Kaunas University of Technology

Faculty of Mechanical Engineering and Design

Investigation of Cleaning Validation in Medical Devices Industry

Master's Final Degree Project

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Kaunas, 2022

Kaunas University of Technology

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Industrial Engineering and Management (6211EX018)

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Investigation of Cleaning Validation in Medical Devices Industry

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Task of the Master's final degree project

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1. Title of the project

Investigation of Cleaning Validation in Medical Devices Industry

(In English)

Valymo validavimo tyrimas medicininių prietaisų pramonėje

(In Lithuanian)

2. Hypothesis:

The reliability of cleaning validation results depends on the validity of the cleaning procedures used.

3. Aim and tasks of the project

Aim: To investigate cleaning validation procedures in medical devices manufacturer company "X"
Tasks:
1. To analyze scientific sources related to the cleaning validation procedures;
2. To describe cleaning validation procedures in the manufacturing company "X";
3. To evaluate cleaning validation procedures and data in the manufacturing company "X";
4. To evaluate the cleaning validation results of the project "Y" in the manufacturing company "X";
5. To evaluate the cost of conducting the indirect testing in external laboratory versus in-house.

4. Initial data of the project

N/A

5. Main requirements and conditions

ASTM F3127-16 Standard Guide for Validating Cleaning Processes During the Manufacture of Medical Devices; EMA Guideline EMA/CHMP/CVMP/SWP/169430/201; EU GMP Volume 4, Annex 15; ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls;

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Study field and area (study field group): Production and Manufacturing Engineering (E10), Engineering Sciences (E).

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Kaunas, 2022. 52 p.

Summary

The main purpose of the research is to investigate cleaning validation procedures in the medical devices manufacturer company “X”. Manufacturer “X” developed new type of urinal catheter, which is in a higher risk of contamination during production. To avoid contamination cleaning validation activities were performed on the new catheter manufacturing machine. Various studies were completed, and cleaning efficiency results were evaluated from microbiological, chemical and visual aspects. Investigation was done by reviewing, describing, and evaluating cleaning validation procedures in the company “X”. Specific cleaning validation project “Y” was chosen to be evaluated and described. After evaluation, results proved that despite the deviations cleaning validation project “Y” was successful and equipment cleaning process was verified and validated. As a result, and as per procedures, after the validation, standard work instructions, cleaning routine monitoring, and maintenance procedures were created. Medical devices manufacturer “X” managed to successfully validate new production equipment and start the routine production. During validation few deviations occurred. Those deviations were related to the HPLC testing conducted in the external laboratory. During the research it was chosen to evaluate the cost of conducting the indirect testing in external laboratory versus in-house. During evaluation it was found that to conduct testing in-house, qualification of new testing machine and test method will be required. Preliminary qualification plan was concluded, resources were assigned to each task and costs of the qualification was calculated. It was found that, to start conducting the testing in-house would cost around 25,391.48 €. This value includes the cost of the qualification activities and the cost of the HPLC testing machine. Comparing this value to the value of conducting testing in an external laboratory, it was found that the cost and risk are significantly lower. But after evaluating time constraints and risk not to use the machine after the studies were done, it was decided to use the outside purchased services, despite higher costs.

Stulgė, Toma. Valymo validavimo tyrimas medicininių prietaisų pramonėje. Magistro baigiamasis projektas, vadovė doc. Rūta Rimašauskienė; Kauno technologijos universitetas, Mechanikos inžinerijos ir dizaino fakultetas.

Studijų kryptis ir sritis (studijų krypčių grupė): Gamybos inžinerija (E10), Inžinerijos mokslai (E).

Reikšminiai žodžiai: valymo validavimas, medicininiai prietaisai, medicininių prietaisų pramonė, valymo efektyvumas, valymo procedūros, įrangos valdavimas OQ, IQ, PQ.

Kaunas, 2022. 52 p.

Santrauka

Pagrindinis tyrimo tikslas – ištirti valymo validavimo procedūras medicininių prietaisų gamintojo įmonėje „X“. Gamintojas „X“ sukūrė naujo tipo šlapimo kateterį, kuriam kyla didesnė užteršimo rizika gamybos metu. Siekiant išvengti užteršimo, naujai sukurtai kateterių gamybos mašinai buvo atlikta valymo validacija. Atlikti įvairūs tyrimai ir studijos, o valymo efektyvumo rezultatai įvertinti mikrobiologiniu, cheminiu ir vizualiniu aspektais.Tyrimas atliktas peržiūrint, aprašant ir įvertinant valymo validavimo procedūras įmonėje „X“. Konkretus valymo validavimo projektas „Y“ buvo pasirinktas būti įvertintas ir aprašytas. Po įvertinimo rezultatai parodė, kad nepaisant kelių nukrypimų valymo validavimo projektas „Y“ buvo sėkmingas, o įrangos valymo procesas buvo verifikuotas ir validuotas. Po sėkmingo projekto įgyvendinimo ir pagal procedūras buvo sukurtos standartinės darbo instrukcijos, rutininės valymo stebėjimo ir priežiūros procedūros. Medicininių prietaisų gamintojui „X“ pavyko sėkmingai validuoti naują gamybos įrangą ir pradėti rutininę gamybą. Validavimo metu įvyko keletas nukrypimų. Šie nukrypimai buvo susiję su HPLC testu, atliktu išorinėje laboratorijoje. Tyrimo metu buvo pasirinkta įvertinti testavimo išorinėje laboratorijoje, palyginti su testavimu įmonės viduje, kaštus. Vertinimo metu buvo nustatyta, kad norint atlikti testavimą įmonės viduje, reikės naujos testavimo mašinos ir testavimo metodo kvalifikacijos. Buvo sudarytas preliminarus kvalifikacijos planas, kiekvienai užduočiai skirti resursai ir apskaičiuoti kvalifikacijos kaštai. Nustatyta, kad pradėti atlikti testavimą įmonės viduje kainuotų apie 25 391,48 €. Į šią vertę įeina kvalifikacijos veiklos išlaidos ir HPLC testavimo mašinos kaina. Palyginus šią vertę su bandymų atlikimo išorinėje laboratorijoje verte, buvo nustatyta, kad sąnaudos ir rizika yra žymiai mažesnės. Tačiau įvertinus laiko trūkumą ir riziką nenaudoti mašinos pasibaigus valymo validacijos veikloms, buvo nuspręsta pasinaudoti iš išorinės laboratorijos pirktomis paslaugomis, nepaisant aukštesnių kaštų.

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Abbreviations:

Assoc. prof. – associate professor;

CAGR – compound annual growth rate;

HVAC – Heating, ventilating and air conditioning;

FMEA – Failure Mode and Effect Analysis;

HACCP – Hazard Analysis Critical Control Point;

ADE – Acceptable Daily Exposure;

PDE – Permitted Daily Exposure;

TDD_{next} – Standard Therapeutic Daily Dose for the next product (mg/day);

MBS_{next} – Minimum batch size for the next product(s) (where MACO can end up) (mg);

MACO – Maximum Allowable Carryover;

WFI – Water for injection;

RnD – Research and development;

QA – quality assurance;

PVP – project validation plan;

PW – Purified Water;

HPLC – High Performance Liquid Chromatography;

TVC – Total Viable Count;

UV – Ultraviolet;

DQ – Design qualification;

IQ – Intallation qualification;

OQ – Operational qualification;

PQ – Performance qualification;

Introduction

Medical devices industry is constantly growing and evolving. According to the report of Medical Devices Market 2021 – 2025, medical devices market is poised to grow by $ 139.19 billions during 2021 – 2025, progressing at a CAGR of 5.21 % during the forecast period [1]. As the industry and the product variation is growing, the requirements for the quality is growing too. Moreover, increasing investments on the Research and Development (R&D) activities across the medical devices market are the reason to expand and expedite the cleaning validation development in upcoming years. Historically, the medical devices industry has approached cleaning validation as a compliance exercise [2]. In the 1990s, Food and Drug Administration (FDA) together with other regulatory offices, started to evaluate cleaning as an action which requires a validation.

Cleaning validation and validation itself as an action is a part of strong quality assurance program in the manufacturing facility. According to the Good Manufacturing Practice (GMP) guidelines, a manufacturer must ensure that the medical device:

- corresponding to the purpose for which they were conceived [3];
- to be accordant to the specific market requirements;
- to be accordant to the safety, quality and effectiveness for patients use.

The regulatory and standards for the medical devices industry are very high and, to be able to participate in this market, manufacturers must comply with them. It is necessary to ensure the cleanliness of equipment to prevent cross-contamination of manufactured products and also it is an important part of the requirements of FDA and GMP Cleaning validation studies are performed to establish documented evidence which demonstrates with a high degree of assurance that a cleaning process will consistently produce results meeting pre-determined specifications and quality attributes. It is necessary to validate cleaning procedures to ensure robust and reproducible methods for the reduction and removal of contamination (e.g., from cleaning agents and microbial contamination) of the next product manufactured on the equipment following a changeover clean. Robust cleaning methods reduce the risk of product contamination, thus, assuring product quality and patient safety.

Cleaning validation consists of two separate activities: development and validation of the cleaning procedure [4]. However, most companies recently introduced three-stages cleaning validation process, which consists of cleaning development, cleaning validation and validation maintenance. The residues of used manufacturing materials and cleaning agents have a significant potential to cross-contaminate the manufacturing line. To detect the residue, it is required to develop or choose selective and sensitive methods that are capable to quantitative evaluation of the traces of contaminant in the system after cleaning procedures is performed. To demonstrate the cleaning procedure effectiveness, it is required to have representative sampling points in the equipment, right sampling methods and eligible testing methods. The purpose to conduct studies and verifying and validating the cleaning procedures is to show that cleaning agents and product residues are removed to an acceptable level to prevent bioburden and carryover of product from batch to batch on product-contact equipment for the manufacture of medical devices.

According to the FDA guide, two different methods of sampling are generally admitted for performing a cleaning control: the direct surface sampling, using the swabbing technique and the indirect sampling based on the analysis of solutions used for rinsing the equipment [5].

The need for cleaning development, validation, verification, or validation maintenance, comes from GMP required production and process control, as well as design inputs and outputs. Any GMP cleaning processes and procedures that have the potential to impact on the quality of the product, directly or indirectly are validated to the extent appropriate for their intended use. Justification for performing these is made by the core team after evaluation of the equipment, the production process, existing cleaning processes, the risk to the customer and for business needs.

Aim: To investigate cleaning validation procedures in medical devices manufacturer company "X"
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1. Cleaning Overview

Medical devices industry encompasses a very wide range of products and technologies. Due to the diversity, their manufacturing technologies/processes vary widely and cover fields of chemical, mechanical, electronics, and their combinations [6]. Because of the diversity, medical devices do not have a clear and specific instructions and approach of validation implementation compared with pharmaceutical process validation. However, both, the medical devices, and pharmaceutical products, are intented for the health application and are regulated under the same standards. Given the similarities between two products, validation processes could be aligned, having in mind the nature of the processes and technologies. Inadequate cleaning disturbs the disinfection and sterilization process [7].

In the medical devices industry, it is well recognized that the manufacturing lines, equipment, and area should be kept as clean as possible. So, it is a responsibility of the Quality Management System (QMS) to ensure the effectiviness of cleaning procedures, it is also endorsed by the regulatory authorities. One of the main challenges that medical devices manuacturers face is to establishes the limits for cleaning validation (How clean is clean?).

With some exceptions, there are some universal principles applied to all cleaning types. Cleaning processes combine mechanical, thermal, and chemical energy sources to remove a soil from a substrate [8].

1.1. Purpose of Cleaning

Medical device manufacturers must establish documented cleaniness requirements. It is necessary to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality and impact patient safety.

Fig. 1. Effective cleaning in a manufacturing environment

As mentioned before, medical devices manufacturers are required to establish documented requirements for the cleanliness of a medical devices, when:

- product is cleaned by the organisation prior sterilization and/ori ts use;

- product is supplied non-sterile and will be subjected to a cleaning process prior to sterilisation and/ori ts use;
- product is supplied to be used non-sterile and its cleanliness is of significance in use;
- process agents are to be removed from product during manufacture.

1.2. Purpose of Cleaning Validation

Cleaning validation is a documented process that shows evidences to demonstrate that the cleaning methods which have been found applicable and acceptable for a process/product, achieve consistently the required levels of cleanliness [9]. Most of the cleaning processes in the industry are executed daily without any documentation or validation and which can be one of the main root causes of such products safety and contamination incidents. It is necessary to validate cleaning procedures to ensure robust and reproducible methods for the reduction and removal of contamination (e.g., from cleaning agents and microbial contamination) of the next product manufactured on the equipment following a changeover clean. Robust cleaning methods reduces the risk of product contamination, thus, assuring product quality and user safety.

An effective cleaning validation requires a deep knowledge [9] about the produced product, the production process, development of the cleaning procedures and recipes, residue limits as well as variety of residue types, analytical testing methods and their validation, sampling points, appropriate documentation, recovery studies and tools for further monitoring, verification or re-validation. The validation of cleaning must be based on sound scientific reasoning with clear explanations [10].

1.3. Regulatory Requirements

Medical devices manufacturers are audited under the Medical Device Single Audit Program (MDSAP) and International Standards Organisation (ISO) standards and GMP compliance audits are performed by regulatory agencies including the FDA and NSAI. The standards applied with respect to cleaning are based in ISO 13485, 21CFR820 and MDR 2017/74. These manufacturers are also audited by EPA under IPC licencing regulations and in accordance to the ISO 14001 standard by BSI. The cleaning validation strategies are also based on the principles outlined in the ASTM F3127-16 guide.

1.4. Routes of Contamination, Contamination, and Cross-contamination

When determining the most appropriate cleaning process for GMP manufacturing and packaging equipment, it is important to consider all possible pathways for the contaminats, e.g., microbial bioburden and chemical residues to accumulate on the equipment and in particular on product contact surfaces. The process inputs and potential routes of the contamination for the manufacturing and packaging processes that could introduce contaminants must be considered and assessed in terms of risk. The routes of contamination to consider when developing a cleaning process and cleaning validation strategy include, but are not limited to, the following:

- retention, which could be defined as a carryover of material on product contact surfaces from one product to another in the same equipment used in a sequential or campaign manner;
- mechanical transfer, which includes all routes by which material can be transferred from contaminated non-product surfaces into the product. This includes product contact surfaces contaminated by contact with contaminated surfaces, inadvertent or transient contact with

other contaminated non-designated product contact areas and direct contact of the product with such surfaces as operator apparel and gloves. The major issue with such routes is the lack of control of contaminated items.

Contamination and cross-contamination by foreign material is considered to have two different types. Cross-contamination is usually through an active ingredient from one product carrying over into subsequent manufactured product [11]. Cross-contamination is one of the highest risks for patients using pharmaceutical products. The carryover of product into another pharmaceutical product is of high risk to the patient. It is extremely important to avoid or minimise the risk of cross contamination when process and equipment are designed. Also, to learn how contamination risks can be detected is high importance. In Fig. 2 the sources of cross-contamination are outlined.

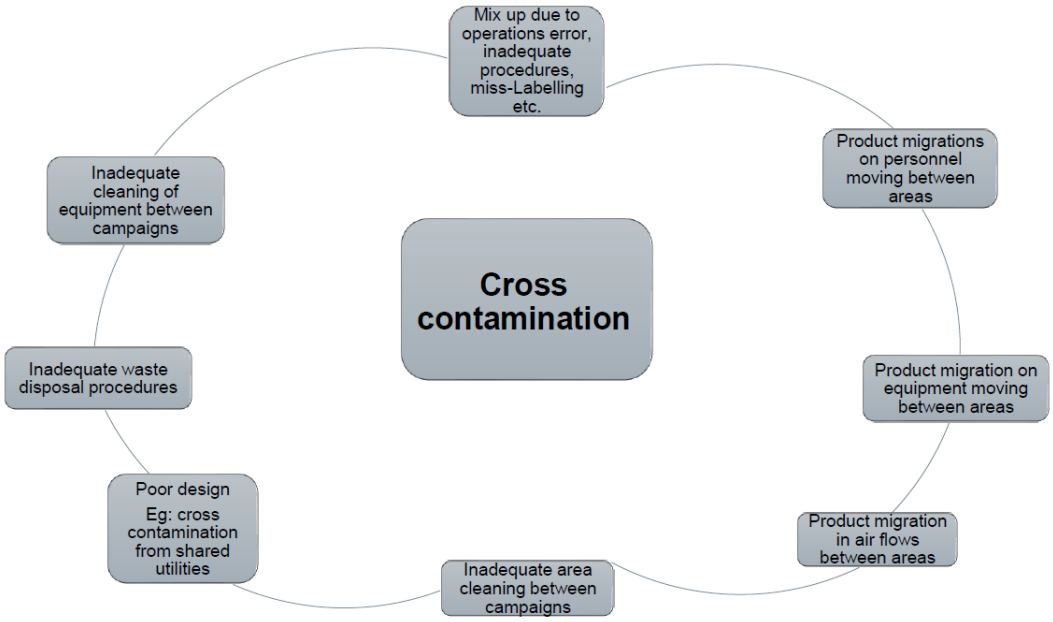


Fig. 2. Sources of cross-contamination

The other type of contaminarion may be microbial in nature. The major part of contamination by bacterial growth is that it can occur at any step of the production, even after cleaning. As a result, this is one of the main reasons why cleaning validation and various studies must be completed before starting the routine production. Microbial contamination could posse problems for sterile products manufacturing, as it could alternate the post manufacturing sterilization dose and results.

The main areas, where cross-contamination in manufacturing facility could occur are premises, used utilities, equipment, processing strategy and personnel. Reasons for cross-contamination consists of:

- poor facility design;
- inappropriate design of the HVAC system;
- contamination due to personnel or primary packaging;
- design of the production process;
- insufficient cleaning;
- uncontrolled release of dust, gases, vapours, sprays, or organisms from: materials and products in process, residues on equipment or operator’s clothing.

1.4.1. Equipment Design

An adequate equipment design is essential to achieve prime cleaning results and reduce the risk of contamination. Equipment design should possess design clarity, materials of construction, cleanability, maintenance, calibration, biohazard control and reflect on need for process closure and monitoring.

Careful vessels design (Fig. 3) can minimize the length of each CIP cycle and the volume of rinse water required to effectively flush the vessel [12]. Also, nozzles and drain piping designs must be taken in consideration (see Fig. 4 and Fig. 5).

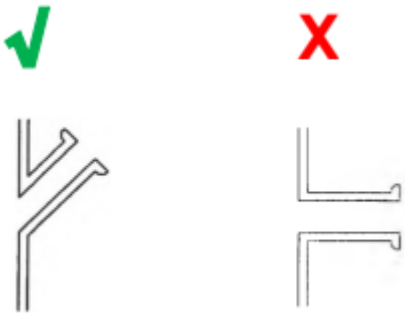


Fig. 3. Vessel design [12]

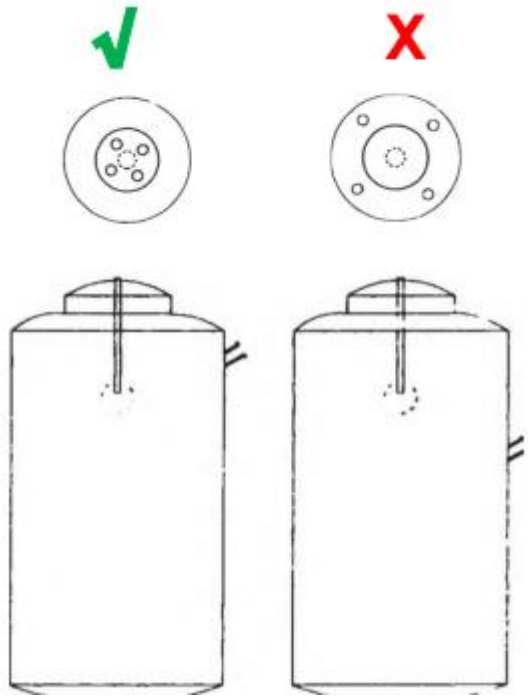


Fig. 4. Nozzle design [12]

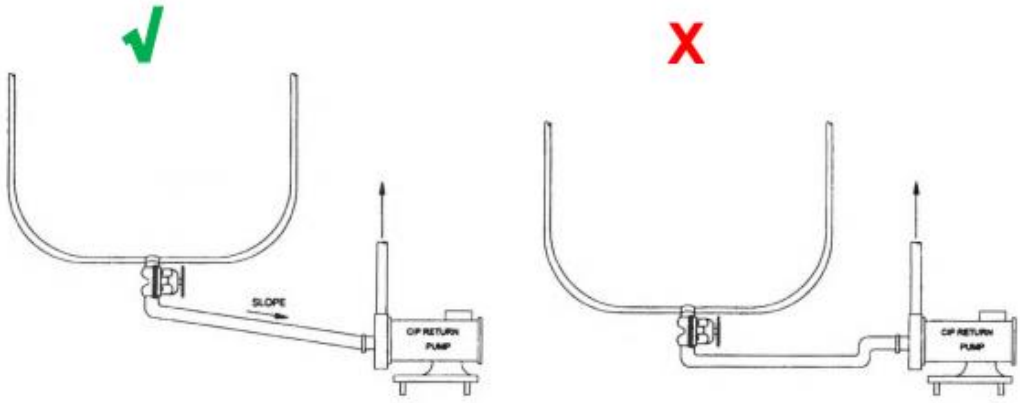


Fig. 5. Vessel drain design [12]

1.5. Cleaning Validation Activities Overview

Any GMP cleaning processes and procedures that have the potential to impact on the quality of the product, directly or indirectly are validated to the extent appropriate for their intented use. A cleaning

process should include the evaluation of the equipment used to manufacture the device and clean the equipment after use, the critical cleaning parameters and the manufacturing materials that should be removed by the process.

Cleaning validation program consists of a three-stage process which includes cleaning development, cleaning validation and validation maintenance, whereby:

- cleaning development involves designing an appropriate cleaning process that provides high degree of assurance of a succesful cleaning validation study;
- cleaning validation is performed after development to demonstrate the cleaning process is robust, repeatable and reproducible;
- validation maintenance provides on-going assurance over the product lifecycle that the cleaning process remains in a state of control.

Cleaning validation required for the product changeover cleans for all product contact equipment. Cleaning validation normally consist of three consecutive successful runs, based on risk, of the cleaning process. Cleaning studies may be performed concurrently or prospectively depending on the nature of the cleaning process and potential product and patient impact.

Documentation is required to detail the cleaning validation strategy, cleaning process and steps required to confirm that all aspects of the cleaning process that are critical to product quality are included in the scope of the validation study. Quality risk management principles will be employed for the definition of the critical aspects of the cleaning process as they relate to the product characteristics.

1.6. Cleaning Development

Cleaning development studies may be initiated under protocol or as a technical report. The cleaning process should be developed cross-functionally with understanding and assesment of the equipment aided by, but not limited to the following factors:

1) Physical disassembly and assembly of the equipment;
2) Review of vendor package, instructions or manuals;
3) Review of engineering drawings;
4) Leveraging on knowledge from similar equipment or parts;
5) Input from vendors and/or other sites with similar equipment;
6) Product contact versus non-product contact parts;
7) Material types and compatibility;
8) Determine the type and compatibility;
9) Determine the type of clean required;
10) Review if equipment is shared or dedicated;
11) Selection of cleaning agent;
12) Investigation of the recovery of product.

During development of a cleaning process, whether manual or automated, the four key operational parameters to consider include time, action, chemical and temperature (TACT). Design of a cleaning process should start with identification of critical cleaning parameters and critical quality attributes (CQA). At the end of cleaning development, a documented cleaning procedure is approved as a

prerequisite to the commencement of cleaning validation. Where manual cleans are performed, the cleaning procedure must provide sufficient detail regarding disassembly, cleaning, drying and visual inspection to ensure the manual cleaning process is repeatable and reproducible each time and by different personnel.

1.6.1. Risk Management Process

It is essential to perform a risk assessment analysis before any operation in GMP plants [13]. Risk management of medical devices is one of the important methods to ensure the quality and safety of medical devices [14]. The purpose of risk assessments for cleaning programs is to identify, assess, reduce/eliminate and control contamination risks to prevent microbial, particulate and chemical contamination that have the potential to impact device quality, safety and efficacy. According to the rules of GMP, basic concepts related to quality assurance, good manufacturing practice, quality control and risk management in quality are interrelated [3]. Effective and integrated risk management system must improve the performance of the company [15].

For risk analysis, it is important to assess the impact of contaminants from a product quality perspective and the intended functionality of the device. Different risk management procedures a used throughout the industry when developing a risk assessment for cleaning studies as they are also used to develop the cleaning validation strategy, to identify equipment/equipment parts in the scope of a cleaning validation program and identification of hard to clean, hard to reach and hard to dry product contact areas, among the others. Typically, medical devices manufacturers use Failure Mode and Effect Analysis (FMEA) as main risk management tool.

Fig. 6. Risk management process

Risk management process consists of six steps as per Fig. 6. Risk identification for cleaning activities could consist of deviation analysis/NCR trends, previous cleaning failures and failure to maintain the cleaning validation status. Risk analysis covers the risk management tools such as qualitative versus quantitative, FMEA, HACCP. It is helpful suggestion to perform a risk analysis study and categorize the products to select the worst case [13]. Risk evaluation involves acceptable and not acceptable

limits to achieve the successful cleaning validation results. Risk control ensures continuous monitoring to ensure cleaning validation status is maintained. While risk reduction/acceptance may involve redevelopment of cleaning procedures or development of entirely new cleaning procedures. Risk communication, as expected, is composed of continuous trainings, SOP updates, communication to management and core team and routine quality management reviews. All parts of the risk management process is inextricably linked.

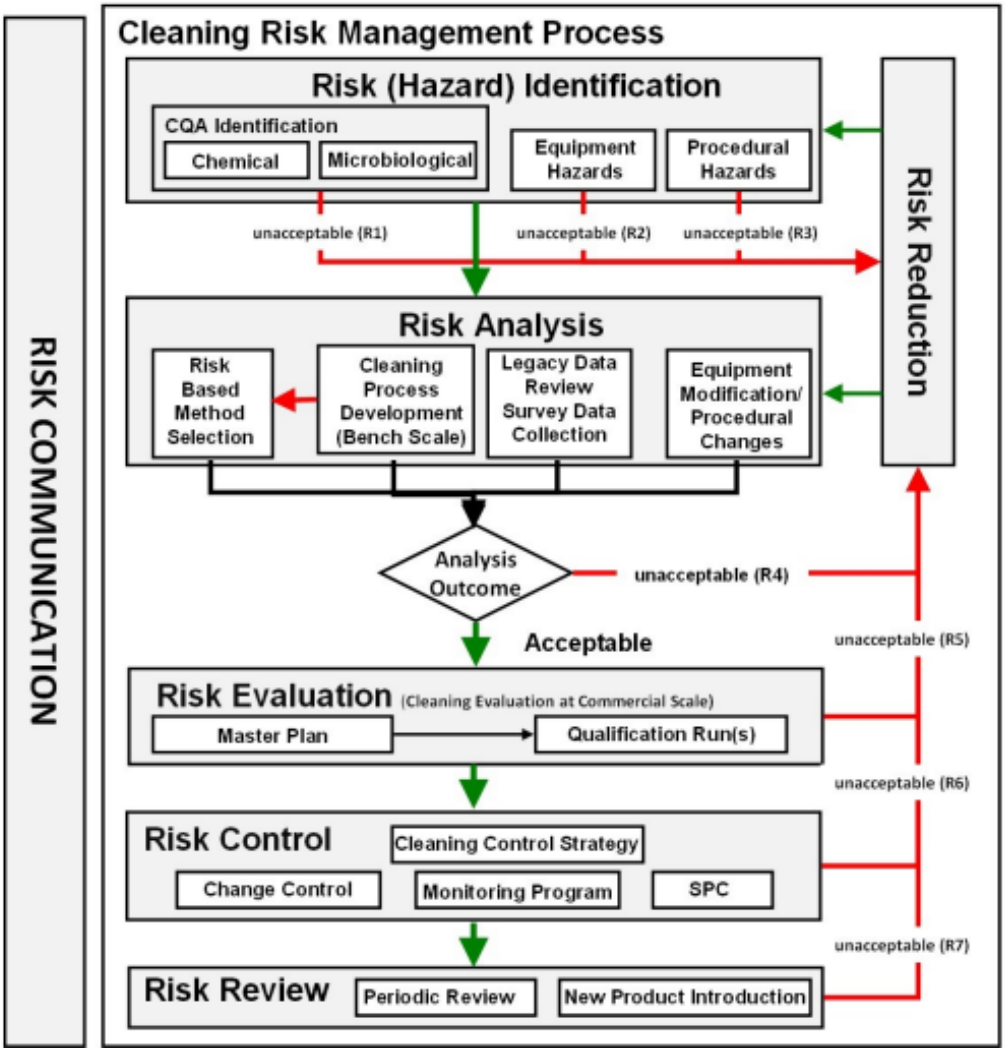


Fig. 7. ASTM E3106 cleaning risk management process [2]

Fig. 7 iliustrates the new ASTM E3106 standard way to minimize the effort and documentation of the cleaning validation by focusing on the early stages of the risk management process – risk identification and risk analysis. By focusing on these stages, the introduction of new products [2] to the market is simplified.

Risk management could be applied to streamline the cleaning process in determination of the number of swab and rinse samples and the areas of required swabbing in the equipment, determination of cleaning validation scenarios and cleaning assesment. Main areas of risk management application are:

- frequency of training (e.g. swabbing procedure);
- continuous verification of the cleaning procedure;

- deviation managment and root cause analysis;
- revalidation criteria determination;
- analytical methods suitability determination (e.g. comparison between specific versus non-specific analytical methods).

To perform a cleaning risk assesment, it is nessesary to identify material inputs, process equipment/equipment parts, cleaning equipment (e.g. clean in place (CIP), utilities used in the process/cleaning process (e.g. purified water, filtered air for drying) and all known cleaning parameters used in the process.

The output of the risk assesment is used to develop a validation plan and protocol that identifies all validation activities required to demonstrate the suitability and effectivness of the cleaning process. The validation plan and protocol should also include a scientific rationale for equipment or product grouping strategies or leveraging data from previous studies, where equivalency could be demonstrated.

The process of moving from the cleaning verification to a validated cleaning cycle usually is carried out under change control process. In order to determine the rigor of validation required change control risk assesment is also completed. This process is alligned with teh cleaning validation plan to ensure that the process is robust and all known risks have been considered.

Regulatory requirements for risk management in quality are outlined in ICH Q9, ISPE: Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), WHO Guideline on Quality Risk Management. More specific requirements of risk management for medical devices are outlined in ISO (e.g. ISO 13485:2016, ISO 14971:2019, ISO 13408-4:2011, ISO 10993-1:2018) and ASTM (e.g. ASTM F3127-16, ASTM G121, ASTM G122, ASTM E3219 – 20).

1.6.2. Selection of a Cleaning Agent

Choosing a surfactant or aqueous detergent for a critical cleaning application requires careful selection of cleaning chemistry and methods to ensure adequate performance without sacrificing worker or environmental safety [16].

For the identification of a suitable cleaning agent to effectively clean the equipment and for the removal of residues and prevention of contamination of the next product to be produced on the equipment, some poins must be considered:

- the nature of the residue to be removed, either the manufacturing materials or microbial bioburden residues, make an impact on the choice of the cleaning agent;
- the materials, which will be in contact with the cleaning agent to ensure compatibility of cleaning agent with the subtrate, must be considered;
- the cleaning process design. As it could be CIP, COP, WIP or manual cleaning;
- the type of the cleaning agent itself. As it is nessesary to effectively remove contaminants;
- safety of cleaning agent;
- environmental impact of teh agent and waste generated from cleaning process;
- analysis for the absence of the cleaning agent post use. It is important that the used cleaning agent could be detected in exceptionally low levels if present;
- stability and shelf life of the cleaning agent;

- the broad spectrum effectivenessacross a range of microbial species ir appropriate solubility of manufcaturing material residues.

Each cleaning validation study specifies a particular detergent and method used for cleaning, as well as the product being manufactured, potential contaminating residue, and equipment used for manufacturing [16]. As a result, there is no universal cleaning agent for every cleaning validation study.

1.7. Cleaning Verification

Cleaning validation and cleaning verification is sometimes confused together. It should be understood that when the cleaning process is validated and is applied on routine basis – such process is verified and monitored. Cleaning verification is documented evidence that an individual cleaning event has met the cleaning requirements for equipment that is acceptably clean. This approach may be used in cases where an unusual processing event may impact cleaning or following a deviation from the validated cleaning parameters. If required, verification must be done every time cleaning is performed. Verification tests may be performed as deemed appropriate by risk analysis. The cleaning validation study protocol/report template can be used to document a cleaning verification study.

1.8. Cleaning Validation Approach

The cleaning validation approach applies to all GMP cleaning processes involved in the manufacturing and packaging of single use medical device products. There are several key aspects that are considered when designing and developing a robust cleaning process and these are detailed in this section.

1.8.1. Types of Cleans

Cleaning could be divided into manual, semi-automated and automated cleaning processes:

- Cleaning can include manual cleaning of equipment and this typically involves the disassembly of equipment down to component parts, followed by washing of parts in a sink/holding vessel with a cleaning agent including some form of appropriate mechanical action or sonication, among others.
- Semi-Automated or Wash in Place systems typically involve some level of automated cleaning followed by a level of disassembly and manual cleaning and/or drying.
- Automated or Clean in Place systems are automated cleaning processes performed using a pre-approved validated recipe.

Another type of cleaning is considered to be interval cleaning process:

- It may be necessary to perform some form of cleaning between batches to reduce the instance of microbial proliferation between batches or prevent a build-up of manufacturing materials between batches in a campaign that could negatively impact process performance over time. Interval cleans do not require validation.

The last type of cleaning is changeover cleaning:

- This type of clean is usually performed when changing over from one product to another or when the process has reached the end of an established campaign and requires cleaning.

1.8.2. Surfaces to Consider for Cleaning Validation

While performing cleaning validation it is important to consider product contact versus non-product contact parts. Validation of cleaning focuses on product contact surfaces. Product contact surfaces are those surfaces with which the product, including manufacturing materials, comes into direct contact. Non product contact surfaces are assessed to determine whether the surface is in close proximity with a product contact surface or with the product and may have the potential to impact product quality, safety and efficacy. In this instance, that non product contact part may be included in the validation study. The cleaning of walls and floors is completed as part of the site Cleaning Contamination Control program.

The surface type and finish of product contact equipment is carefully considered when designing a cleaning validation program. Surface finish is chosen to ensure easy removal of manufacturing materials and prevent build-up of bioburden due to crevices or cracks that are difficult for the cleaning agent to penetrate. Porous materials such as filter membranes are typically dedicated. Filter integrity testing is performed at a minimum before use to confirm the integrity of filters to remove potential microbial contaminants in the process where filtration is employed. Tubing and hoses can include flexible plastics and fixed stainless-steel piping. A scientific risk based approach is used when considering tubing and hoses as single or multiple use. Biocompatibility and inertness of tubing with contact materials is considered prior to use. Tubing and hoses, if not dried before storage is stored on the slope to allow free drainage and is covered with special hose-end fittings to reduce the risk of microbial contamination during storage. Tubing and hoses are inspected periodically for any physical damage, shedding and pressure tested as necessary, to assess the useful lifetime for the manufacturing process.

1.8.3. Equipment Types

Equipment type have a huge impact on the cleaning validation strategy and approach. Shared equipment or equipment used to manufacture or package more than one product family, whereby the manufacturing materials used in the process may have the potential to impact product quality, safety or efficacy of the next product manufactured on the same equipment after a changeover clean. Cleaning validation is required for shared equipment.

Equipment that is reserved to the manufacture and packaging of one product family is described as dedicated equipment. Cleaning validation considerations for dedicated equipment include removal of cleaning agent and microbial contamination that poses a risk of contamination to the next batch of the same product.

1.8.3.1. Validation Strategy

Cleaning validation can be performed prospectively or concurrently depending on the nature of the study or change being assessed. Prospective validation ensures the final cleaning validation report is approved prior to release of batches in the scope of the cleaning study. Concurrent validation allows batches in the scope of the validation program to be released concurrent with the validation execution program based on an interim validation report. A final validation report is prepared and approved on completion of the cleaning validation program. The approach taken will be justified in the cleaning

validation protocol. Retrospective validation involves using historical data to confirm validation status of programs. Concurrent and Prospective validation approaches are the preferred options when developing a cleaning validation strategy.

1.9. Preparation for Cleaning Validation

Cleaning validation may be initiated after a recommendation from a development study. Pre-requisite studies may need to be completed as part of the the Cleaning Validation Study. These include Dirty Hold Time (DHT), Clean Hold Time (CHT) and Campaign length. The cleaning validation strategy will be defined in a Project Validation Plan (PVP). Any pre-requisites are to be listed in the PVP.

CHT is defined as the time between cleaning and next use. Establishing a CHT is required to reduce the possibility of re-contamination of equipment from an external source and also to reduce the microbial proliferation due to moist conditions during cleaning, inadequate drying and potential condensation accumulation in the equipment during storage of inadequately dried equipment. Covering and protection of cleaned equipment and appropriate storage conditions are critical for the prevention of recontamination of cleaned equipment.

DHT hold time is defined as the time from the end of the manufacturing process to the start of a cleaning cycle for a piece(s) of equipment. When establishing a DHT, the DHT start is when the final manufacturing material is removed from the equipment and ends when the CIP cycle or for manual cleans, when all product contact parts are wetted down. The number of cleans to establish a DHT should be based on sound scientific risk-based rationale.

A campaign duration establishes the batch size or number of batches that could be processed on the GMP equipment system before the requirement to perform a changeover clean. It determines the size and duration of manufacturing the same batch until there is a negative impact on the process and product. Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises [17].

1.10. Revalidation

Once validated, it is necessary to maintain the cleaning process in a validated state. Changes to the cleaning process should be assessed and the impact to the validation documented under the site change control system. Changes to manufacturing materials or cleaning equipment used may impact the validated cleaning procedures, therefore, any process and equipment changes should be assessed for cleaning validation impact. The requirement to repeat the cleaning validation study or part of, is determined through a scientific, documented and risk-based decision.

The addition of new products to the equipment must be assessed to determine the impact on the current validated cleaning process. If a new product is introduced, the original cleaning assessment performed should be updated to determine the requirement for revalidation. If medical device manufacturers take a methodical approach and base each decision on sound scientific rational, they will be able to establish a cleaning process that will consistently provide clean medical devices to the market [18].

1.11. Continuous Process Monitoring and Verification

A periodic monitoring program is established on completion of the cleaning validation program. The process parameters used during the cleaning validation program should be routinely monitored in accordance with documented procedures. Critical process inputs to monitor during ongoing process monitoring can be the results on rinse or swab samples. For newly developed cleaning process, monitoring should be performed at an increased frequency and adjusted based on the data gathered and as confidence in the cleaning process is developed.

A periodic review program should be established per site to ensure continued cleaning cycle performance. This could include trending of cleaning cycle performance, trending analytical data from periodic monitoring, and reviewing any process alarm trends from cleaning cycles. The goal of any monitoring method is to provide feedback on cleaning failure to assist in the management and improvement of environment cleaning within health care settings [19].

1.12. Maintaining the Validated State

A periodic monitoring program is established on completion of the cleaning validation program. The process parameters used during the cleaning validation program should be routinely monitored in accordance with documented procedures.

Critical process inputs to monitor during on-going process monitoring can include the same test types and methods used for previous verification and validation studies, but at a lesser quantity or frequency. For newly developed cleaning process, process monitoring should be performed at an increased frequency and adjusted based on the data gathered and as confidence in the cleaning process is developed. A periodic review program should be implemented in the facility, considering the evaluation of the cumulative impact of process changes over a pre-defined period, trending of cleaning cycle performance, analytical data from periodic monitoring trending and reviewing any reaches to the alarm and action limits from past cleaning cycles.

1.13. Development of Acceptance Limits for Cleaning

It is an important step to set the acceptance limits of residues after the equipment cleaning. Each limit setting approach (Cleaning Process Capability, Safety Factor, Toxicology Threshold, and Performance Control) ensures patient safety and no impact to subsequent product quality [20]. Residue limits are set for any residue that has the potential to impact product quality, safety and efficacy. Limits are set for contaminants including cleaning agents, bioburden, and manufacturing materials. The formerly accepted methods for establishment and calculation of cleaning validation acceptance limits including visually clean, 0.1% dose, and 10-ppm criteria have become obsolete [21]. Andrew Walsh, Michel Crevoisier, Ester Lovsin Barle, Andreas Flueckiger, David G. Dolan, and Mohammad Ovais discusses and proves that the 10-ppm limit, alongside with 0.001 dose limit, are not truly risk-based approaches and are also unsound from an operational standpoint as they have caused unnecessary difficulties for many companies [22]. According to the authors risk-based approach is much more friendly to the industry than the artificially low limits that were used before. The acceptance criteria preferably should be based on the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) calculations whenever this data is available [23].

As per APICS guidance on cleaning validation the acceptance criterias for successful equipment cleaning usually is based on the visual inspection and analytical methods/limits. The acceptance criteria for cleaning agent residue can be performed using Maximum Allowable Carry Over (MACO) calculations, by using Equation 1:

Equation 1. MACO calculation

$$MACO = \frac{ADE/PDE_{previous} \times MBS_{next}}{TDD_{next}}$$

During the equipment cleaning validation hard to clean and dry areas of the equipment may be detected. Those locations are usually considered as swabbing points. Recovery studies and method validation are necessary when applying swabbing as a method to determine residues [23].

1.13.1. Types of Sampling

The main types of sampling used during cleaning studies are visual inspection, swab sampling and rinse sampling. When selecting a sampling method, it is important to understand the nature of the residue being measured, what residue limit is being used and the equipment to be sampled.

The sampling and samples are critical to the success or failure of the cleaning validation. Main types of sampling are:

- Visual inspection/sampling is one the most effective qualitative methods to determine equipment cleanliness. The major advantages of the visual inspection is simplicity of the method and requirement of very little tools and instruments. On the other hand, as simple as this method is, not all of the equipment is inspectable, which could lead to the failure. Although a surface may look clean, human vision cannot detect microscopic-level contamination [24].

- For rinse samples, the sample is removed post final rinse water or solvent recirculated over all product contact equipment surfaces. When performing rinse extractions, successive rinses are conducted and studied to determine how much water or solvent is required and the duration of rinsing prior to removal of the sample for analysis. Rinse sampling is very commonly used throughout the industry as it has a broad application for testing methods.

- When performing swab sampling for conductivity or other non-specific analysis, the area being investigated is swabbed with a swab moistened using purified water or Water for injection (WFI).

  The swab technique is a standartised multi-pass technique that prevents swabbing of the same surface area multiple times. Standartised swab methods prevent inaccuracy of results by ensuring that the same swab technique is performed for all swab areas in the scope of the cleaning study. As swabbing is quite good method for microbial bioburden determination, the results after testing is delayed by at least 48 hours.

2. Research Methodology

Starting the research, current cleaning validation procedures in the medical devices manufacturing company "X" were reviewed and analyzed. It is clear that there are multiple benefits to thoughfully designes, effective procedures and instructions, including satisfied surgical customers, satisfied staff, improved reprocessing quality, a potential decrease in medical device repair costs, productivity gains from improved compliance, and most importantly, a potential decrease in risk to patients [25].

The main focus of this investigation will be to describe the equipment cleaning validation process and results in the company "X". However, in the next section brief introduction to manufacturer "X" produced product and how cleaning validation procedures are implemented in the facility internally will be given.

2.1. Manufacturer "X" Produced Product

Medical devices manufacturer "X" produces urinary catheters for males and females. Urinary catheters are considered to be Class I sterile medical devices. This product consists of flexible plastic (PVC), silicone or rubber tube and a bag.

Catheter device is designed to manage urinary incontinence by draining urine. The catheter achieves this by insertion into the urethra and allowing passage of the urine from the bladder. Abstract diagram of the catheter is provided in the Fig. 8.

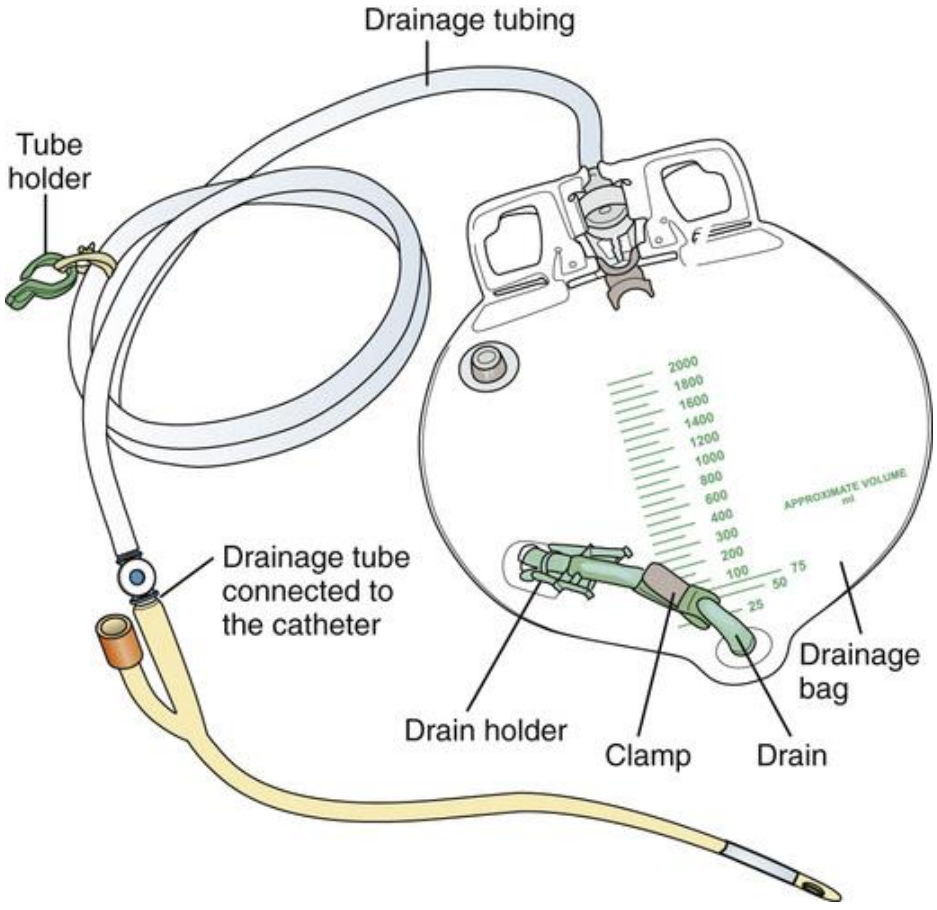


Fig. 8. Urinary catheter diagram [26]

Manufacturer “X” designed new type of the female urinary catheter, hich addresses the needs of women of full to reduced hand dexterity (able to self-catheterize), who independently perform self-intermittent catheterization to manage neurogenic bladder conditions primarily due to spinal cord injury and multiple sclerosis.

2.2. Cleaning Validation Procedure in Medical Devices Manufacturing Company “X”

It is advisable for medical devices manufacturers to hold on official procedures on how processes are implemented. These procedures should be approved by the management and serve to provide a general guideline and direction for company personnel, regulatory authorities and customers as to how the company deals with areas associated with cleaning validation [27]. Procedures of cleaning validation in medical devices manufacturing company “X” is guided by and works according to the:

- ASTM F3127-16 Standard Guide for Validating Cleaning Processes During the Manufacture of Medical Devices;
- EMA Guideline EMA/CHMP/CVMP/SWP/169430/2012 (20 Nov 2014) Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities;
- EU GMP Volume 4, Annex 15;
- ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls;
- All internal procedures (e.g. Change control procedure, process validation procedure, deviation report procedure)

The global cleaning validation procedure in the facility is called - Cleaning Development, Cleaning Verification & Cleaning Validation Procedure. The purpose of internal cleaning validation procedure in company “X” is to instruct engineers in the procedures necessary to conduct cleaning development, cleaning verification and cleaning validation studies to show cleaning agents and product residues are removed to an acceptable level to prevent bioburden and carryover of product from lot to lot on product-contact equipment for the manufacture of medical devices. Cleaning validation procedures also provide the instructions neccessary to develop the protocols, and the corresponding reports, associated with the cleaning studies.

Internal cleaning validation procedure is applicable to the cleaning of product-contact process equipment used in the hydration processes directly impacting the manufacture and product quality of finished medical devices, in all company’s “X” manufacturing locations, where this specific process is applied.

In this procedure several sections are outlined:

- Purpose;
- Scope;
- Definitions;
- References;
- Roles and responsibilities;
- Determination of the type of cleaning study;
- Cleaning development;
- Cleaning verification;

- Cleaning validation/revalidation;
- Continuous process monitoring and verification.

2.2.1. Roles and Responsibilities of Cleaning Validation

As mentioned in the section above, internal facility's "X" cleaning validation procedure has outlined the roles and responsibilities. It is necessary to list each contributing area and the associated tasks for which it is responsible [28] in cleaning validation procedures. Typically, the validation project team is concluded from representatives from manufacturing, engineering, quality control and research and developments. As a result, it can be seen from the Table 1, that in manufacturing facility "X" many departments and positions are involved in the planning and excuting the validation of the cleaning as it is accountable and complex task. In the procedure this task segregation serves as a clarification and ensures that no important parts are overlooked during the project.

Table 1. Roles and responsibilities to fulfill cleaning validation in facility "X"

Responsibility	**Role**
Engineering Quality Engineering	Define cleaning development/verification/validation scope and approach
Engineering	Develop cleaning processes
Engineering Quality Engineering Sterilisation Specialist RnD	Validate analytical methods used for cleaning development/verification/validation studies
Engineering Quality Engineering	Prepare cleaning development/verification/validation Protocols
Engineering Operations Quality Engineering	Review and approve cleaning development/verification/validation protocols
Engineering Operations Quality Engineering	Execute cleaning development/verification/validation studies
Engineering Quality Engineering	Investigate events/deviations related to execution of cleaning

	development / verification /validation studies
Engineering Quality Engineering Sterilisation Specialist RnD	Analyze cleaning samples, report results and investigate OOS results/test failures
Engineering Quality Engineering	Prepare Cleaning development/verification/validation reports
Engineering Quality Engineering	Review and approve final cleaning development/verification/validation reports

Also, for every project core team is formed. Core team members must be competent in the field of the project. Usually, core team members are senior management representatives from each department. They are primary responsible for documentation, compliance, technical excellence, support for the extended team and overall success of the project. Cleaning validation is no exception in the facuility "X" – as validation procedures indicates the core and extended team importance and responsibilities.

Quality assurance (QA) department has an exceptionally high importance in every project as well as cleaning validation. As QA team members prepares and approves all documentation and other representatives review and approve documents as needed in their area of expertise and responsibility [29]. The site Quality Manager is responsible for ensuring that the cleaning validation strategy is in place and that cleaning valiation programs are performed in line with regulatory requirements and expectations for medical devices.

The process flow and responsibilities are shown in the Fig. 9 very clearly. It can be seen that different departments have different responsibilities, but all those responsibilities overlap in between, as the project is very complex.

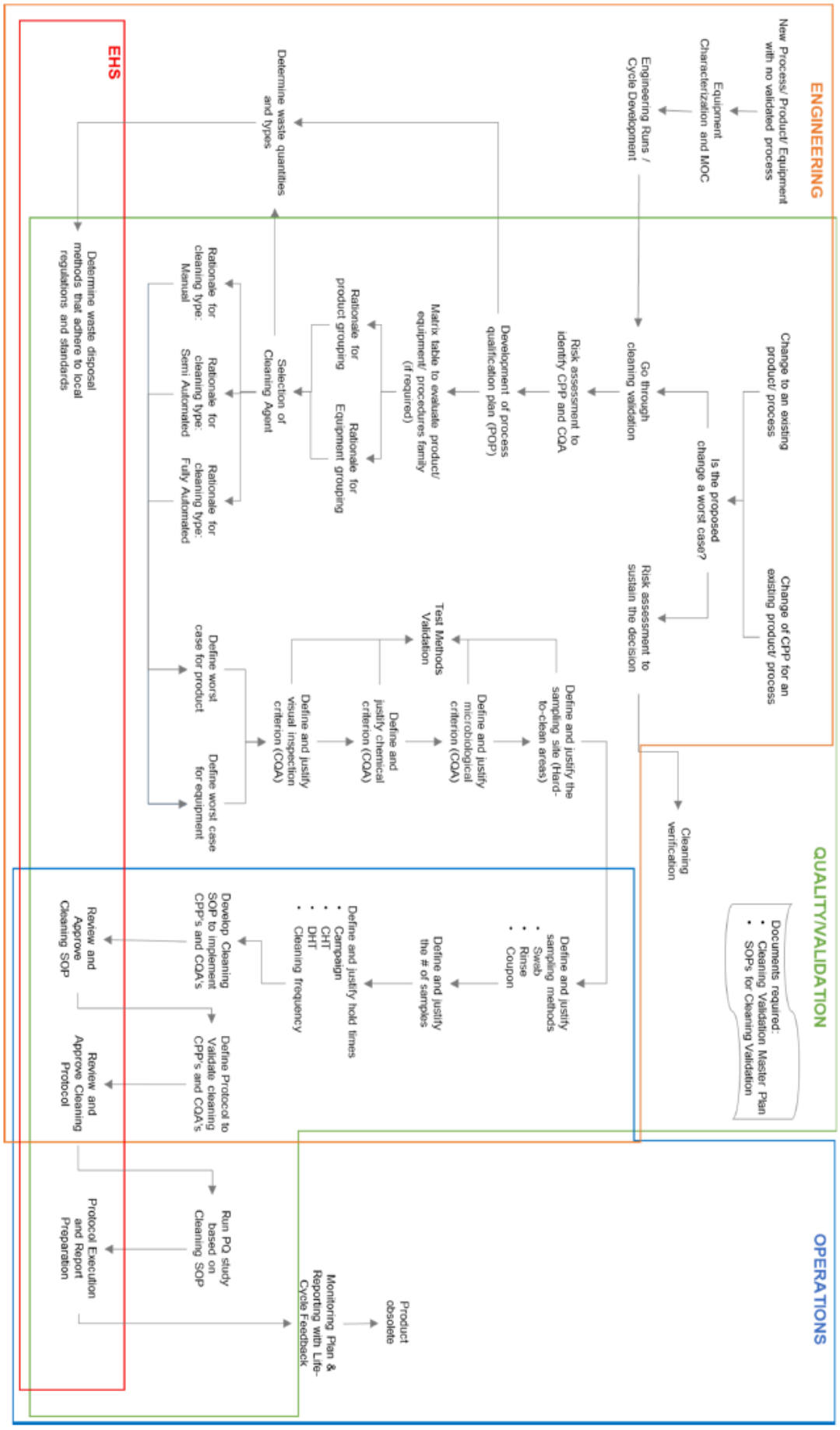


Fig. 9. Process flow of the cleaning cycle for the new model catheter cleaning validation

2.2.2. Procedure of Cleaning Validation

Medical devices manufacturer's "X" Cleaning Development, Cleaning Verification & Cleaning Validation Procedure has clearly indicated parts how cleaning of the equipment should be validated. The types of cleaning studies required prior to use of the equipment for the routine manufacturing of medical device are clearly indicated and are as the following:

- cleaning development;
- cleaning verification;
- cleaning validation/re-validition;
- validation maintenance/Continuous process validation.

The parts indicated matches the requirements of GMP guide for production and process control, design inputs and outputs and the recommendation from previously conducted studies in other facilities. Justification for performing these is made by the core team after evaluation of the equipment, the production process, existing cleaning processes, the risk to the customer and for business needs.

Procedure also clearly indicated required documentation package and requirements for each document after the cleaning validation is conducted. The outcome after the cleaning development stage should be consisted of at least three documents:

- cleaning development technical report;
- cleaning development protocol;
- cleaning development report.

Each document should summarize each study execution and results.

The outcome of the cleaning verification stage should be consisted of at least two documents:

- cleaning verification protocol;
- cleaning verification report.

Each document summarizes the execution and results of the event of cleaning verification.

As per procedure the outcome of the cleaning validation stage should be consisted of following documents:

- project validation plan (PVP);
- cleaning validation protocol (may be consisted of different protocols for DHT, CHT and campaign length studies);
- cleaning validation report (as per protocol, may be consisted of different reports for each study executed).

As discussed above, each document should summarize the events during the cleaning validation stage. After documents are approved and cleaning process is validated, a periodic monitoring program should be established on completion of the cleaning validation program, as per procedure. The process parameters used during the cleaning validation program should be routinely monitored in accordance with documented procedures. The package of documentation may be created to control

the routine monitoring and maintenance process. Those documents could be in a form that it is suitable for the company. However, Cleaning Development, Cleaning Verification & Cleaning Validation Procedure states that after the validation internal site procedures and standard work instructions for each process should be created.

Cleaning Development, Cleaning Verification & Cleaning Validation Procedure is mainly based on and summarized the best by Fig. 10 process flowchart for cleaning validation activities from ASTM F3127-16 Standard Guide for Validating Cleaning Processes During the Manufacture of Medical Devices.

After reviewing the procedure, it was verified that the process is implemented as required. The procedure includes all necessary parts for validating the cleaning of equipment as per all guides and standards required. The cleaning validation approach for manufacturing facility "X" applies to all GMP processes involved in the manufacturing and packaging of single use medical device product. There were several key aspects that was considered when designing and developing a robust cleaning process for this facility.

The cleaning validation of the equipment that will be discussed in the following sections was the initial validation for that equipment, and as such, it was necessary to consider some of the pre-requisites to it.

A cleaning development study was initiated with the introduction to this equipment into the facility "X" from the supplier and the study was completed by a cross-functional team with, the outcome of which was reported as a technical study which included:

- the type of cleaning required;
- the surfaces to be cleaned;
- material types and compatibility;
- a review if equipment is shared or dedicated;
- investigate the hard to clean areas, dead legs;
- a determination of the most optimal cleaning agent to use;
- the development of the most optimal cleaning cycle and verification of this;
- a determination of sampling and testing plan;
- review of test methods for sampling testing;
- a determination of residue limits;
- report the test results achieved.

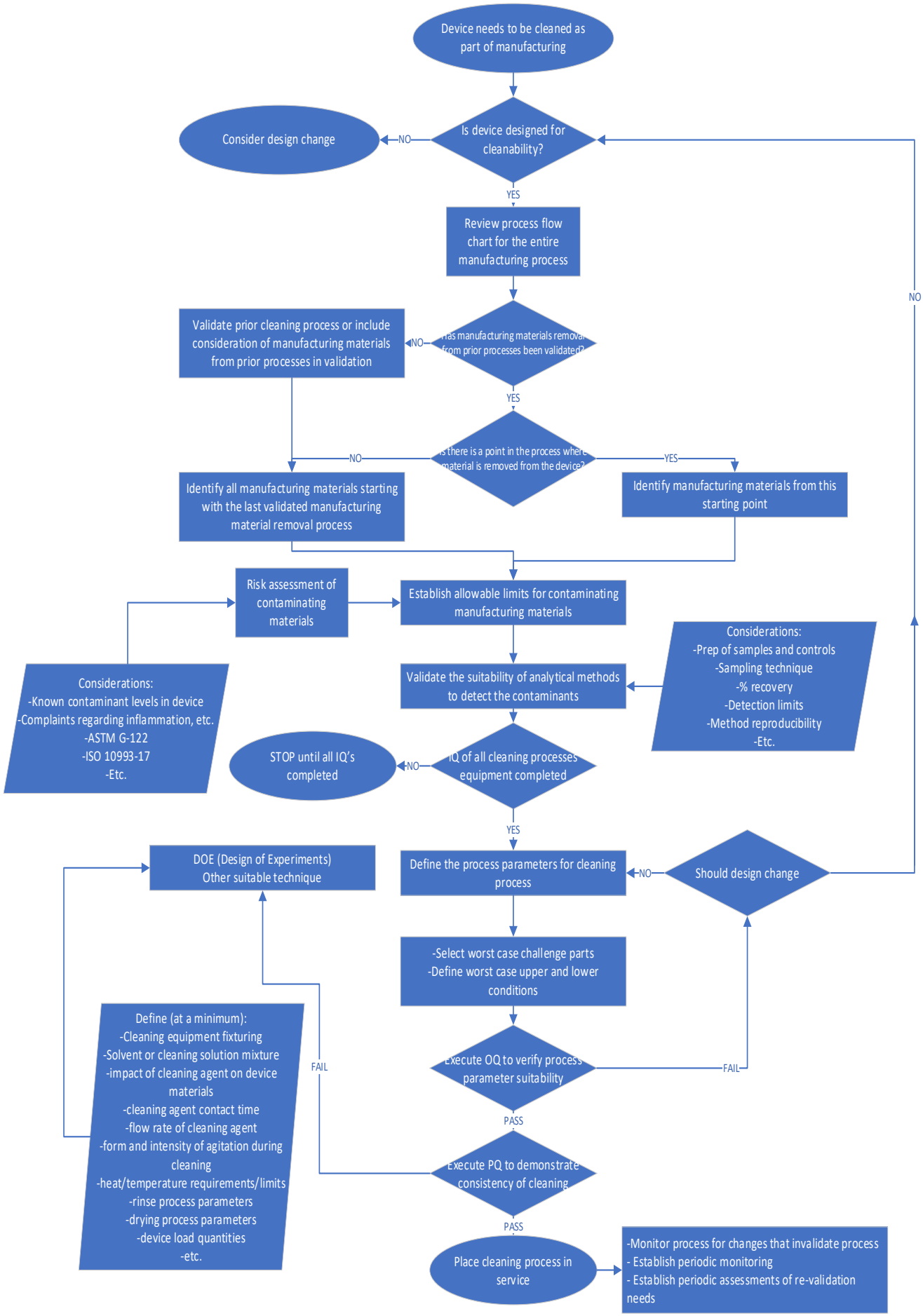


Fig. 10. Process flow for a cleaning validation [30]

2.3. Cleaning Validation of the Project “Y” Results in the Medical Devices Manufacturing Company “X”

The purpose of cleaning validation project “Y” is to establish documented evidence which demonstrates with a high degree of assurance thata cleaning process will consistently produce results meetingpre-determined specifications and quality attributes. It is necessary to validate cleaning procedures to ensur robust and reproducible methods for the reduction and removal of contamination of the next product manufactured on the equipment following a changeover plan. Robust cleaning methods reduce the risk of product contamination thus assuring product quality and patient safety.

2.3.1. Background of the Cleaning Validation Project “Y”

Medical devices manufacturing company “X” has developed a new and improved medical device, which must be hydrated for easier insertion to a patient body pre-use. The device is manufactured from a TPE material, it is coated and directly hydrated with a developed hydration solution and coating, which were developed by the manufacturer “X” pre sterilization.

For this new product new equipment is developed to satisfy the program requirements. The system seen in the Fig. 11, was created and built by the external supplier. New production equipment is aimed to be used only in the cleanroom environment and only for producing the new product. The need for cleaning validation occurred because the machine will use the hydration fluid, which is of biological nature. As a result, this new material has a high potential to contaminate the product.

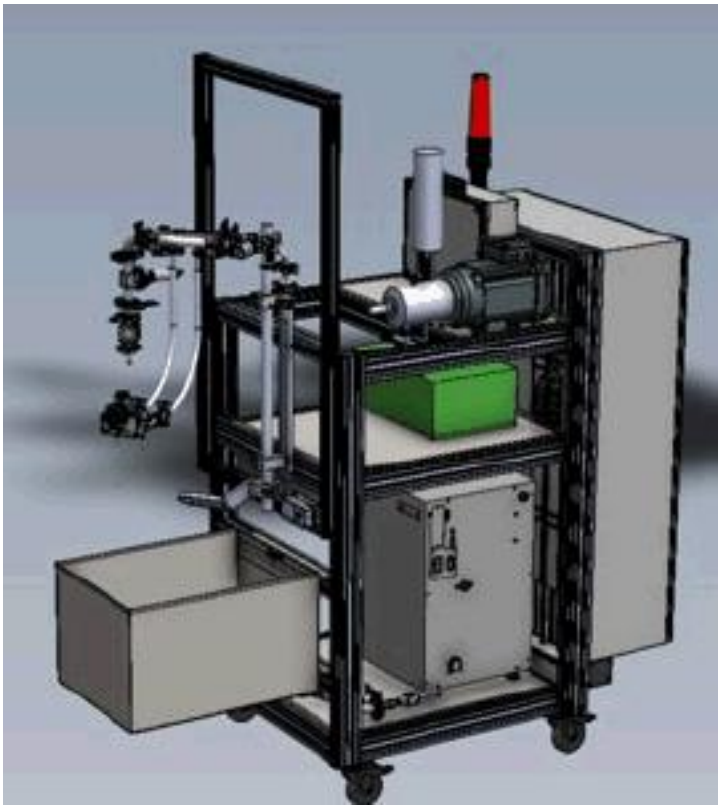


Fig. 11. New developed manual catheter hydration equipment

2.3.2. Equipment Overview

The new developed equipment dispenses foam into female catheter case according to the product specification. The foam hydration process remains the same for all charrier sizes, only the quantity of hydration foam dispensed will change according to charrier size.

The operator places two empty catheter cases with rubber collar into the empty product nests on the manual slide into position where proximity sensors on the unit will detect that the cases are in the correct filling position and sensors detect the product (cases) is in the correct position. The operator then push the fill button to call for foam hydration solution. The foam hydration solution is pumped to a manifold which supplies the 2 dispensing valves. The manifold is fitted with a pressure transducer and a back pressure valve to monitor and maintain consistent pressure. A needle dispensing nozzle attached to the dispensing valves dispenses the foam into the catheter case. A fork sensor will detect that the foam is being dispensed. Once the foam is dispensed, the operator pulls the manual slide into position where a foam height sensor will verify that the correct quantity of foam is dispensed into the case. All parts of the equipment are illustrated in the Fig. 12.

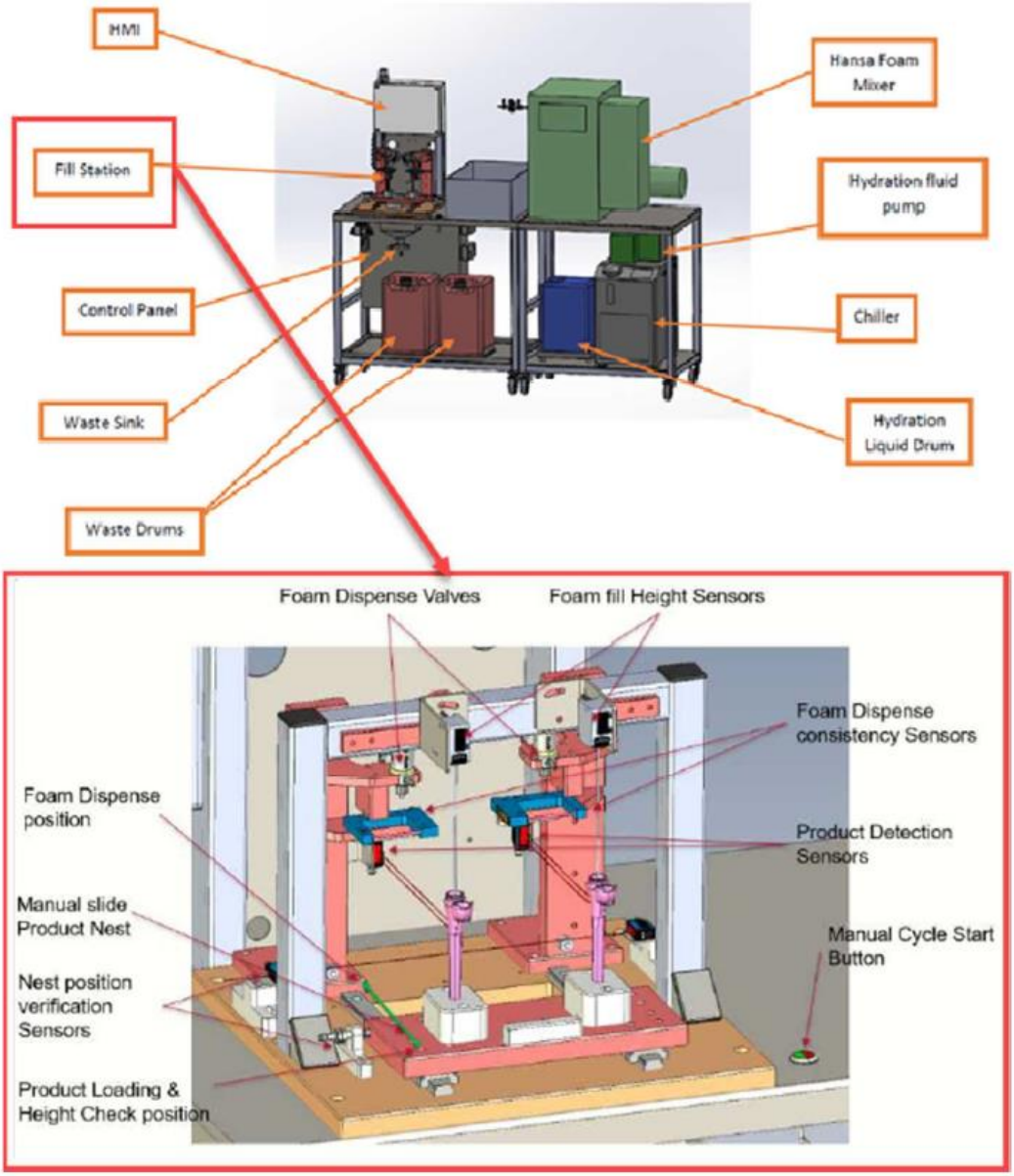


Fig. 12. Equipment overview

2.3.3. Cleaning Process Development of the Cleaning Validation Project “Y” Approach and Overview

The cleaning development work completed to establish a suitable cleaning process for the newly developed production equipment was documented as a study report rather than set predetermined test criteria in a protocol due to the phased approach, this allowed scope to modify the variable process parameters as required in response to results from the preceding batches.

External supplier carried out an initial PACE (Process and Cleaner Evaluation) study to establish a recommended cleaning agent, cleaning agent concentration and cleaning process conditions. This study was documented in an internal study report and summarized cleaning cycle diagram is provided in the Fig. 13.

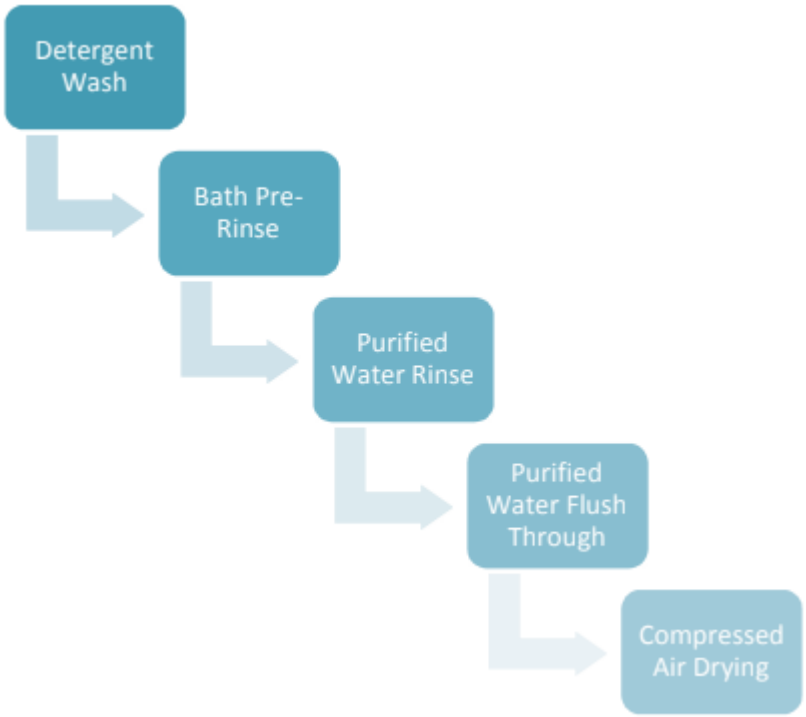


Fig. 13. Cleaning cycle summary

Two cleaning cycles were carried out to establish a suitable cleaning process for the cleaning of the equipment fluid dispensing manifold and header vessel. For both runs, the equipment had been left in a contaminated state (wetted with hydration solution, which will be used in production) for 90 hours (3 days 18 hours) prior to the commencement of the cleaning cycles.

The first cleaning cycle was carried out using high process settings, to challenge the removal of detergent residues. All results were within specification.

The second cleaning cycle was carried out using low process settings to challenge the ability to effectively clean and remove hydration solution residues. The results of all samples tested results were within specification.

For both cycles, the equipment was moisture free and free of residue on cycle completion. Based on the process parameters determined during the cycle development it was recommended that certain

cleaning process should be performed on the equipment. The exact recommendations of time, concentration and etc. were provided as appendixes in the cleaning development study report.

Several cleaning verification cycles have been run under various cleaning verification protocols. These protocols were executed using the parameters of the previous cleaning development study. By evaluating those results of the verification runs, provided assurance that the cleaning cycle, which is shown in the cleaning process flow Fig. 14 below, was capable of the reproducible results and was effective in removing detergent residues and bioburden down to predetermined acceptable limits.

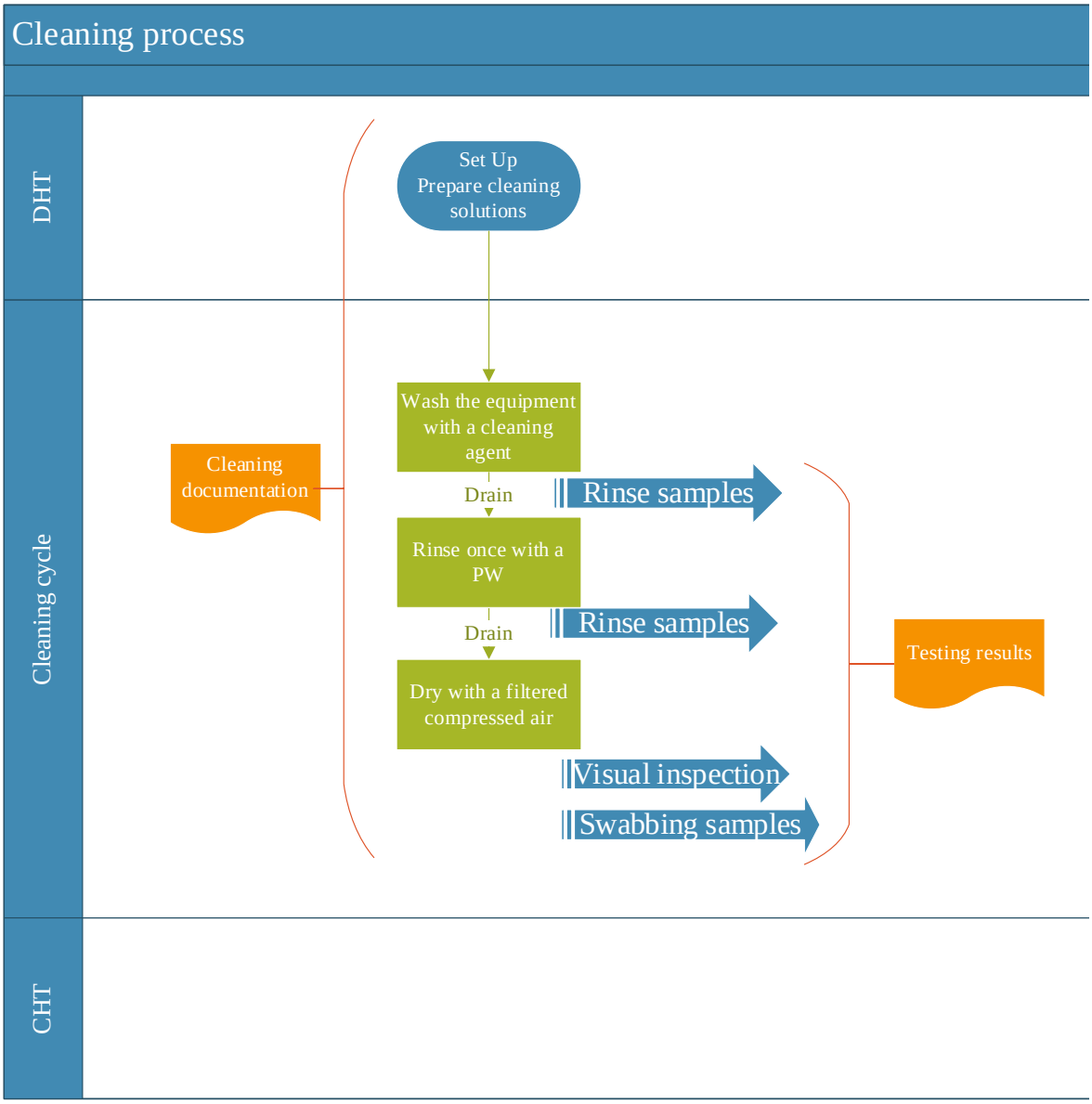


Fig. 14. Equipment cleaning process for cleaning validation project “Y” flow

Additional control were included in the validation of equipment:

- establishment of the equipment DHT;
- establishment of the equipment CHT;
- process requirements with respect to hold times;
- equipment reiquirements with respect to hold times;
- any justifications or assumptions made.

The purpose of the cleaning validation was outlined in the project "Y" protocol and it is to define the testing procedures and acceptance criteria to be used to achieve satisfactory verification that manufacturing equipment is clean and ready for use in routine production. Within the predetermined time window and campaign length.

Protocol also outlined the main parts of the project, which is:

- verifying that the cleaning cycle was run within the DHT and CHT parameters;
- verifying the equipment setting and parameters;
- verifying cycle parameters;
- samples testing against the predetermined acceptance criteria;
- completing three concecutive runs of the cleaning process.

2.3.4. Sampling methods and sampling location of the cleaning validation project "Y"

The sampling methods and sampling locations, shown in the Fig. 15, were determined under the cleaning development studies and also indicated in the cleaning validation project protocol. These locations have been selected due to the design of the fluid path, the orientation and drainability of the equipment, and the contamination risk due to the sampling process itself.

The sampling used during the project are visual inspection, swab sampling and rinse sampling. The methods were selected based on the residue being measured, the residue limit and equipment being sampled and is provided in the Table 2.

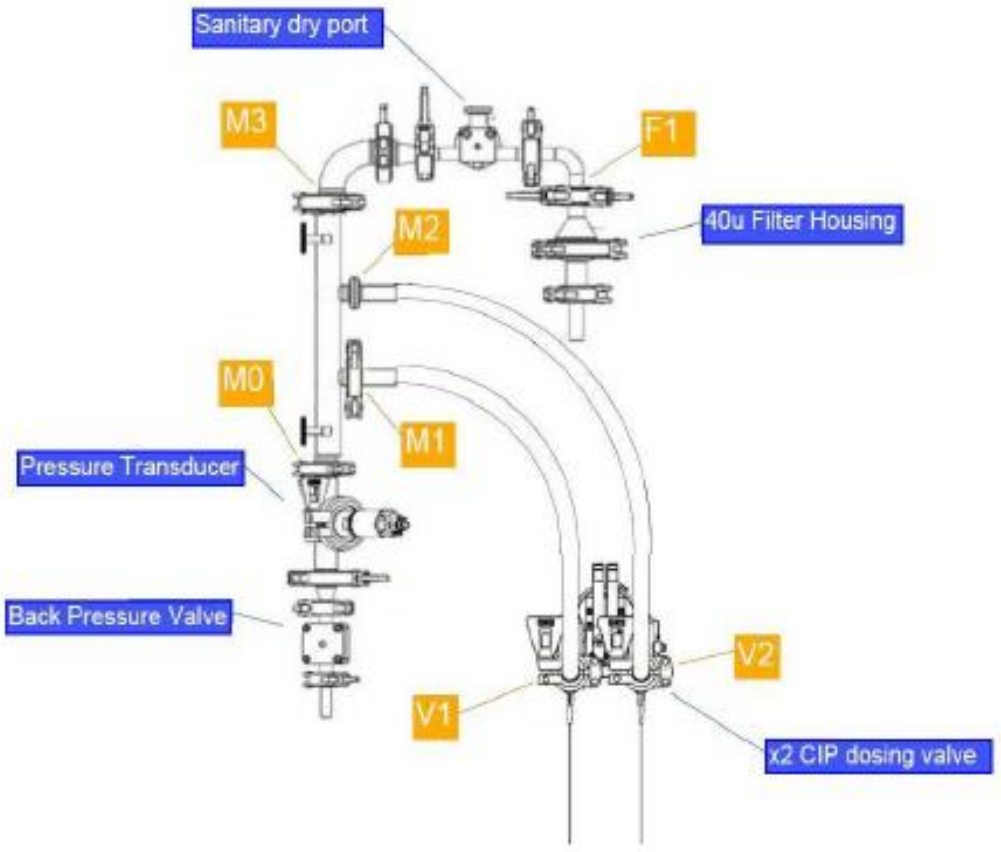


Fig. 15. Swab sampling locations

Four tests were completed during the cleaning validation project "Y" – two of the tests were performed in-house and two were sent to the outside supplier for completion, refer to Table 2. Analytical methods for detection of the residues of concerns were validated. All of the analytical testing methods used during this cleaning validation protocol have been selected based on the nature of the expected residue after the cleaning process is completed. The residue detection methods used for this protocol included both – specific and non-specific residue detection methods:

- HPLC is the specific method;
- Conductivity is the non-specific residue detection testing method.

As it can be seen from the Table 2, HPLC and conductitivy testing methods must be performed outside the manufacturing facility, as manufacturer does not have validated testing methods and required equipment in-house to complete them. The testing was completed outside Lithuania, which introduced the additional risks to the succession of the protocol. Both test methods must be performed on the samples in certain time window from the sampling time. Later in the project the possibility and costs to transfer those methods will assessed.

Table 2. Testing methods and testing locations

Test method	**Testing location**
Total viable count (TVC)	In-house
Conductivity testing	Outside purchased services
High Performance Liquid Chromatography (HPLC)	Outside purchased services
Bioburden testing	In-house

The external supplier who provides the testing services to the manufacturer "X" have validated test methods. The supplier is also qualified and approved as per internal procedures, specifications requirements and expectations, and audited once a year. All audits were passed with no major findings, so the conclusion was made that the supplier is reliable to complete the testing required and provide the well-grounded results.

The in-house performed test methods were also validated under the different protocols to be reliable. During validation of those testing methods certain standards must be relied on.

Manufacturing facility/environment must comply with:

- EN ISO 13485 Medical Devices – Quality Management Systems – Requirements for regulatory purposes.

Testing methods must comply with:

- Ph.eur.2.6.12. – Microbiological examination of non-sterile products (total viable aerobic count);
- USP 42 – NF 37 General Chapters: <61> Microbiological examination of non-sterile products: microbial enumeration tests;
- USP 42 – NF 37 General Chapters: <1227> Validation of Microbial Recovery from Pharmacopeia Articles.

The tests methods validation protocols were executed successfully, and no deviations were recorded. The conclusion was made that the samples have no effect on routine testing, therefore, compendial

methods are suitable to be used for cleaning validation at internal laboratory and there were no additional steps required to neutralize any antimicrobial activity.

2.3.5. Cleaning validation of the project “Y” discussion

Cleaning validation protocol was performed on required time window as planned; those cleans were ran prior to the excetutiom to the created protocols on the equipment module located in the maufacturers “X” cleanroom.

Prior to each study, a cleaning was iniated according to the created procedures, and details of this was recorded. The cleaning studies were iniated individually confirm that the cleaning processes associated with the cleaning of the equipment are capable of cleaning to the required specifications.

The CHT protocol was executed with one deviation, which will be discussed below. CHT study was executed for a duration of 16 days. The samples were taken on the required days. All testing results indicates that the chemical residues from the cleaning agent do not remain present as no residue was detected in the samples by HPLC and conductivity testing methods. However, the HPLC analysis was performed with the deviation, as the samples reached the external laboratory outside the required time window for sample stability. In the Fig. 16 those results are provided as for informational purposes only. As a result, it was relied upon the comductivity testing results to be assured that no residue of the cleaning agent was present in the rinse sample. Rinse samples for TVC and swab samples were taken for microbiology analysis and tested by sterilization specialist in manufacturer “X” plant. Final rinse samples from the cleaning cycle process indicate that the cleaning cycle was successful in reducing equipment bioburden level below the required limit of ≤100 cfu/ml with a result of <1 cfu/ml. Swab samples taken at the end of the cleaning process also indicate that the cleaning cycle was successful in reducing equipment bioburden level below the required limit of ≤100 cfu/ml with a result of 6 cfu/ml.

The results of the testing confirmed that the CHT study and cleaning cycle was successful.

Machine	Parameter	Test Method	Sample Description	Hypothesis	Result	Conclusion
[redacted]	Conductivity (Stage 1)	As per USP <645> and [redacted]	Detergent Rinse Sample A	For Information Only	16730.0 µS/cm	Accept
	HPLC	[redacted]	Detergent Rinse Sample A	For Information Only	6890ppm	Accept
	Conductivity (Stage 1)	As per USP <645> and [redacted]	Rinse Sample B	≤1.0 µS/cm @ 15°C	1.1 µS/cm	Proceed to Stage 2
	Conductivity (Stage 2)	As per USP <645> and [redacted]	Rinse sample B	CT5 – CT0 <0.1 µS/cm CT5 ≤ 2.1 µS/cm	CT5 – CT0 = 0.0 µS/cm CT5 = 1.9 µS/cm	Accept
	HPLC	[redacted]	Rinse Sample B	<328.53ppm	<LOD (not detected)	For information only**

Fig. 16. Chemical tetsing results with a deviation

The DHT protocol was executed with two deviations. Rinse samples for conductivity and HPLC were taken for chemistry analysis and sent to external laboratory. Chemical analysis of the rinse sample by HPLC indicated that detergent residues did not remain as no detergent residues detected in the rinse samples when analyzed, however, the HPLC analysis was performed past stability both times the

samples were sent to be tested. Chemical analysis of the rinse samples by conductivity indicated that residues did not remain as no residues were detected in the rinse sample when analyzed. Rinse samples for TVC and swab samples were taken for microbiology analysis and tested by trained specialist internally. Also, visual inspection was completed, the results are shown in the Fig. 17. Based on the below findings it can be concluded that full fluid path surface coverage can be achieved for cleaning with cleaning solutions, no dead spots or air locks were identified. The system subsequent to drying study is deemed to be self-draining and capable of being sufficiently dried using the predetermined CIP drying sequence. The example images of Riboflavin coverage Before & After completion of wetting cycle is presented in the Fig. 18, the difference between clean and dirty equipment is clearly visible.

Sample point ID	Result (Pass / Fail)	
	Free from florescent residue	Suitably dry & residue free
V1	Pass	Pass
V2	Pass	Pass
M0	Pass	Pass
M0	Pass	Pass
M1	Pass	Pass
M3	Pass	Pass
F1	Pass	Pass

Fig. 17. Visual inspection results

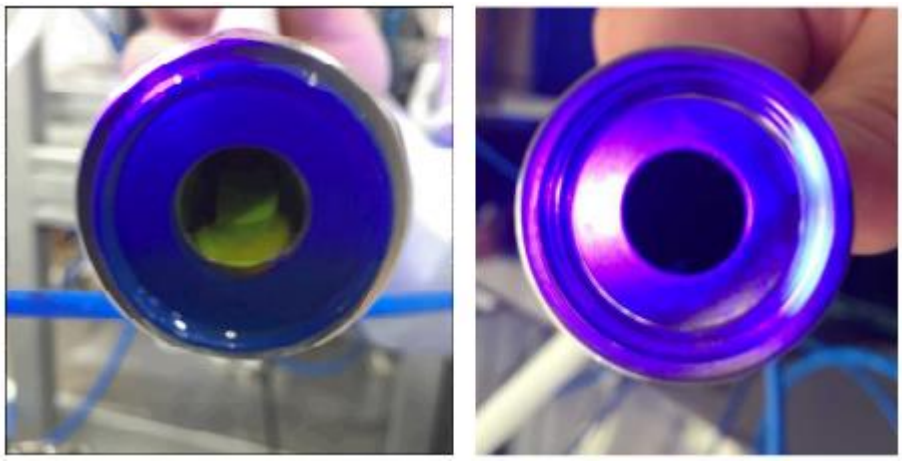


Fig. 18. Example images of Riboflavin coverage Before & After completion of wetting cycle

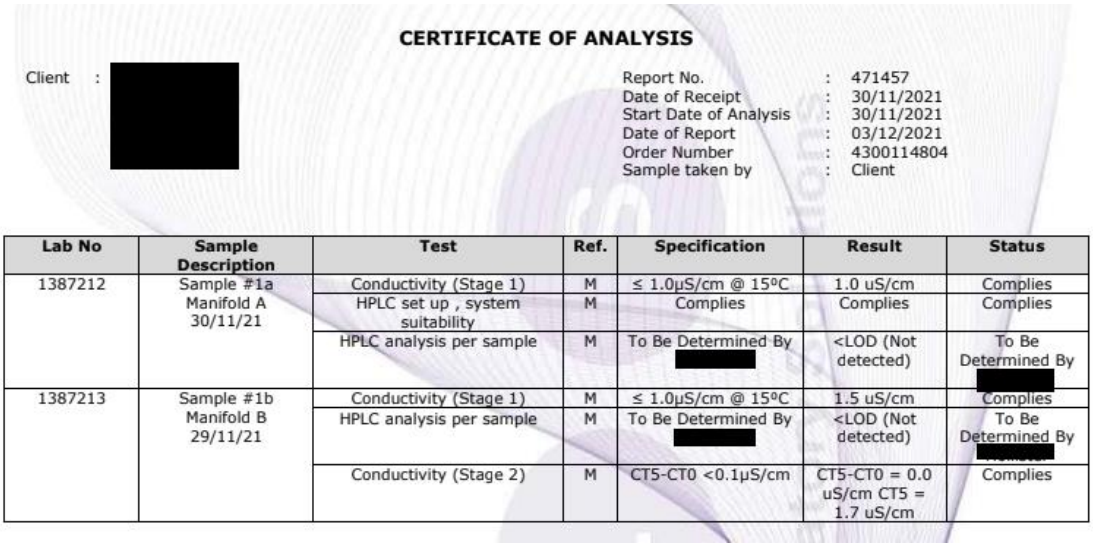
The results of all required testing confirmed that the DHT study and cleaning cycle was successful even with the deviations that occurred.

Cleaning Validation protocol consisted of consecutive three runs:

- cleaning Validation Run 1 was executed for a period of 3 days:

Rinse samples for conductivity and HPLC were taken for chemistry analysis and sent to external laboratory. The results provided by the external supplier and shown in the Fig. 19 indicated successful

removal of cleaning agent as no residue was found present in the samples. The acceptance limits were provided by the manufacturer "X" based on cleaning development studies.



CERTIFICATE OF ANALYSIS

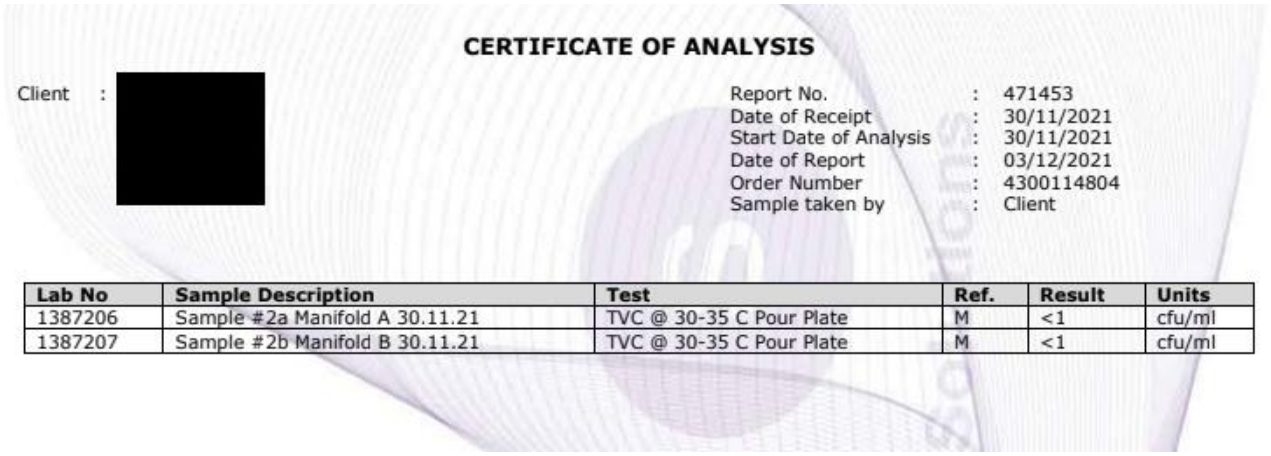
Client : [redacted]

Report No. : 471457
Date of Receipt : 30/11/2021
Start Date of Analysis : 30/11/2021
Date of Report : 03/12/2021
Order Number : 4300114804
Sample taken by : Client

Lab No	Sample Description	Test	Ref.	Specification	Result	Status
1387212	Sample #1a Manifold A 30/11/21	Conductivity (Stage 1)	M	≤ 1.0µS/cm @ 15ºC	1.0 uS/cm	Complies
		HPLC set up , system suitability	M	Complies	Complies	Complies
		HPLC analysis per sample	M	To Be Determined By [redacted]	<LOD (Not detected)	To Be Determined By [redacted]
1387213	Sample #1b Manifold B 29/11/21	Conductivity (Stage 1)	M	≤ 1.0µS/cm @ 15ºC	1.5 uS/cm	Complies
		HPLC analysis per sample	M	To Be Determined By [redacted]	<LOD (Not detected)	To Be Determined By [redacted]
		Conductivity (Stage 2)	M	CT5-CT0 <0.1µS/cm	CT5-CT0 = 0.0 uS/cm CT5 = 1.7 uS/cm	Complies

Fig. 19. Results of HPLC and conductivity testing

Swab and rinse samples for TVC testing taken at the end of the cleaning process also indicated that the cleaning cycle was successful in reducing equipment bioburden level below the required limit. As shown in the Fig. 20 results for rinse samples were less than 1 colonies forming units per milliliter.



CERTIFICATE OF ANALYSIS

Client : [redacted]

Report No. : 471453
Date of Receipt : 30/11/2021
Start Date of Analysis : 30/11/2021
Date of Report : 03/12/2021
Order Number : 4300114804
Sample taken by : Client

Lab No	Sample Description	Test	Ref.	Result	Units
1387206	Sample #2a Manifold A 30.11.21	TVC @ 30-35 C Pour Plate	M	<1	cfu/ml
1387207	Sample #2b Manifold B 30.11.21	TVC @ 30-35 C Pour Plate	M	<1	cfu/ml

Fig. 20. Total viable count results

- cleaning Validation Run 2 was executed for a period of 7 days:

Cleaning validation Run 2 was executed as a part of DHT study protocol. On day 7 of the study a sample of Hydration Solution was taken from the 25 L drum for control purposes. Results were below the required limit of ≤100 cfu/ml with a result of 20 cfu/ml. A rinse sample of Hydration Solution was taken from nozzles V1 and V2. Results were below the required limit of ≤100 cfu/ml with a result of 14 cfu/ml for V1 and 13 cfu/ml for V2. Swab samples were taken from V1, V2, M0, M1, M2, M3, F1. Results were below the required limit of ≤100 cfu/ml with a result of 11 cfu/ml. More details and results were discussed earlier.

- cleaning Validation Run 3 was executed for a period of 5 days:

The cleaning validation protocol Run 3 was completed successfully. As before, rinse samples were sent to the external laboratory for HPLC and conductivity testing. No chemical residues were found during the studies. Samples for the microbiological testing also showed positive results, which was below required limit.

As a part of cleaning validation study campaign length establishment study was excuted. The purpose of this study was to establish the number of batches/lots (Campaign) that can be processed on the equipment before it's necessary to perform a cleaning cycle in routine production. Along with DHT and CHT, "Campaign Lenght", is one of the parameters required for cleaning validation.

For this protocol few consecutive lots were produced on the equipment for a three-day period, prior the protocol start cleaning process was completed. Samples from each lot were tested in-house for TVC and recorded no microbiological growth. This campaign length study was run as a single run as it was deemed a low risk based on its history of passing cleaning cycles throughout the cleaning qualification.

All equipment used in analytical testing of samples for these studies (CHT, DHT, Campaign length, cleaning validation) is in the control of external labs and was calibrated as per their procedures.

These results proved that the cleaning validation project was performed successfully, and the equipment cleaning process is verified and validated.

As a result, after the successful project, standard work instructions, cleaning routine monitoring, and maintenance procedures were created. All required documentation package was created and approved as per requirements and uploaded to the internal documents management system.

3. Cost of conducting the indirect testing in external laboratory versus in-house

Cleaning validation at medical devices manufacturing company "X" required the testing outside the facility. The decision to use outside purchased services was made for convenience and velocity as the contracting local laboratory or getting ready to perform the testing in-house would have been postponed the start of the project significantly.

As outside testing facility is outside Lithuania, located in Ireland, not only the services pricing is under consideration, also transporting the samples in the controlled environment in fixated time window must be taken in account. As a result, in this part of the project, I will research the possibilities on getting ready to conduct HPLC testing internally by buying the required testing equipment, validating it and validating the testing method itself.

3.1. Price of the testing in external laboratory

Each cleaning validation run produces two samples, which are needed to be tested using HPLC testing method. The samples must be kept in refrigerated environment (2 – 8 ℃) until it will be tested and tested in the 48 hour window. If tested later, samples are considered to be past their stability, as the cleaning agent in the samples starts to degrade and the results are invalid. As it can be seen from the **Table 3** the total price for transportaing and testing the samples by HPLC testing method costs 2210.00 € per one run. Please be noted that prices specified in the Table 3 is averaged, as for example transportating costs may vary depending on many different variables.

Table 3. The prices for services completed

Service	**Price, €**
Transportation to the external laboratory	500.00
Temperature data loggers	30.00
Equipment set up in the laboratory	1860.00
Conducting testing for two samples	240.00
Report	80.00
Total	**2210.00**

Also, if the samples are delivered later than expected and supplier must test them later than planned additional costs of keeping the equipment set up may be charged.

3.2. Price of the testing in-house

Acccording to the research the price of the HPLC with UV detection machine, model BK-LCI5100, is 13683.48 €/unit [31]. This model would satisfy all requirements for the test method and any other future aspirations. The medical devices manufacturer "X" would be satisfied by having one unit in the facility. Installation and service after the purchase must taken under consideration. The testing unit will be requiring the qualification and yearly calibration services.

Equipment qualification is a formal process that provides documented evidence that an instrument is fit for its intended use and kept in a state of maintenance and calibration consistent with its use [32]. As any other piece of equipment, the HPLC unit will require DQ, IQ, OQ and PQ. The DQ part will be completed in vendor's facility, but the other parts will be completed internally when equipment arrives. The qualification plan must be created. The example of the qualification plan and required resources is provided in the Fig. 22 and Fig. 21.

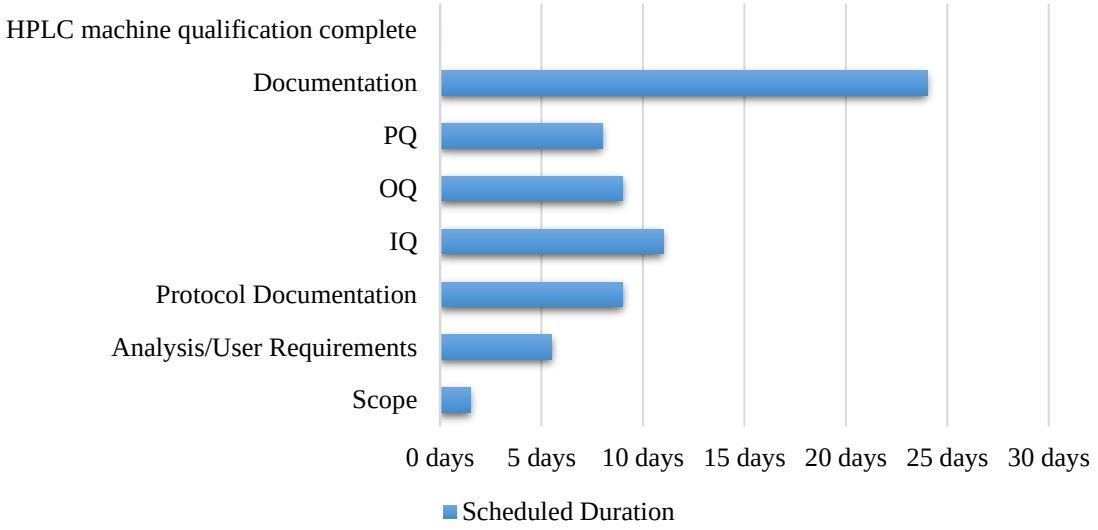


Fig. 21. HPLC machine qualification project duration overlook

The entire HPLC machine qualification project will take up to 64 days, as can be seen from the Fig. 23, if there will be no delays. It will require Validation team supervisor, Quality Engineer, and Quality control technician from the internal resources (as per Fig. 22) and the supplier's representative to support the entire project. Detailed qualification plan is provided in the Fig. 23, Fig. 24 and Fig. 25 below.

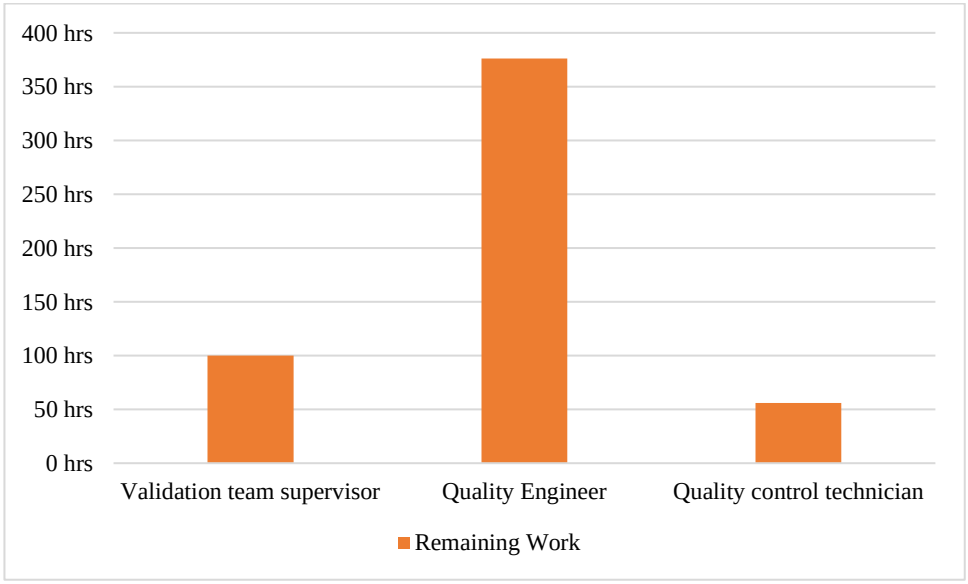


Fig. 22. Resources work hours for the project

Task Name	Duration	Start	Finish	Resource Names
HPLC machine qualification	**64 days**	**Mon 04/04/22**	**Thu 30/06/22**	
Scope	**1.5 days**	**Mon 04/04/22**	**Tue 05/04/22**	
Determine project scope	4 hrs	Mon 04/04/22	Mon 04/04/22	Validation team supervisor
Secure core resources	1 day	Mon 04/04/22	Tue 05/04/22	Validation team supervisor
Scope complete	0 days	Tue 05/04/22	Tue 05/04/22	
Analysis/User Requirements	**5.5 days**	**Mon 04/04/22**	**Mon 11/04/22**	
Draft PVP including SW Plan	4 days	Tue 05/04/22	Mon 11/04/22	Validation team supervisor
Software risk assessment	3 days	Mon 04/04/22	Wed 06/04/22	Supplier
Analysis complete	0 days	Mon 11/04/22	Mon 11/04/22	
Protocol Documentation	**9 days**	**Thu 07/04/22**	**Tue 19/04/22**	
IQ protocol draft	3 days	Thu 07/04/22	Mon 11/04/22	Quality Engineer
OQ protocol draft	3 days	Tue 12/04/22	Thu 14/04/22	Quality Engineer
PQ protocol draft	3 days	Fri 15/04/22	Tue 19/04/22	Quality Engineer
Documentation ready	0 days	Tue 19/04/22	Tue 19/04/22	
IQ	**11 days**	**Wed 20/04/22**	**Wed 04/05/22**	
IQ protocol preparation	2 days	Wed 20/04/22	Thu 21/04/22	Quality Engineer
IQ protocol on internal documents system	1 day	Fri 22/04/22	Fri 22/04/22	Validation team supervisor
IQ execution	3 days	Mon 25/04/22	Wed 27/04/22	Quality control technician, Quality Engineer
IQ report	5 days	Thu 28/04/22	Wed 04/05/22	Quality Engineer
IQ complete	0 days	Wed 04/05/22	Wed 04/05/22	

Fig. 23. Detailed HPLC machine qualification plan, Part I

Task Name	Duration	Start	Finish	Resource Names
OQ	**9 days**	**Thu 05/05/22**	**Tue 17/05/22**	
OQ protocol preparation final	2 days	Thu 05/05/22	Fri 06/05/22	Quality Engineer
OQ protocol on internal documents system	1 day	Mon 09/05/22	Mon 09/05/22	Validation team supervisor
OQ execution	2 days	Tue 10/05/22	Wed 11/05/22	Quality control technician, Quality Engineer
OQ report	4 days	Thu 12/05/22	Tue 17/05/22	Quality Engineer
OQ complete	0 days	Tue 17/05/22	Tue 17/05/22	
PQ	**8 days**	**Wed 18/05/22**	**Fri 27/05/22**	
PQ protocol preparation	2 days	Wed 18/05/22	Thu 19/05/22	Quality Engineer
PQ protocol on Qumas	1 day	Fri 20/05/22	Fri 20/05/22	Validation team supervisor
PQ execution	2 days	Mon 23/05/22	Tue 24/05/22	Quality control technician, Quality Engineer
PQ report	3 days	Wed 25/05/22	Fri 27/05/22	Quality Engineer
PQ complete	0 days	Fri 27/05/22	Fri 27/05/22	

Fig. 24. Detailed HPLC machine qualification plan, Part II

Task Name	Duration	Start	Finish	Resource Names
Documentation	**24 days**	**Mon 30/05/22**	**Thu 30/06/22**	
Develop Help specification	5 days	Mon 30/05/22	Fri 03/06/22	Supplier
Review Help documentation	2 days	Mon 06/06/22	Tue 07/06/22	Quality Engineer, Validation team supervisor
Incorporate Help documentation feedback	2 days	Wed 08/06/22	Thu 09/06/22	Supplier
Develop user manuals specifications	5 days	Mon 30/05/22	Fri 03/06/22	Supplier
Develop user manuals	2 wks	Mon 06/06/22	Fri 24/06/22	Supplier,Quality Engineer
Review all user documentation	2 days	Mon 27/06/22	Tue 28/06/22	Quality Engineer, Validation team supervisor
Incorporate user documentation feedback	2 days	Wed 29/06/22	Thu 30/06/22	Supplier
Documentation complete	0 days	Thu 30/06/22	Thu 30/06/22	
HPLC machine qualification complete	0 days	Thu 30/06/22	Thu 30/06/22	Validation team supervisor

Fig. 25. Detailed HPLC machine qualification plan, Part III

The most expensive human resource would be Quality Engineer, as this resource is required to perform many important tasks and also work overtime. Also, supplier has a service fee for the support during qualification. The cost of the HPLC machine qualification per task was reviewed also. The value for documentation part is the biggest, as it consumes a lot of time and resources. The overall cost per resource is provided in the Fig. 26 and overall cost per tas kis provided in the Table 4.

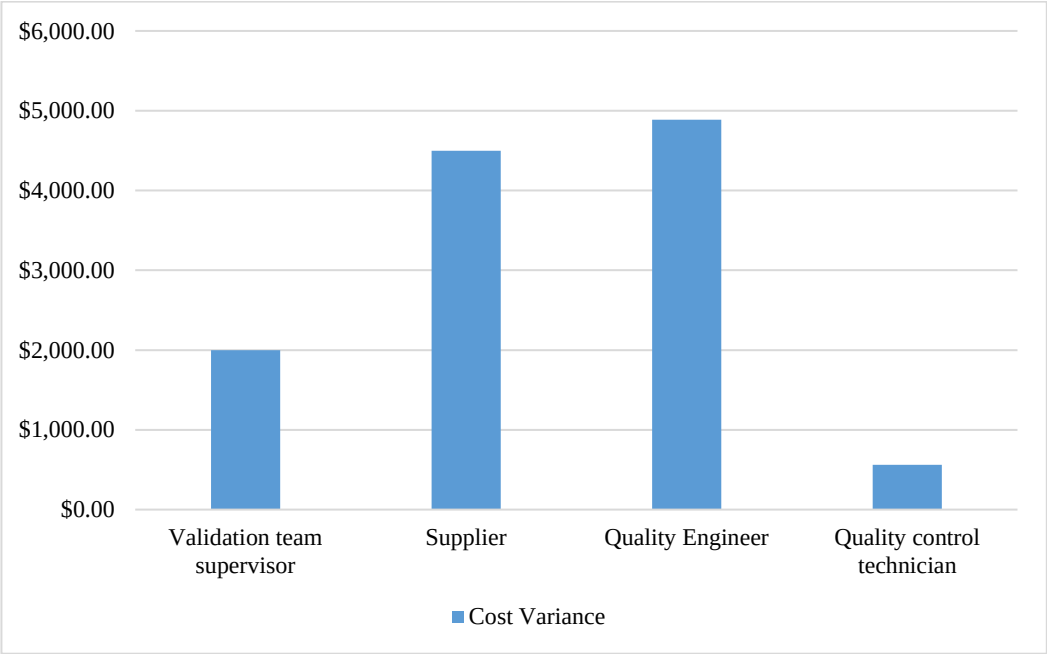


Fig. 26. Cost per resource

Table 4. Cost per task

Name	**Cost**, €
Scope	240.00
Analysis/User Requirements	640.00
Protocol Documentation	936.00
IQ	1,440.00
OQ	1,152.00
PQ	1,048.00
Documentation	6,492.00
HPLC machine qualification complete	0.00
Total	11,708.00

The complete cost of the HPLC machine qualification is 25,391.48 € and it is provided in the Table 5.

Table 5. Cost per qualification

Name	**Cost, €**
Cost per qualification	11,708.00
Cost of the HPLC machine	13,683.48
Total	25,391.48

During cleaning validation services of the external testing laboratory was used approximatly 15 times, which equals to 33,150.00 €. Due to time constraints and doubts that the new testing machine and test method will be useful in the future, it was decided to choose the more expensive option.

Conclusions

1. In the medical devices industry, it is well recognized that the manufacturing lines, equipment, and area should be kept as clean as possible. The most requirements for cleaning validation regulated by the appropriate standards and regulatories, such as GMP, FDA and ISO.
2. Medical devices manufacturer's "X" Cleaning Development, Cleaning Verification & Cleaning Validation Procedures clearly indicates how cleaning of the equipment should be validated, the types of cleaning studies required prior to use of the equipment for the routine manufacturing of medical device, roles and responsibilities and documentation requirements.
3. Medical devices manufacturing company "X" has strict and clear procedures how to perform cleaning validation, the documentation is clear and ready in timely manner. Manufacturer "X" requires to provide the documentation how validation is completed, its results and deviations. Every document is uploaded to the internal documents management system and is approved by dedicated team.
4. Cleaning validation of the project "Y" was successful. As a result, standard work instructions, cleaning routine monitoring, and maintenance procedures were created. All required documentation package was created and approved as per requirements and uploaded to the internal documents management system. During the project some deviations occurred, but it was resolved and was insignificant to the success of the project.
5. The cost of conducting the indirect testing in external laboratory versus in-house was evaluated. Conducting the testing in an outside laboratory cost 33,150.00 € per whole cleaning validation, while qualifying the HPLC machine and test method internally cost 25,391.48 €. But after evaluating time constraints and risk not to use the machine after the studies were done, it was decided to use the outside purchased services.

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