Cleaning Validation-Regulatory Guidelines For Pharmaceuticals

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DOI: 10.47750/pnr.2022.13.S08.628

Abstract

Cleaning validation is a process used by pharmaceutical manufacturers to ensure that their equipment and facilities are thoroughly cleaned and free of any residual contaminants that could potentially compromise the quality of their products. This process is guided by regulatory guidelines set forth by FDA and European Medicines Agency (EMA) are two examples of such agencies.

Cleaning validation protocols are typically required by these guidelines, which outline cleaning procedures, acceptance criteria for evaluating the effectiveness, as well as testing and documenting the results. The protocol should also include a risk assessment to determine which equipment and areas of the facility are most critical to the product's quality and safety.

Manufacturers are also expected to periodically review and update their cleaning validation protocols as necessary, and to keep detailed records of all cleaning validation activities. A manufacturer's cleaning validation protocol and the presence of contaminants may also be verified by FDA or EMA inspections. To ensure consistently high quality, pharmaceutical manufacturers must control cross-contamination. There must be a comprehensive cleaning regime in place to demonstrate that the methods employed in a facility consistently control the carryover of product (including intermediates and impurities), cleaning agents, and extraneous material into subsequent products. An effective cleaning regime provides documented evidence that these aspects are consistently controlled within a facility. As a pharmaceutical manufacturer, it is your responsibility to ensure that your cleaning process complies with cGMP regulations, first and foremost.

Keywords: Therapeutic Goods Administration (TGA), Parenteral drug Association (PDA), Active Pharmaceutical Ingredient Committee (APIC), Food Drug Administration (FDA), European Medicines Agencies (EMA) and World health Organisation (WHO).

INTRODUCTION:

Validating a system or piece of equipment requires documented evidence that it can be consistently cleaned within prescribed limits. A good manufacturing practice (GMP) is essential to prevent contamination of pharmaceutical products and starting materials. It has been demonstrated that pharmaceutical products are susceptible to contamination from a variety of contaminants, including microorganisms, past products (including active pharmaceutical ingredients and excipients), residues of cleaning agents, dust, particulates and lubricants, as well as dust from previous products [1]. Contamination and cross-contamination can be prevented by ensuring that adequate cleaning procedures are followed properly. Clean equipment suitable for its intended use can only be ensured through the validation of cleaning methods [2].

DEFINITION:

Documented evidence must be provided that residues from the manufacturing process and the cleaning agent are effectively removed in a manner that poses no safety threat to patients. Pharma production equipment validation refers to the documented process that verifies that the equipment has been cleaned consistently and effectively [3]. It is critical to validate equipment cleaning procedures in the pharmaceutical industry to prevent cross-contamination and adulteration of drugs; therefore, validations are of extreme importance to prevent these issues [4].

BENEFITS OF CLEANING VALIDATION:

1. Taking good business decisions
2. Quality costs are reduced
3. The reuse of equipment
4. Integrity of batches
5. Cross contamination avoidance
6. Quality and safety assurance
7. Regulations by the government
8. Integrity of microbes
9. Integrity of products

1. Tests and Materials Society of America (ASTM)

The American Society for Testing and Materials (ASTM) is an international standards organization that develops and publishes technical standards for a wide range of industries and products, including pharmaceuticals [5]. ASTM's standards cover various aspects of the manufacturing, testing, and quality control of pharmaceutical products, including cleaning validation.

ASTM's standards for cleaning validation include guidelines for developing and implementing cleaning validation protocols, as well as methods for testing and measuring the effectiveness of cleaning procedures [6]. These standards provide manufacturers with a common framework for developing and implementing cleaning validation protocols and can be used to demonstrate compliance with regulatory requirements set forth by FDA and European Medicines Agency (EMA) are two examples of such agencies.

ASTM standards are voluntary, but are widely recognized and respected, and are often used as a reference by industry and regulatory bodies.

2. APIC is an acronym for Active Pharmaceutical Ingredients Committee.

The Active Pharmaceutical Ingredients Committee (APIC) is a committee of the International Pharmaceutical Excipients Council (IPEC) which is focused on the quality and safety of active pharmaceutical ingredients (APIs) [7]. APIC's mission is to promote the safe and responsible use of APIs in the pharmaceutical industry through the development and promotion of guidelines, standards, and best practices.

APIC develops guidelines and standards for the manufacturing, testing, and quality control of APIs, including guidelines for cleaning validation. These guidelines provide manufacturers with best practices for developing and implementing cleaning validation protocols and procedures, as well as methods for testing and measuring the effectiveness of cleaning [8]. They also provide guidance for monitoring and controlling the quality of APIs during the production process.

APIC guidelines are widely recognized and respected in the pharmaceutical industry and are often used by manufacturers as a reference for demonstrating compliance with regulatory requirements set forth by agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

3. International Society for Pharmaceutical Engineering (ISPE)

An international non-profit organization serving the pharmaceutical and biopharmaceutical industries, the International Society for Pharmaceutical Engineering (ISPE) was founded in 1994. Its mission is to advance the technical and operational excellence of the pharmaceutical industry through education, training, and the development of best practices and guidelines [9].

ISPE has a number of initiatives and guidelines related to cleaning validation. A comprehensive guide for commissioning and qualification of pharmaceutical manufacturing facilities, equipment, and systems, including cleaning validation, is available in the ISPE Baseline® Guide: Commissioning and Qualification (2nd Edition) [10]. The guide provides detailed information on the documentation, testing, and procedures required for cleaning validation, as well as best practices and considerations for the design, construction, and commissioning of pharmaceutical facilities.

ISPE also provides training and educational resources, such as seminars and webinars, on cleaning validation and other topics related to pharmaceutical manufacturing [11]. These resources can be helpful for pharmaceutical professionals to stay current with industry best practices and regulatory requirements.

4. (PDA) Parents' Drug Association

Pharmaceuticals and biopharmaceutical industries are served by the Parenteral Drug Association (PDA) [12]. It aims to advance the science of pharmaceutical manufacturing, with a particular focus on parenteral (injectable) products. PDA provides educational resources and guidelines for the industry, including guidance on cleaning validation.

PDA's guidelines for cleaning validation provide detailed information on the documentation, testing and procedures required for cleaning validation of parenteral manufacturing facilities and equipment. The guidelines cover topics such as the development of cleaning validation protocols, risk assessment, cleaning methods, and acceptance criteria [13]. They also provide guidance on the use of analytical methods, such as swabbing, rinse sampling, and endotoxin testing, to evaluate the effectiveness of cleaning.

PDA also provides training and educational resources, such as seminars and webinars, on cleaning validation and other topics related to parenteral manufacturing [14]. These resources can be helpful for pharmaceutical professionals to stay current with industry best practices and regulatory requirements

5. Health Canada

Health Canada is the national regulatory agency responsible for the safety and effectiveness of health products in Canada. They have specific guidelines for cleaning validation for the pharmaceutical industry, which are outlined in the "Guideline for Cleaning Validation" document [15]. This document provides guidance for manufacturers on the development and implementation of cleaning validation protocols for pharmaceutical facilities and equipment.

Health Canada's guidelines for cleaning validation cover topics such as the assessment of cleaning requirements, the selection of cleaning agents and methods, the development of acceptance criteria, and the use of analytical methods to evaluate the effectiveness of cleaning [16]. The guidelines also provide information on the documentation and record-keeping requirements for cleaning validation.

Manufacturers are expected to establish and follow written cleaning validation protocols in accordance with Health Canada's guidelines and to keep detailed records of all cleaning validation activities [17]. Health Canada may also conduct inspections to verify that manufacturers are following their cleaning validation protocols and to ensure that their products are free from contaminants[18].

In summary, Health Canada's guidelines for cleaning validation provide manufacturers with best practices for developing and implementing cleaning validation protocols and procedures, as well as methods for testing and measuring the effectiveness of cleaning[19]. They also provide guidance for monitoring and controlling the quality of pharmaceuticals during the production process.

It is interesting to note that Health Canada has listed quite a few requirements in its Guidelines for Cleaning Validation (Guide-0028) that are well known to the industry, but it is surprising that they are not mentioned in many other guidelines that discuss cleaning validation. We disagree slightly with Principle 3.5, which states that incorporating best-case risk into the actual risk is acceptable[20]. It is not advisable to promote taking the worst-case risk rather than identifying the actual risk, as that encourages the lazy attitude of taking the worst-case risk [21].

6. Administration for Therapeutic Goods and Services (TGA)

The Administration for Therapeutic Goods and Services (TGA) is the national regulatory agency responsible for the safety, quality, and efficacy of therapeutic goods in Australia, including pharmaceuticals. TGA has specific guidelines for cleaning validation which are outlined in the "Manufacturing Principles and Guidelines for Medicinal Products" document. These guidelines provide manufacturers with best practices for developing and implementing cleaning validation protocols and procedures, as well as methods for testing and measuring the effectiveness of cleaning.

TGA's guidelines for cleaning validation cover topics such as the assessment of cleaning requirements, the selection of cleaning agents and methods, the development of acceptance criteria, and the use of analytical methods to evaluate the effectiveness of cleaning. The guidelines also provide information on the documentation and record-keeping requirements for cleaning validation[22].

Manufacturers are expected to establish and follow written cleaning validation protocols in accordance with TGA's guidelines and to keep detailed records of all cleaning validation activities. TGA may also conduct inspections to verify that manufacturers are following their cleaning validation protocols and to ensure that their products are free from contaminants. Our new Standard Operating Procedure (SOP) for Cleaning Validation is science-based and risk-based, and we expect it will be a great success for the remaining countries. PIC/S Guide to GMP, without Annexes 4, 5, and 14, has been adopted by the TGA to formulate manufacturing principles for medicines, active pharmaceutical ingredients, and biologicals containing live cells, tissues, and organs.

7. Pharmaceutical Inspection Co-operation Scheme (PIC/S)

PIC/S acted quickly in response to EMA's new guidelines by quickly releasing its own version and setting HBELs in shared facilities PI 046-1 Guideline to prevent cross-contamination as of July 1, 2018 (effective from July 01, 2018). PIC/S will follow EMA's guidelines and will set the HBELs in sharing facilities as of July 01, 2018 [22]. A global organization with around 50 national members, PIC/S has transformed its cleaning validation program into one that is risk-based. Over 50 countries' regulators may begin to require compliance with EU standards for their cleaning programs as a result of this Medicines Agency's regulations. An AIDE-MEMOIRE, which shows in very specific detail what the regulators are looking for, was released in addition to the PIC/S guideline mentioned above. A failure to follow it will lead to many regulatory problems. It is an absolute must-read. The link below refers to it.

An inspection should consider cross-contamination risk management; however, time allocated depends on the amount of hazardous molecules involved, the number of products handled, and the isolation and dedication of the facility. Cross Contamination in Shared Facilities is another AIDE-MEMOIRE from PIC/S [23]. There is no way to overstate how highly this document should be regarded. If you want to mitigate cross-contamination in shared facilities, this document must be read several times. Pharmaceutical companies and regulatory authorities work together through PIC/S, an organization created in November 1995.

8. World Health Organization (WHO)

There are many similarities between WHO Cleaning Validation Guidelines and FDA Guidelines. WHO good manufacturing practices standards for active pharmaceutical ingredients outline this in Sections 5.2 and 12.7. The following points should be kept in mind. A representative API methodology is accepted by WHO as a means to validate cleaning procedures by selecting the worst product. A residue limit should be calculated based on potency, toxicity, and stability of the residue, as well as its solubility and difficulty of cleaning.

Stability cannot be incorporated into residue limits, however [23]. In order for continuous monitoring to be effective, WHO recommends analytical testing as well as visual inspection. However, a lack of further details undermines its

effectiveness despite the fact that it hints at the risk-based methodology. For the purposes of establishing carryover limits when validating cleaning in shared facilities, the World Health Organization released in May 2020 a working draft for comments that considers the various approaches, including HBEL.

All major regulators have begun to take notice of the HBEL revolution that has gained momentum across all major industries in the last few years. As well as including an indicative risk scale to measure hazard based on PDE values, the document actually contains an indicative risk distribution scale that fails to provide a continuous scale of risk, but displays risk as a discrete quantity. In the August 2020 draft, this has been removed, so I am glad to report that this is no longer an issue.

9. European Medicines Agency (EMA)

Medicines in the European Union are evaluated, supervised, and monitored for safety by the European Medicines Agency (EMA). A set of guidelines has been developed by the EMA for cleaning validation, which is outlined in the document "Guidelines on setting health-based exposure limits in shared facilities for risk identification".

These guidelines provide manufacturers with best practices for developing and implementing cleaning validation protocols and procedures, as well as methods for testing and measuring the effectiveness of cleaning. The EMA's guidelines cover topics such as the assessment of cleaning requirements, the selection of cleaning agents and methods, the development of acceptance criteria, and the use of analytical methods to evaluate the effectiveness of cleaning. The guidelines also provide information on the documentation and record-keeping requirements for cleaning validation. In response to the release of the guidelines, a Q&A session was conducted regarding their implementation. Here are a few key items from the full Q and A. All medicinal products should have HBELs. As a product's lifecycle progresses, toxicological or pharmacological data are regularly reassessed to ensure that the calculated HBEL is still relevant. It is only the beginning of the process to establish HBELs. As part of the Quality Risk Management process, these values are used to determine whether additional controls are needed.

Manufacturers are expected to establish and follow written cleaning validation protocols in accordance with EMA's guidelines, and to keep detailed records of all cleaning validation activities.

10. U.S. Food and Drug Administration (USFDA)

The US Food and Drug Administration (FDA) has several guidelines and regulations in place that govern the cleaning validation process for pharmaceutical manufacturers. These include:

Current Good Manufacturing Practices (cGMPs): These regulations outline the general requirements for the manufacturing, testing, and quality control of drugs [24]. They include specific requirements for cleaning validation, such as the need for written cleaning validation protocols, the use of appropriate cleaning agents and methods, and the documentation and record-keeping of cleaning validation activities.

"Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing": This guidance document provides recommendations for manufacturers of sterile drug products on the design and operation of aseptic processing facilities, including cleaning validation protocols. It includes information on the risk assessment, selection of cleaning agents and methods, acceptance criteria and analytical methods.

"Guidance for Industry: Inspection of Pharmaceutical Quality Control Laboratories": This guidance document provides information on the FDA's inspection process for pharmaceutical quality control laboratories, including the inspection of cleaning validation activities.

"Guidance for Industry: Inspection of Manufacturing Plants": This guidance document provides information on the FDA's inspection process for manufacturing plants, including the inspection of cleaning validation activities [24].

In summary, the FDA's regulatory guidelines for cleaning validation provide manufacturers with best practices for developing and implementing cleaning validation protocols and procedures, as well as methods for testing and measuring the effectiveness of cleaning [25]. They also provide guidance for monitoring and controlling the quality of pharmaceuticals during the production process and ensure compliance with the FDA's regulations.

CONCLUSION

Equipment that is used in production cannot be guaranteed to be 100% clean. Traces of active product within the equipment parts can be detected and quantified if they remain within an acceptable limit, as long as we are capable of detecting and quantifying them. A cleaning validation program can only be effective if equipment and products are assessed, impacts of a process on routine processes are assessed, appropriate cleaning agents and methods are chosen, residue acceptance criteria must be determined, a degree of evaluation must be determined for validation of the procedure, and a cleaning validation program must be clearly defined in this article.

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