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Process Validation of manufacturing process of solution of NaOH 32% w/w according to EU GMP Part II.

Validación del proceso de producción de la solución de NaOH 32% p/p según la normativa EU GMP Parte II.

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A David Carreras i Viñas, per la seva ajuda, dedicació i implicació per guiar-me, aconsellar-me i confiar en mi per a la realització d'aquest projecte.

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A la meva família i amics pel seu suport.

CONTENTS

SUMMARY

One of the main quality requirements for GMP regulations is the process validation in order to guarantee the consumer satisfaction. Therefore, the manufacturers have to control the critical points of the manufacturing process through the qualification and validation during the product's life cycle.

The intention is to show what is the process validation and all the factors that are involved in it as well as the importance of the process validation to demonstrate that a manufacturing process is consistent and produces a product which complies with predefined specifications. For that purpose, participation on the process validation of the manufacturing of NaOH 32% w/w solution GMP has been performed. The process validation of NaOH 32% w/w GMP started in December 2017 and its ending is scheduled at the end of the 2018.

Firstly, the performance of a risk assessment with the establishment of the possible risks of the process through the detailed study of the manufacturing process of NaOH 32% GMP. The identified risks have allowed the creation of cleaning and operating procedures, and the development of corrective actions to reduce the possibilities of having quality or safety issues.

Secondly, the engagement in the equipment qualification of vessel. The tasks involved in it have been consisted in create and complete the documentation of Design Qualification, Installation Qualification, Operational Qualification and Performance Qualification.

Thirdly, due to the fact that NaOH 32% GMP is manufactured in multiproduct plant, the determination of Barium Hydroxide 8-Hydrate as the "worst case" through the performance of the risk analysis based on the solubility, toxicity and the hardest to clean of whole the products manufactured in the equipment in order to validate the cleaning procedure suggested.

Fourthly, some improvements and recommendations has been suggested during this project as a result of the current process study performed to elaborate the Product Quality Review such

as the approach of water system qualification, the reconsideration of the products specifications and the application of a tool to collect the information obtained from the product and the process.

To achieve these tasks, it has been necessary to gaining knowledge and understanding about Good Manufacturing Practices (cGMP) and the concepts of validation. This knowledge has been based on guidelines and regulations of ICH (*International Council for Harmonisation*), EMEA (*European Medicines Agency*) and FDA (*Food and Drug Administration*).

Keywords: GMP, Process Validation

RESUMEN

Uno de los principales requisitos de calidad bajo la normativa GMP (*Good Manufacturing Practices*) es la validación de procesos para garantizar la satisfacción del consumidor. Así pues, los fabricantes deben controlar los aspectos críticos de los procesos de fabricación mediante la cualificación y validación a lo largo de la vida del producto.

Se pretende mostrar en qué consiste una validación de proceso y todos los factores que intervienen en ella, así como también su relevancia para demostrar que un proceso productivo es consistente y produce un producto que cumple con las especificaciones predeterminadas. Para ello, se ha participado en la validación del proceso productivo de la disolución de NaOH 32% p/p GMP. La validación del proceso empezó en diciembre del 2017 y está planeado terminarla a finales del 2018.Se debe mencionar que dicha validación ya estaba en curso, y que, por lo tanto, partes de ella ya habían sido realizadas antes de la incorporación de este proyecto. Aun así, tareas de la validación han quedado pendientes de realizar.

En primer lugar, se ha realizado una evaluación de los riesgos del proceso productivo. A través de un análisis de riesgos, se han identificado los posibles riesgos del proceso a mitigar. Su evaluación ha llevado a la creación de procedimientos de operación/limpieza y al desarrollo de acciones correctivas con el objetivo de minimizar riesgos del proceso.

En segundo lugar, la cualificación del equipo R-127 (vessel) se ha realizado mediante la elaboración de documentos pertinentes a las partes de Cualificación de Diseño, Cualificación de la Instalación, Cualificación Operacional y Cualificación del Desempeño.

En tercer lugar, debido a que la fabricación de la disolución de NaOH 32% p/p GMP se realiza en una planta multiproducto, para validar el procedimiento de limpieza propuesto se ha determinado el Bario Hidróxido 8-Hidrato como el “peor caso” a través de un análisis de riesgos

basado en la solubilidad, toxicidad y dificultad de limpieza de todos los productos que se fabrican en dicho equipo.

Por último, se han planteado diferentes recomendaciones y propuestas de mejora a través del estudio del proceso y la realización del Product Quality Review. Éstas mejoras son relacionadas con la cualificación del sistema de agua de refrigeración, la reconsideración de las especificaciones de los productos que participan en el proceso y la aplicación de mejoras en el registro de los tiempos de trabajo.

Para hacer posible la realización de todas estas tareas, ha sido necesario un conocimiento y orientación sobre las Buenas Prácticas de Fabricación para encaminar la validación. Este conocimiento se ha basado en las guías y normativas que pertenecen a ICH (*International Council for Harmonisation*), EMEA (*European Medicines Agency*) y FDA (*Food and Drug Administration*).

Palabras clave: GMP, Validación de Proceso

1. INTRODUCTION

The project addresses the validation process of solution of NaOH 32% w/w GMP in an actual production plant. The company is devoted to the development, manufacture and commercialization of inorganic salts, laboratory reagents and excipients for pharmaceutical, veterinary and food industry. Its production plant has available facilities which enable to carry out the production of different products with different amounts of them.

In general, the products are classified in two main groups depending on the strictness during the production process. As a result, the products are distinguished between those manufactured under ISO regulations or GMP regulations.

The ISO regulations are those which are produced according to ISO regulations. The regulations meet those products necessary requirements that enable the manufacturer to commercialize its product, but nevertheless it does not give the importance to some factors that take part in a production process. Nowadays, the concept of *Good Manufacturing Practices* (GMP) is becoming more popular and gaining strength rapidly. These regulations are much more specific in production processes and they focuse on having all the process under control. The main objective is to ensure the manufacturing of the products by a consistent and controlled production process with strict quality standards according to the current legislation. In some way, GMP regulations cover areas as validation process, personnel qualification or cleaning validation. Moreover, special emphasis is placed in data integrity and well-documented stages of the processes because they provide the traceability of products and enable the withdrawal of the product in case of nonconformity.

1.1 PROCESS VALIDATION

1.1.1 Understanding of Process Validation under ISO or GMP regulations

One of the main issues of current GMP is validation process. In comparison with ISO the process validation has different meanings. ISO and GMP have different points of view on the concept of validation of the process. On one hand, ISO regulation considers that the process should be validated if the final product cannot be verified through follow-up activities or subsequent measurements. On the other hand, GMP rules are say the opposite. It is considered that all the process must be validated to guarantee that the process, method or specific system can reproduce repetitively the same result in compliance with acceptance criteria. In broad strokes, it comes with the idea to design and control a process to assure that in-process materials and the final product meet the predetermined quality requirement in an accurate way. Besides, the cGMP incorporates sampling and in-process controls to develop production processes and even to well-designed process to assure the quality of the product. The sampling methods and in-process controls are provided with established procedures following the norms of cGMP regulations. In addition, facilities must have a suitable size, which is well designed and located in the right place to ensure a proper manufacturation.

1.1.2 General considerations of Process Validation

The product quality is related to the validation of its manufacturing process. An effective validation process helps to assuring its quality. The basic principles of a validation process are the following:

1. Quality, safety and efficacy are designed into the product. (1)
2. Quality must be guaranteed throughout the process. (1)
3. Every step of the manufacturing process is controlled to make sure that the quality of the final product is within specified quality attributes. (1)

So, Process Validation is defined as a collection and evaluation of data from the process operated within established parameters, which set scientific evidence that a process is capable of consistently delivering quality product. The main objective is to demonstrate the consistency of a production process and the robustness of the knowledge about the process. Different types of validation process are shown in the table 1:

Table 1. Types of Validation [2]

TYPES OF VALIDATION	
Retrospective Validation	Is applied to an existing process with historical data. It consists of compiling an amount of information from accumulated results of all the manufactured batches. The analysis of critical points in the manufacturing process should be done.
Prospective Validation	Normally, prospective validation is applied to new products or APIs. The purpose of this method is to validate a process based on previously planned activities.
Concurrent Validation	Concurrent validation is applied in normal production. The variations have no influence in the whole manufacturing process. Nevertheless, the experience and understanding of the process as well as the documentation and approbation before starting the validation are the main requirements.

1.1.3 Stages of Process Validation

The process validation has different activities that should take place during the lifecycle of the product and can be classified into the next stages as shown in table 2:

Table 2. Stages of process validation and definitions [1]

STAGES OF PROCESS VALIDATION	
Process Design	Building and capturing knowledge and understanding of the process and establishing a strategy of process control.
Process Qualification	Design of facility or Qualification of utilities and equipment Process Performance Qualification (PPQ) PPQ Protocol and PPQ Execution Report
Continued Process Verification	Ensuring the validated state

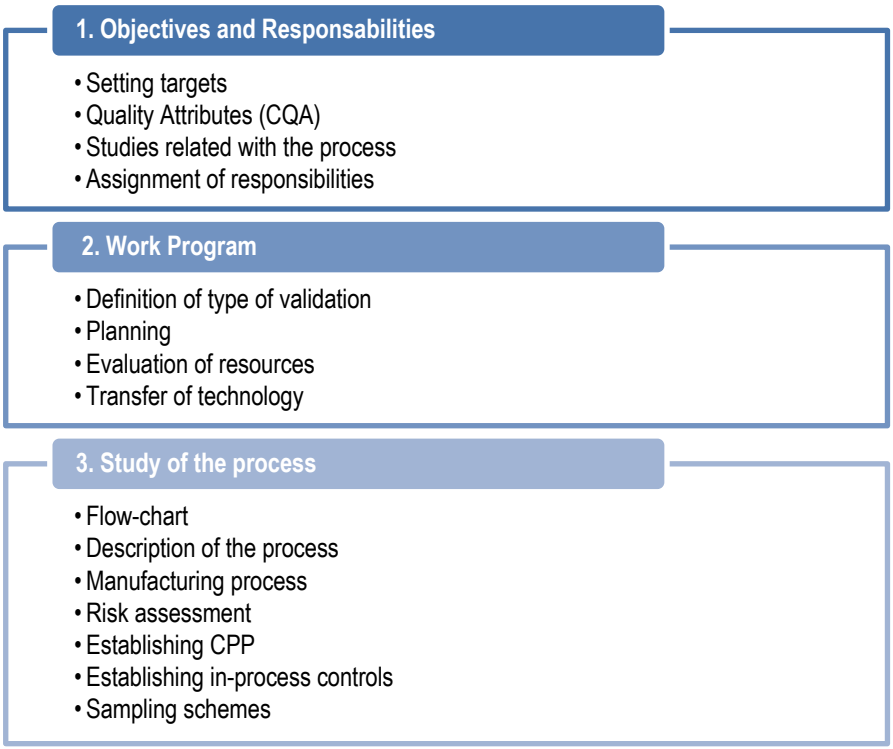
In the first step of process validation, *Process Design*, the production process is designed based on knowledge and experience from development, scale-up activities and with aid of technology transfer. The cGMP is not necessarily followed in this phase of validation instead of the next steps (Process Qualification and Continued Process Verification) in which products must be manufactured according to these regulations. Basically, the two main concepts related to this stage are Design of Experiment (DOE) and Quality by Design (QbD). The first one (DOE), has useful studies to develop knowledge of the process making a relation between the variable inputs and resulting outputs. The second one, Quality By Design refers to the idea of introducing the quality into the product since its first steps. Studying all possible parameters that can affect to the quality attributes of the final product – called Critical Process Parameters, CPP - and consequently, starting a design of manufacturing process considering them. QbD is a good way to provide better designed predictions. (1)

In *Process Qualification*, the process design is evaluated to determine if the manufacturing process is reproducible. In this stage the cGMP procedures must be followed. The design of facility and qualification of equipment and utilities together with the process performance qualification (PPQ) are done during this phase. On one hand, the main objective of qualify facilities and equipment is to demonstrate that they are suitable for their intended use. So, the activities of qualification can be summed in three aspects: choosing the equipment utilities and construction materials adequately, ensuring that the equipment is build/installed as defined in the design specifications and ensuring that it works as expected. On the other hand, the process performance qualification (PPQ) has to demonstrate and confirm that the process design is being carried out as expected. This objective is achieved with the actual utilities and equipment, trained personnel and with well-written control procedures among others that are summed in PPQ Protocol. PPQ Protocol compiles all the activities related such as the manufacturing conditions, processing limits, data to be collected and sampling plans. When PPQ is executed, a report called PPQ Report should be elaborate. (1)

In *Continued Process Verification*, all the collection and evaluation of product data generated provides necessary information to assure that the process remains in state of control during all the manufacturing process. It brings the opportunity to identify issues and take corrective actions to solve these problems and maintain the validated state. (1)

1.2 PROCEDURE FOR VALIDATE A PROCESS

A Manufacturing Process Validation of a manufacturing process involves different scopes such as cleaning validation, personnel qualification, utilities and equipment qualification, risk assessments and many more activities. Tasks related with the validation of a process must be planned. The overarching document that reflects these tasks is called Validation Master Plan (VMP) [2]. It includes the elaboration of a PPQ document, a document that must be followed to perform a successful validation. In addition, to validate a new or an existing process, the creation of PPQ is an important requirement because it represents the main guidance to manage and organize the process validation where the objectives, responsibilities, procedure to follow and other tasks are defined. The description of the tasks involved in validation process (described in PPQ) are shown in figure 1:



4. Qualification of equipment

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operating Qualification (OQ)
- Performance Qualification (PQ)
- Calibration Plan

5. Water system qualification

- Water specification
- Microbiological tests

6. Cleaning Validation

- Evaluation of products to be cleaned regarding to other products in plant.
- Cleaning procedures
- Cleaning Holding Time and Dirty Holding Time

7. Operating procedure

- Procedures related

8. Control

- Copy of Specifications and Analytical Methods
- Specification and control of water
- Developing analytical methods
- Studing of impurities profile
- Study of degradation and stability program
- Study of the shelf life

9. Qualification of personnel

- Job description
- Continuous training

10. Qualification of suppliers

- Qualified Suppliers list

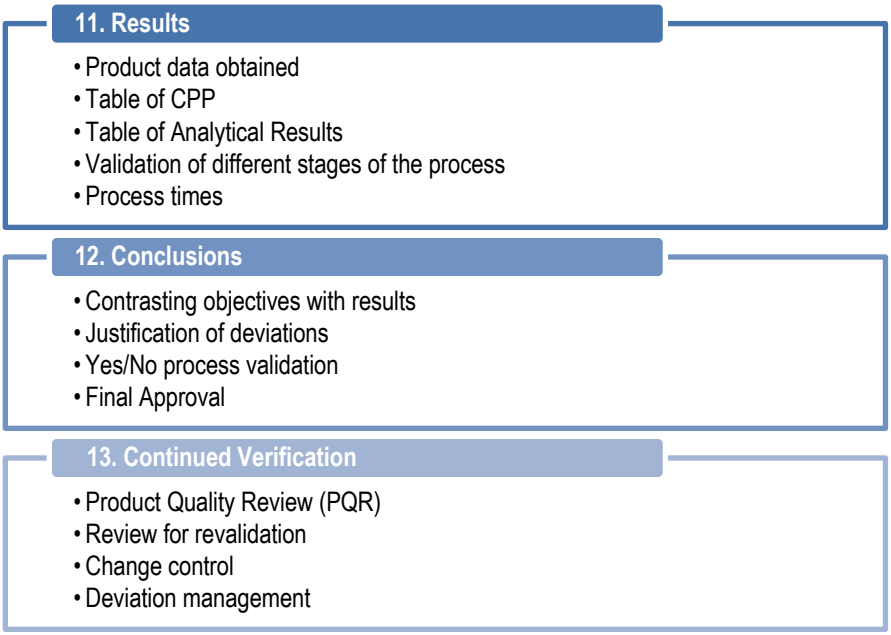


Figure 1. Scheme of the activities in validation process

1.2.1 Objectives and responsabilities

One of the first steps of Process Validation is establishing the starting targets to be achieved in validation and assignment of responsibilities. The tasks should be distributed according to EU-GMP Part II among Quality Unit and Production Unit. [3] Both independent Units should cover all the responsibilities of process validation such as the development of validation plans, validation activities, the authorization and approbation of validation protocols, the evaluation of resources, the evaluation of the personnel training for doing validation activities and the regularly evaluation of validation results.

1.2.2 Work Program

Depending on the production process, product class, historical data of the process and the validation criteria applied among others, the type of validation – retrospective, prospective or current – must be chosen. The activities are organized, and the actual resources together with technology transfer are provided.

1.2.3 Study of the process

Studying the process involves the definition of CPP and the establishment of the in-process controls such as temperature, density or another product features. Consequently, the sampling schemes are included in this part because they are specifics for the process.

One of the bases of Process Validation is the concept of *Risk Management*. According to ICH Q9, risk management comes to the idea of identifying, analyzing and evaluating the risks of the process. It treats to ensure the uncertainty of every point in an important task, process or business. It can confer many areas such as public health, financial markets or pharmaceutical industry. From pharmaceutical industry appears a field of risk management called *Quality Risk Management* and it is carried out by the quality system. (4)

The objectives of the quality risk management are evaluating risks and reduce/eliminate them to the maximum through a detailed procedure. It is necessary to highlight that quality risk management is a subjective task and the activities involved in it should be done by decision makers. They make the important decisions to assure that the process is defined and reviewed as well as coordinated by the different departments which take part in it. The process to accomplish a quality risk management is based on three points:

- *Risk Assessment*: The risk assessment is composed of *Risk Identification*, *Risk Analysis* and *Risk Evaluation*. In *risk identification*, the main objective is having a well-defined risk and identifying the main hazards and the less important as well. In *risk analysis* the hazards are related to the severity of harms by risk management tools. In *risk evaluation* the idea is to compare the identified risks with the analysis of them and to give conclusions that point out the worst risks of the process. (4)
- *Risk Control*: In this part of the process, the decision related to acceptance of risks is taken. It is composed of risk control, risk reduction and risk acceptance. A limit of acceptance is suggested, and the objective is to reduce all risk above this limit. This is achieved by thinking if there is something that can be done to reduce/eliminate these risks using available resources or thinking about if it is possible to invest in different resources to reduce it (Corrective and Preventive Actions, CAPA). It depends on the level of the risk and the process. However, if risk was unacceptable, a revision of risk analysis would be done. (4)

- *Risk Review*: It involves doing a revision of results of quality management process. It can be useful to get more knowledge about the process and experience for another case. A revision should reconsider the decision that had been taken when the risk analysis has been performed. (4)

An overview of quality risk management process is shown in figure 2:

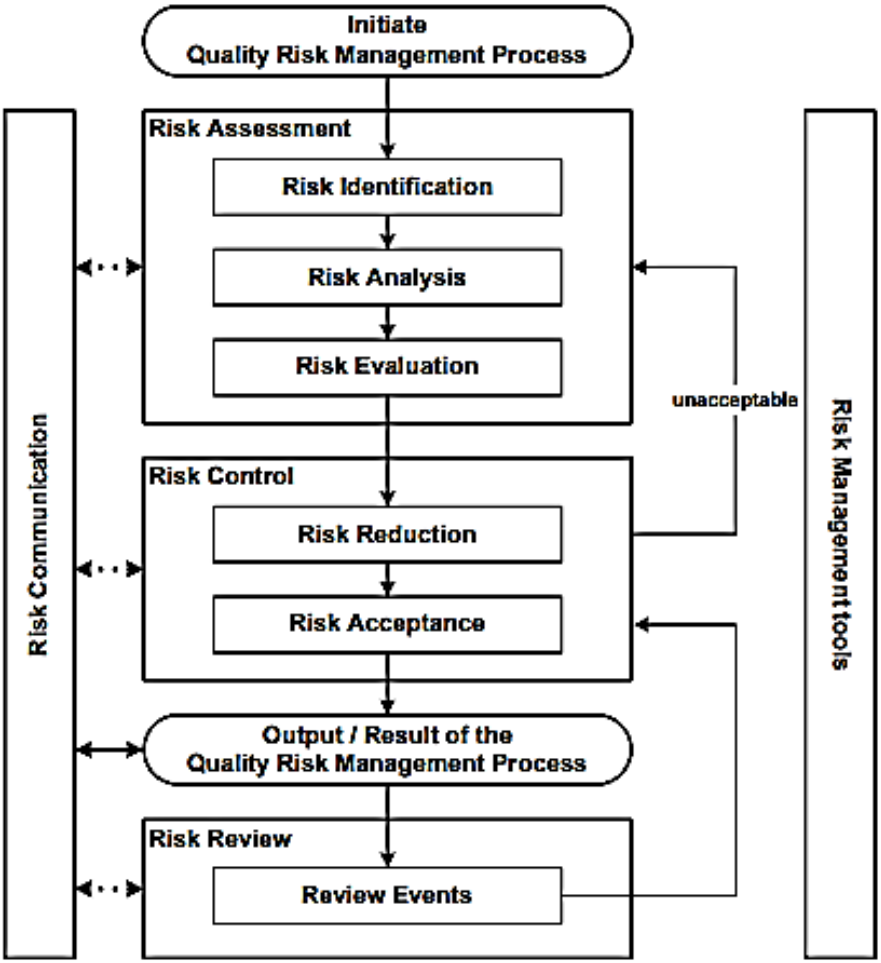


Figure 2. Schedule of Quality Risk Management Process (4)

1.2.4 Qualification of Equipment

One of the main parts of Process Validation is the qualification of facilities or equipment. Under the terms of GMPs, any item that has an impact on the quality of the intermediate or API must be qualified. The qualification of new equipment has different guidelines that should be followed to get it right, but in case of existing equipment is different. To qualify an existing equipment is necessary to follow a specific guidance. Usually, an existing equipment is rarely qualified at all because it lacks specific verification documents. (5)

The Quality Unit and the Production Department are responsible of organizing all the activities of qualification plan and both of them are independent from each another. Basically, qualifying a facility has a demonstration and a documentation that assures the proper functioning of equipment and the good product data. (5) Therefore, the qualification process consists of:

- Design Qualification (DQ)

Collection of documented evidence that verify the proposed design of the facilities, systems and equipment are suitable for the intended purpose. (2)

- Installation Qualification (IQ)

Documented verification that the equipment or facility (as installed or modified) comply with the approved design, the manufacturer's recommendations and user requirements. (2)

- Operational Qualification (OQ)

Documentary verification that the equipment or system (as installed or modified) work within the previous established ranges. (2)

- Performance Qualification (PQ)

Documented verification that the equipment or system work effectively and reproducibly based on the approved process method and product specifications. (2)

1.2.5 Water system qualification

Water is one of the most commodities used in the manufacturing processes. The Committee for Proprietary Medicinal Products (CPMP) and Committee for Veterinary Medicinal Products (CVMP) provide the "note for guidance on quality water for pharmaceutical use" (CPMP/QWP/158/01, EMEA/CVMP/115/01) to industry with different grades of water in the

manufacture of pharmaceutical ingredients and medicinal products and veterinary uses. In this guidance, there is a distinction in water grades as shown in the table 3:

Table 3. Grades of water [6] *The European Pharmacopeia provides the standards of these grades of water.

Quality of water	Description
Potable Water	Must comply with the regulations of water laid down by the competent authority.
Water for Injections*	Used for preparation of medicines for parenteral administration.
Purified water*	Used for the preparation of medicinal products or those that require the use of sterile water.
Highly Purified Water*	Used to preparation of products which require high microbiological quality.

According to the guideline, APIs and excipients should be manufactured with potable water. However, a water specification needs to be stated to demonstrate that the water used does not affect the quality of the final product. It is important to emphasize that a significant part of water qualification is referring to the microbiological quality – actually, it is one of the issues with major concern (6) – but there are some other parameters such as conductivity, acidity or lead content that are recommended to be controlled to meet the specification for the intended use of the final product.

Besides, to perform the water system qualification a programme should be defined. The different tasks to organize the qualification are detailed in a document called Water Process Control. This plan should contain different parts:

1. Introduction and water specifications
2. Sampling locations
3. Sampling plans
4. Warning levels and sanitation plan
5. Revision plan of water system

All the results obtained in samplings are recorded and well-documented to be able to guarantee that the water involved in processes meets the specifications needed.

1.2.6 Cleaning Validation

Cleaning procedures of the equipment involved in the manufacturing process must be stated and validated. [3] Cleaning procedures should be well-written and approved. Nowadays, great importance is placed to the cleaning validation particularly to multiproduct plants because of the high risk of cross-contamination. Therefore, cleaning validation is defined as the method to assure that a cleaning process removes residues of the previous product manufactured in the equipment. Besides, it includes the study of microbial attributes in equipment and in the cleaning supplies. The main objective of these cleaning procedures is reducing the residues to a specified level so as not to influence in the quality of the next product that will be manufactured in the same equipment. It consists on successive applications of the cleaning procedure complying with the criteria defined, in a minimum of three successful applications.

In general, there are three stages in cleaning validation, as shown in table 4:

Table 4. Stages of Cleaning Validation [7]

STAGES OF CLEANING VALIDATION	
Cleaning Process Design	Designing, developing and understanding the cleaning process residues Establishing of cleaning process control
Cleaning Process Validation	Demonstrating that the cleaning procedure works as expected
Cleaning Continued Process Verification	Ensuring that the cleaning process remains in state of control. The stage includes post validation monitoring, change control and periodic management review

The activities carried out in these three stages are compiled in a Cleaning Validation Protocol (CVP) and results are reported in a Validation Report. [7]

The cleaning validation process as well as process validation should have a master plan which compiles all the activities to perform its validation. The procedure to carry out the cleaning validation is described in CVP. Product features, sampling methods, a description of equipment

to be cleaned, methods of analysis, cleaning acceptance levels and other activities are included in this document. The validation of cleaning procedures used to clean the equipment is a clear requirement of cGMP. So, every company sets its own cleaning validation protocol with some objectives to achieve. In general, the main parts of the protocol are [7]:

a. Background
b. Objective
c. Scope
d. Responsibility
e. Cleaning Procedure (SOP)
f. Sampling Procedure
g. Testing Procedure
h. Acceptance criteria
i. Group of products and worst case
j. Classification of products to be cleaned according to solubility, cleaning difficulty, therapeutic dose, etc.
k. Deviations or non-conformances of cleaning procedure

All the results are recorded in a Validation Report. It also includes all the deviations of cleaning validations related with sampling methods, tests and procedures. So, it is useful to make a decision to change methods and to identify and solve problems.

Cleaning validation process is performed following the steps according to CVP, which can be seen in figure 3:

Cleaning Validation Process

- Establishment of starting targets and assignment of responsibilities
- Define the cleaning level and the acceptance criteria
- Elaborate and execute the cleaning procedure
- Sampling methods (Swab, Rinse, Microbiological tests)
- Testing procedure (Analytical Methods)
- Points to consider: Worst case, DHT, CHT
- Reporting of results and conclusions if the cleaning process can be validate or not

Figure 3. Scheme of Cleaning Validation Process

1.2.7 Operating Procedures

The procedures to perform all the activities to carry out the process validation should be created and approved. [3] The most common procedures that take part in the process are operating, maintenance manual and sampling procedure.

1.2.8 Control

In the stage of control, the tasks involved are for example the development of analytical methods or the study of impurities.

1.2.9 Qualification of personnel

There is a requirement that everyone involved in the manufacture of intermediates and APIs needs proper teaching for the task to be performed. This teaching needs to be supplemented by training and experience in the particular task to be carried out. [2]

The responsibilities of all personnel engaged in the manufacture should be specified in writing (job description). [2] This can be accomplished in a generic way for a group of personnel e.g. warehouse personnel, production plant operators or quality control analysts.

Employees have to receive initial GMP awareness training as well as more focused training such as Master Batch Record Training, ALCOA principles, Clean Rooms, Standard Operational Procedures (SOPs) to name a few, which are involved.

GMP training has to be scheduled in an annual training plan and the training records have to indicate [2]:

- Names of the people trained
- Subject of training
- Date of training
- Name of trainer

Effectiveness of training needs to be verified by direct (questionnaire) or indirect means (periodical assessment interview or internal audits).

1.2.10 Qualification of suppliers

According to the EU GMP Part II, materials must be purchased against agreed specifications [3]. Companies have to prepare a list of starting materials and critical raw materials based on good scientific rational and impact on the quality of the final product. This list is approved and controlled by the Quality Unit.

All suppliers need to be evaluated by a risk based on:

- Historical experience with the supplier and reliability
- Quality questionnaire (paper audit)
- Checking/comparing own analytical results (common practise: three batches) with those on the suppliers Certificate of Analysis.
- Audit

The audit is not mandatory, but a documented risk assessment is needed to determine the necessity of performing an onsite audit as part of the supplier qualification.

A change, according to the Change Control procedure, of the source (e.g. manufacturer or supplier) of a starting material and critical raw material should be handled [3].

Currently, not only the suppliers of materials need to be qualified. Services such as External Laboratories, Transport Companies and Pest Control Companies also need to be qualified by a risk based on:

- Historical experience with the service
- Quality questionnaire (paper audit)
- Contract defining the Responsibilities of each Company

1.2.11 Results

The results of Process Validation should be collected and organized. Product data, CPP and analytical results of three successful batches are recorded and well-documented to draw conclusions about the process.

1.2.12 Conclusions

Contrasting results with the starting targets is important to demonstrate the validation. Also, the main issues of the process can be identified and justified. Through the conclusions the validation or non-validation is defined. So, if the process is validated it must be approved and established as commercial manufacturing process.

1.2.13 Continued Verification

Making a revision of the process regularly includes re-evaluating the process and determining if the process should be re-validated. [1] All the aspects and changes for the improvement of the process are recorded and documented as part of the change control and the deviation management. Nevertheless, the Product Quality Review (PQR) is the main tool to make sure that the process is in state of control.

A Product Quality Review (PQR) is a rolling quality review of a product. The purpose of PQR is verifying the consistency of a process. It is a tool that compiles product data, trends and can be useful to improve the production process. With the information compiled in PQR, it might conclude in considering of revalidation of the process and to do some changes to optimize the production as stated above. The European Medicines Agency (EMA), US Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) support this idea because all of them found it necessary to do a quality review of the products manufactured in order to know their consistency and quality standards. [8]

2. OBJECTIVES

The purpose of the current project is the participation on the process validation of the manufacturing process of solution of NaOH 32% w/w solution GMP. To achieve it, the following tasks have been performed.

- The performance of the risk assessment according to International Conference on Harmonisation, Quality Risk Management Q9 (ICH Q9).
- The creation of documents related with the process validation.
- The performance of equipment qualification and the participation in the creation of the documentation needed in this stage of validation.
- The study of the approach of water system qualification in the current production plan.
- The understanding of cleaning validation and the establishment of the worst case as a system management together with the purpose of a cleaning procedure to be validate. Also, the understanding of the sampling methods and Dirty Holding Time/Cleaning Holding Time concepts.

3. PRODUCTION PROCESS

The NaOH 32% w/w GMP manufacturing process is carried out according to EU GMP II. There are different stages in the process that should be done by specific way. The process is under control from starting materials to final package. In this case, this control is achieved thanks to *Master Batch Record* (MBR). MBR is a dossier that compiles all the parameters that are taken during the process such as efficiency of the process, the critical parameters or the recount of labels that have been used for the final labeling. According to the ALCOA principle (Data Integrity) [9], the worker must fill the gaps of the MBR correctly with demanded information in each part of the process. In a way, this working methodology represents the traceability of the product needed to fulfill the GMP requirements.

3.1 MANUFACTURING PROCESS

The whole process of NaOH 32% w/w GMP is manufactured in discontinuous batches and in general, the main process consists in making dilution of NaOH 50% in deionized water.

$$NaOH_{(l)}\ 50\% + H_2O_{(l)} \rightarrow NaOH_{(l)}\ 32\%$$

The manufacturing process can be summarized in the following scheme (figure 4):

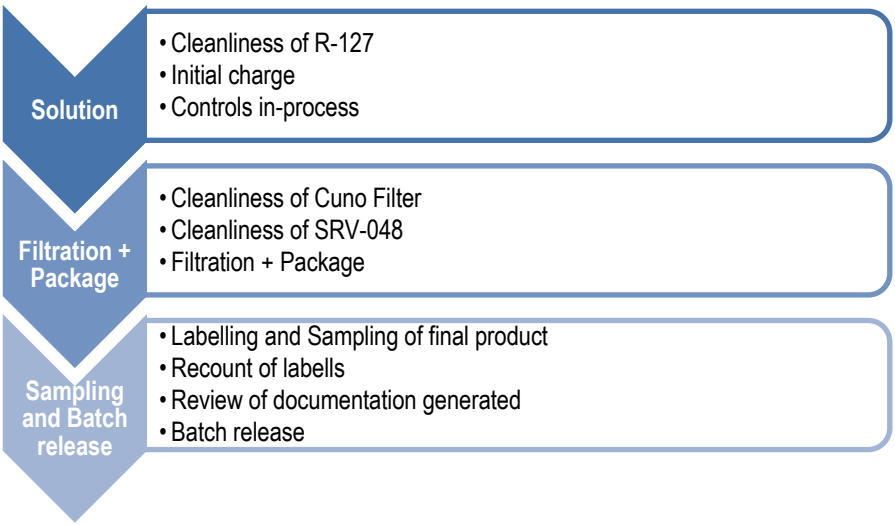


Figure 4. Overview of NaOH 32% w/w GMP manufacturing process

According to MBR, the procedure to follow during the manufacturing process can be divided in three parts. Each part has different tasks related to the cleaning and operation methods. In order to understand the process, a flowchart of the process is shown in figure 5:

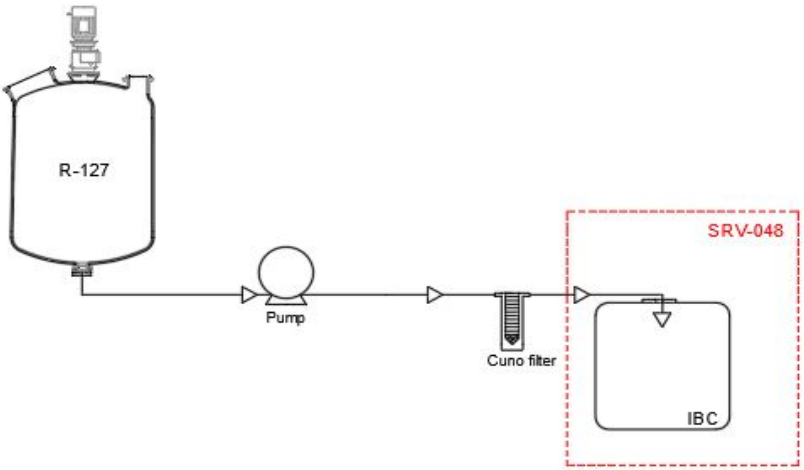


Figure 5. Flowchart of the process

As can be seen in the flowchart, the process equipment required consists in:

- Stainless steel jacket Vessel which capacity is 4860L and is encoded as R-127 (Technical Data Sheet of R-127 is shown in Annex I, IQ, c). This equipment is used to carried out the first stage of the process, the solution.
- Pneumatic Teflon Pump ((Almatec Series E15), which is required to pump the solution through the Cuno Filter. An overview of its characteristics is shown in Annex IV (a).
- Cuno Filter and Clean room (SRV-048), which are used to perform the filtration of the solution and its packaging. It is understood as a clean room, a place where the environment is controlled. The Cuno Filter specifications are shown in Annex IV, (b).

3.1.1 Solution

The first step of the manufacturing process is carrying out the solution. This step consists in performing a visual inspection of the cleanliness of equipment, carrying out the initial charge and making the controls in-process. All these three parts are documented correctly.

Firstly, the revision of the cleanliness of equipment and tools is an important part that should be done correctly. Personnel must check the condition of vessel and decide if it is necessary to be cleaned or not through visual inspection. Nevertheless, the cleaning procedure is applied in the next contexts:

- The last cleaning has overtaken the period of time established in fifteen days.
- There is a changing of product in the same equipment.
- If sequential operations in equipment are more than 10.

Cleaning is performing according to a specific procedure (PL-RINOX).

Secondly, the raw materials are NaOH 50% w/w and deionized water. Both of them must be fresh and should be a control above them. To achieve it, personnel complete parts from MBR about the starting materials. For example, the NaOH 50% is storage in IBCs. Every IBC of starting material has its particular code and is really important to check its condition (IBC should

be clean without breaks, and the conservation time in IBC of the starting material must be less than 30 days). So, all this information should be recorded before the process starts.

The initial charge may be different depending on the batch size. The size of the batch could be two, three or four IBC (1000L) and the quantity of starting materials varies as it is shown in the table 5.

Table 5. Raw materials for each batch size

Nº IBC	Starting materials	
	NaOH 50% p/p GMP [kg]	**Deionized water [L]**
2	1750	990
3	2625	1480
4	3500	1975

The initial charge is carried out adding in the first the deionized water in vessel (R-127) with agitation system switched on. Subsequently, the cooling water is opened and the NaOH 50% is added (previously, the IBC should be weighed in a scale, recording it the exact weight).

Thirdly, different controls in-process should be done during the process. When the addition of starting materials is complete, it is necessary to maintain the agitation about thirty minutes and let the solution cools down. So, a control of solution temperature is carried out during the process before the adjustment of the assay. The solution temperature should be under 30 ºC.

The other control in-process is the adjustment of assay. The upper and lower limit is 31,7-32,3%. The worker has to take a sample of 200mL of solution and take it to the laboratory. If the samples are conforming, the next phase of the process is proceeded.

3.1.2 Filtration and Packaging

When the assay of solution is consistent, filtration and packaged are carried out. These two tasks are take place simultaneously. While solution is filtering, the solution is packaged in IBCs. According to cGMP, the final product should be in a controlled environment. Because of that, this stage is carried out in a clean room (SRV-048).

Before the solution discharges to be filtered and packaged, a visual inspection is performed to verify the state of Cuno filter and the clean room. In the same way as the cleaning of R-127, in case of Cuno filter, the cleaning is applied if there is at least one of the following conditions:

- Detection of residues in the equipment through visual inspection.
- There is a product changeover.
- The time established in fifteen days from the last cleaning has passed.
- The filter has used ten operations without applied the cleaning.

In some case, the cleaning procedure that must be followed is PL-FILTC (Annex I).

In case of the clean room, SRV-048, there are two points to consider about the clean room: the cleanliness and the controlled environment. On one hand, the cleaning of SRV-048 is checked by visual inspection. If it needs to be cleaned, the procedure QSAC-005 must be followed. In any case, the clean room must be clean to perform this stage of the process. On the other hand, the clean room guarantees that the final product is in a controlled environment (ISO 8/Class D).

In addition to the visual inspection performed at the beginning of the step, a verification of the condition of final IBC (High Density Polyethylene, HDPE 1000L) and the scale calibration must be done as well. So, when utilities and equipment have been revised the process of filtration and the packaged starts. The procedure to follow to perform correctly packaged is described in IOP-ENVAS.

The final product can be packaged in two, three or four IBC depending on the batch size. The remaining NaOH 32% GMP is re-classified to an ISO product, analyzed and stored in the warehouse.

3.1.3 Sampling and batch release

Once the packaged is fully completed, the personnel labels the IBC. Every package is labelled with two labels: one Master label with the product's name, batch number, net weight and another label with the product's name, packaging order, and package's number. Subsequently, Quality Control takes samples of the batch and analyzes them to determine if the

final product is in accordance with specifications. If the samples are conformed, Quality Assurance review all the documentation generated during the process and release of the batch.

4. VALIDATION PROCESS OF SODIUM HYDROXIDE 32% W/W GMP

The solution of NaOH 32% w/w GMP is manufactured for a pharmaceutical company. So, the solution is destined to the cleanliness of the pipes of a production plant which manufactures a medicinal drug. Although the use of NaOH 32% is not and API, the customer considers, by a risk assessment, that it needs to be manufactured under GMP conditions because the cleaning process is critical for their manufacturing process plant.

Consequently, the company must manufacture NaOH 32% w/w under GMP and validate its manufacturing process by a Prospective Validation.

4.1 PPQ NaOH 32% GMP PROCESS

According to the chapter 1.2, a Process Validation protocol (PPQ) is stated to define the entire task that needs to be considered during the validation of the production of NaOH 32% w/w solution GMP. For example, one of the main parts are the objectives to achieve about the quality of the product, which are shown in table 6:

Table 6. Specifications of NaOH 32% w/w GMP

Specification	Guarantee	Units
Identification A	Passes test	**-**
Identification B	Passes test	-
Assay	31.5 – 32.5	%
Appearance of solution	Passes test	-
Sodium Carbonate	Max. 0.5	%
Chloride	Max. 50.0	ppm
Sulphate	Max. 50.0	ppm
Heavy metals (as Pb)	Max. 5.0	ppm
Iron	Max. 3.0	ppm

In PPQ the specifications of raw materials are defined as well. The specifications of deionized water can be seen in the point about the water system qualification (Point 4.6) and the specifications of NaOH 50% are shown in the following table 7:

Table 7. Specification of NaOH 50%.

Specification	Guarantee	Units
Identification	Passes test	**-**
Appearance	Passes test	-
Assay	Min. 47	%
Chloride	Max. 0.006	%
Iron	Max. 0.001	%
Heavy metals (as Pb)	Max. 0.001	%
Sulphate	Max. 0.01	%
Potassium	Max. 0.1	%

During the review of the PPQ stated, a risk that could affect the final product specifications has been detected. A 10 ppm limit value for lead content is stated for the starting material NaOH 50%. If the starting material is released with a lead content of 10 ppm, the final product NaOH 32% GMP would be out of specification (6 ppm) due to the guaranteed limit, which is 5 ppm.

Although the historical results of lead concentration of the starting material NaOH 50% show that this concentration is always under 2 ppm, it is suggested during this project the reconsideration of lead specification limit in raw material and the purpose to make a reduction in it (under 7 ppm) to avoid the possible out of specification on the final product.

In addition to the definition of the specifications of the final product and raw materials, the main objectives of the NaOH 32% GMP process are established in the PPQ Protocol:

1. **Batch size to validat**e: The current validation is performed in campaign of three batches. It means that is necessary to produce three batches of every batch size (two, three and four IBC). The batch sizes to be validated are defined in table 8:

Table 8. Expected weigh of batch sizes

Batch size (Nº of IBC)	**NaOH 32% w/w GMP [**kg**]**	
2	2466	2740
3	3695	4105
4	4930	5475

2. **Homogeneity of batch:** The study of the homogeneity is performed to demonstrate the homogeneity of the batch produced. The extra controls are performed at each package after performing the filtration step. The acceptance criteria is shown in the table 9:

Table 9. Parameters object of study to determine the homogeneity of batch

Parameter	Acceptance
Assay	The values should be within the final product specification of 31,5 – 32,3 % and in a range of average $\pm$ 2σ.
Appearance of solution	Must be clear and colourless.
Iron	The values should be within the final product specification of max. 3.0 ppm and in a range of average $\pm$ 2σ.
Chlorides	The values should be within the final product specification of max. 50.0 ppm and in a range of average $\pm$ 2σ.
Sodium Carbonate	The values should be within the final product specification of max. 0.5 % and in a range of average $\pm$ 2σ.

The activities involved in validation such the division of responsibilities, the definition of critical in-process parameters, equipment, cleaning process involved and methods of analysis among others are defined as well.

4.2 RISK MANAGEMENT OF THE NaOH 32% W/W GMP PROCESS

Given that it is a product that has to be manufactured under GMP conditions, the quality risk management is carried out considering all the lifecycle of product from starting materials to the packaging and labelling of the product. Besides, the documentation of the quality risk management process should be commensurated with the level of risk. So, the guideline to realize the risk management of the actual production process is ICH Q9.

According to these guidance, an overview of the procedure planned to follow in NaOH 32% w/w GMP process is shown in figure 6:

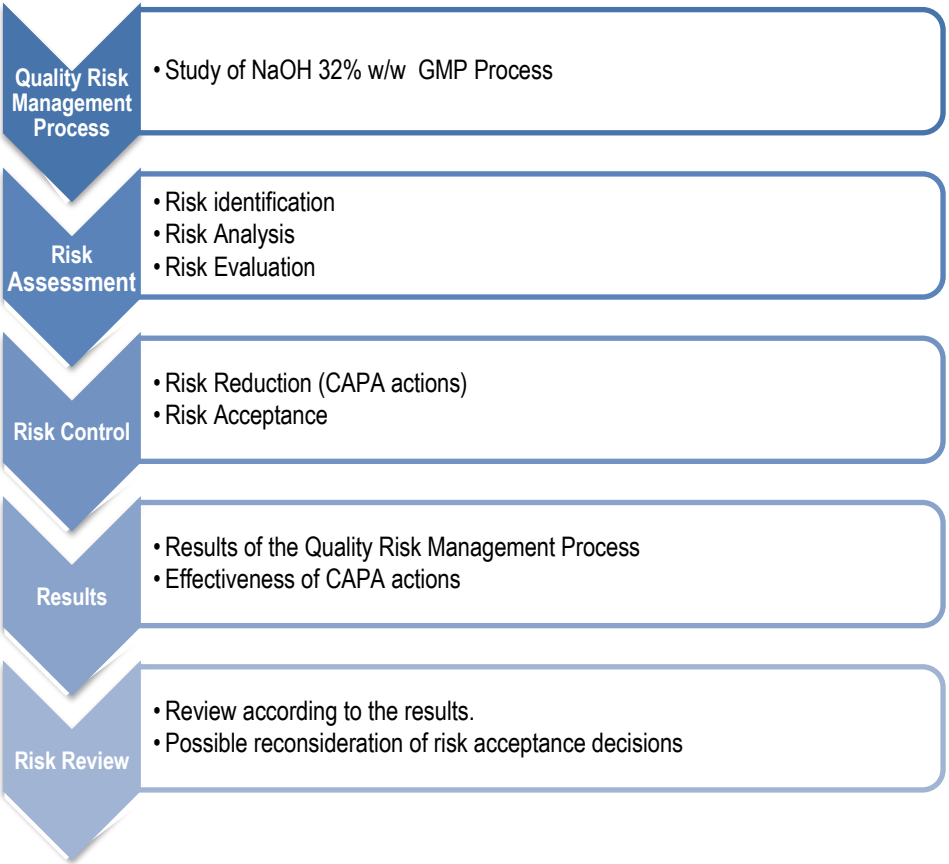


Figure 6. Overview of the stages of Risk Assessment

4.2.1 Risk Assessment of the manufacturing process

4.2.1.1 Risk Identification

The first issue in NaOH 32% w/w GMP process validation is to proposes the risk assessment. In this point, an exhaustive study of the process leads to determinate all the risks involved in the procedure. So, having a well-defined risk is the key to analyze the related hazards and severity of harms.

Firstly, to make possible the risk identification the process is divided in parts. Every part is analyzed accurately, that is to say, the synthesis and its related parts (cleaning equipment and tools, initial charge and solution). Also, the filtration and package with its parts (cleanliness of clean room and Cuno Filter, filtration and packaging) are studied with MBR to find possible points of conflict or doubt that suppose a process risk. These risks can affect the quality of the product or can represent a waste of time/economic loss.

Secondly, the risks considered in each part of the process is focused in human mistakes and quality issues. Due to the manual work of the process, the risks are greater. It has been considered that the risks of the process can start from warehouse – wrongly labelled feedstock, for example - when raw material (NaOH 50% w/w) is provided to production plant for starting the initial charge. Also, the experience of trained personnel influences because not all of them work equally and have the same accuracy when performing the procedures related to the whole manufacturing process.

The risks considered have an impact on the quality of the product and on the process. So, the main question during the risk identification is: "What might go wrong?". Indirectly, the possible causes and consequences are defined according to the supposed risk of the process.

Every risk identified is coded with "RX", being X the number of risk in order of the process. The stage in whole NaOH 32% w/w GMP process, the process concretely, risk causes and consequences of it are recorded in the first part of risk assessment. The information is the basis for doing the risk analysis.

4.2.1.2 Risk Analysis

Risk Analysis is the part of risk assessment that evaluates quantitatively the risk. It allows to determinate a range of risk that provides an idea of the level of it in our process and the magnitude of the actions that should take place to improve.

When risk identification is established, the main questions are:

- "What is the likelihood of occurrence of these risks?" (4)
- "What are the severe consequences?" (4)
- "How easy is to detect the risk?" (4)

Basically, the parameters to evaluate of every risk are: probability, severity and detectability. Evaluating risks involves the application of criteria related to these three parameters. The criteria used are characteristic depending on who realizes the risk analysis, the conditions of the manufacturing process and the requirements of the process. Therefore, the criteria that have been used to carry out the risk analysis of NaOH 32% w/w GMP attribute values from 1 to 3, and it is described in the next paragraphs.

Probability is understood as the probability of appearing the cause of process failure. (4) So, the probability is divided in these three stages, that shown in table 9, with the value attributed and the understanding of the level:

Table 10. Probability criteria

Level of Probability	Definition	Value
High	The success usually happens during the process. These values are based on experience from different batches that had been done before, and what is thought that will probably take place next.	3
Medium	The success occasionally happens during the process although it isn't considered a habitual incident.	2
Low	The success is unlikely to happen in normal conditions. It is considered that these incidents are unusual.	1

Severity is a measure of the possible consequences. (4) It evaluates the impact on the quality of the product and on the process. In the same way, the severity has been divided in three stages with different values. This information is shown in table 11:

Table 11. Severity criteria

Level of Severity	Definition	Value
High	In this level, the fail affects directly the quality of the product. It should result in an immediate rejection of the product.	3
Medium	The quality has no impact, but it affects the manufacturing process and the effectiveness of it.	2
Low	Anything that doesn't affect the quality or process. Usually, these failures can be solved.	1

When severity and probability have a value attributed, is possible to calculate the vulnerability of the process, also called "risk level". If this vulnerability value increases, the process will be less robust. So, a new number appears and brings a value to provide an idea of how robust is our process. Depending on the value of this parameter in every risk defined, the limitations of the manufacturing process can be detected, and the risk associated becomes an objective to improve. According to the next mathematical expression, giving the value to vulnerability/robustness is possible:

$$Risk\ level/Vulnerability = Probability\ \times Severity$$

Detectability is understood as the probability of detecting a failure before and after it occurs [4]. The classification of the three levels as well as probability and detectability, is shown in the table 12:

Table 12. Detectability criteria

Level of Detectability	Definition	Value
High	The detection of the failure is immediate. It is also seen as the detection of a failure just doing a visual inspection of the equipment.	1
Medium	The detection of the failure occurs during the following stages of the process. In this case, the failure is usually detected in laboratory controls.	2
Low	The failure goes unnoticed.	3

The combination of risk level or vulnerability with the probability of detection gives the Risk Priority Number (RPN). This value indicates the real level of risk. As higher is this value in a determinate risk, much more priority it has. The application of corrective actions to reduce/eliminate the risk should be thought as soon as possible. The calculation method is the following:

$$RPN\ (\ Risk\ Priority\ Number) = Vulnerability \times Detection$$

In risk analysis, the first evaluation of risks brings an initial RPN which will be modified when the mitigation actions have an effective in risk. So, a final RPN should appear.

As a result of the criteria application, the ranges of acceptance have been done to decide the priority of the risk, that is to say, how serious are the different risks. Some intervals are built based on the values of RPN.

The risk analysis of NaOH 32% w/w GMP can be found in the CD enclosed. The intervals of acceptance are made taking the highest value of RPN (18) and dividing it in three groups, as can be shown in table 13:

Table 13. Acceptance levels defined

Acceptance Levels	
Unacceptable Risk	From 12 to 18
Improvable Risk	From 6 to 12
Acceptable Risk	From 1 to 6

4.2.1.3 Risk Evaluation

The identified and analyzed risks are evaluated through respective RPN. The values are grouped in the three intervals of acceptance. The highest priority is giving in all the risks within the interval of unacceptable risk.

4.2.2 Risk Control

The implementing actions in a process to improve and eliminate the causes of a high-level risk or non-conformance are called Corrective and Preventive Actions (CAPA actions) [4]. These actions range from changes in equipment or production process to the related documentation such as training of personnel or production of background. In analysis risk, CAPA actions are taken to reduce the highest values of the risk.

The main objective is to reduce the risk to an acceptance level or eliminate it. To carry out this task, once the risks are grouped within the acceptance intervals, some questions have been done to determinate the application of (CAPA actions). So, the questions of risk acceptance/risk control used to as a guide:

- "Is the risk in acceptance level?" (4)
- "Is it possible to reduce/eliminate these risks?" (4)
- "What CAPA actions can be done?" (4)

These questions have been useful to determinate in NaOH 32% w/w GMP process what CAPA actions should be applied and what are the already CAPA actions applied in present.

In the table 14 can be found in detail what are the highest risks obtained in risk analysis and the overview of suggested actions to reduce them:

Table 14. Risk identification with its description and CAPA actions

Risk Identification	Risk description	CAPA action
R1	Dirty equipment or remains of another product.	Revision and validation of cleaning method.
R3	Starting materials are contaminated.	Revalidation of shelf life of NaOH 50% in IBC (Actually, is established in 30 days).
R9	Deionized water does not agree with the required specifications.	Adding R-127 to a point on water system qualification
R11	The temperature is higher than 80ºC, the process is out of control.	Creation of stainless steel R-127 procedure including cooling/heating system.
R13	Presence of carbonate in solution.	Validation of Dirty Holding Time (DHT).
R16	Dirtiness in Cuno Filter.	Established Cuno Filter cleaning procedure.
R17	Product leakage.	Established a place to storage the hoses especially for NaOH 32%.
R18	Foreign particles in final product.	Established of final IBC cleaning procedure.
R19	Packaging less product than it is required.	Installing a charge cell/ volum meter.

An overview of what CAPA actions have been applied during the current project are shown in the table 15:

Table 15. CAPA actions executed

Risk Identification	CAPA executed? (Yes/No)	Observation
R1	Yes	The revision of the preceding cleaning method has been revised. A new document has been generated. It can find in Annex I (PL-RINOX V02).
R3	No	The revalidation of shelf life of NaOH 50% is unattainable of the current project because of its task is planned out of project time. So, is pending to realize.
R9	No	The water system qualification is overdue and becomes unattainable of the current project
R11	Yes	The procedure of stainless steel R-127 has been done. It can find it in Annex I (P-OP-I07_I11).
R13	No	The validation of DHT Is in process. The determination of DHT is planning and its realization is out of actual project time.
R16	Yes	A cleaning procedure of Cuno Filter has been done during this project. Can be find in Annex I (PL-FILTC V01).
R17	Yes	An especially place has been dedicated to the storage of NaOH 32% hoses. Hoses are storage covering with plastic inside boxes.
R18	Yes	A procedure to clean the IBC has been done. It can be find in Annex I.
R19	No	This method is already suggested.

Before the application of these CAPA actions is expected an enhancement in RPN of risk shown in risk analysis. This enhancement is represented in the next bar chart in which the first bar of identified risk represents the RPN initial and the second bar represents the RPN final once the CAPA actions will be implemented. It can be seen in figure 7:

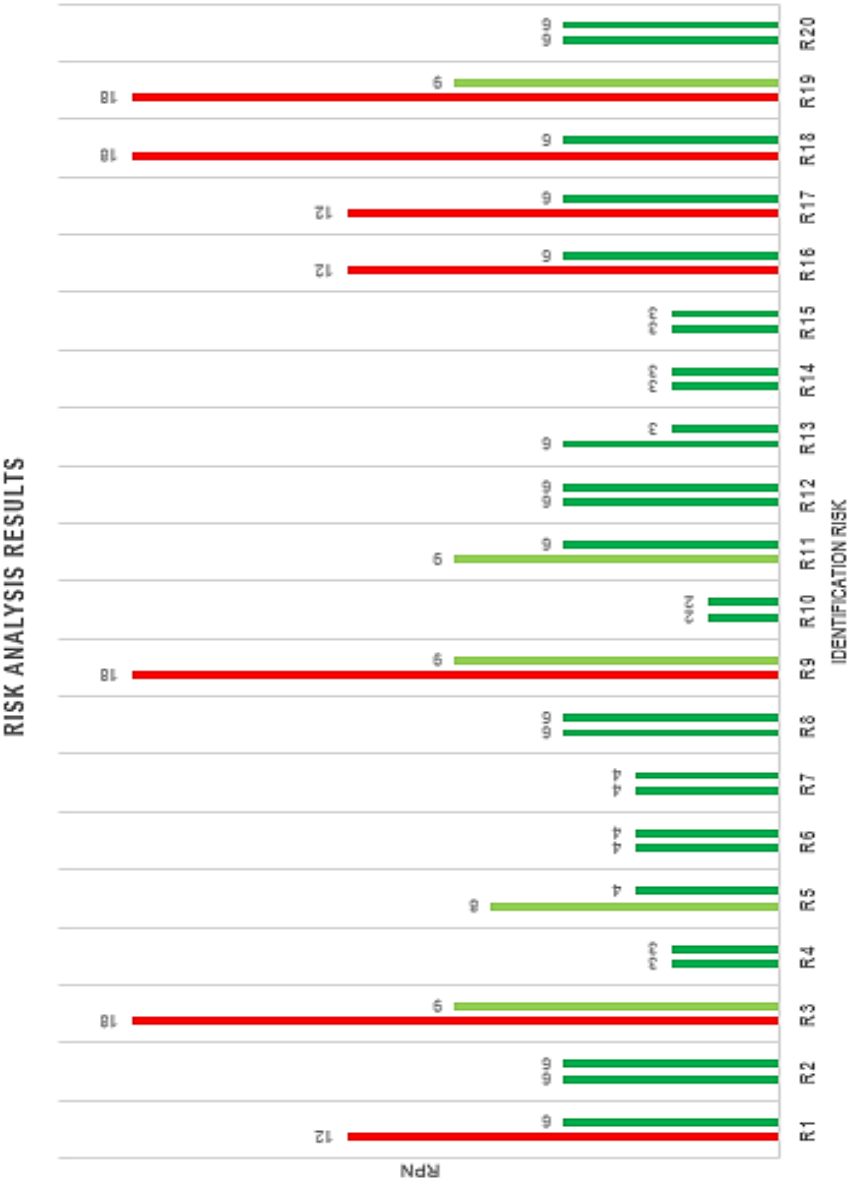


Figure 7. Analysis Risk results and the values of risk expected after the application of CAPA actions for each risk.

The diagram represents the initial values of risks in comparison with the final values expected. So, it shows the risk expected before the performance of CAPA actions proposed in risk analysis. In a way, is the expected effectiveness of these corrective actions to reduce the risks to an acceptance levels.

As mentioned, in this project the CAPA actions described in table 14 have been proposed to achieve a decrease in RPN values. The CAPA actions proposed to NaOH 32% GMP process have an impact on R1, R3, R11, R16, R17 and R18. As it can be seen in diagram, the main unacceptable risks are within the numbered risks and these risks are expected to be reduced to an acceptance levels. Those who are in unacceptable levels (R9 and R19), to be able to reduce it RPN, huge and long projects are required.

From the beginning, there are also some risks such as R2, R6 or R10 among others that are in acceptance levels. In this case, the CAPA action is not needed to be implemented immediately and the corrective action should be thought or applied in long-term.

4.2.3 Risk Review

The risk management of the process should be reviewed to gain knowledge/experience and make a reconsideration of the suggested risks in initial phase. So, when all the CAPA actions take place henceforward a review of the risks of NaOH 32% GMP process must be done. It is sure that some changes will be considered, and other values will be assigned. Derived risks that force to reconsider the risk acceptance decisions will probably appear.

4.3 QUALIFICATION OF EQUIPMENT

The qualification of equipment is the main part of the second stage of Validation Process. The qualification of equipment in which NaOH 32% GMP is manufactured has been done during the project. The process of qualification involves different activities that should be well-documented. In each part of qualification, a documentation is required.

The equipment to manufacture NaOH 32% GMP involves a Vessel encoded as R-127 and Cuno Filter. The qualification has been done only for R-127 as the company required. In this case, a qualification of an existing equipment has been done. Therefore, not all the stages

involved in qualification process (DQ, IQ, OQ, PQ) have had to be performed. Nevertheless, all the process qualification has been performed according to Validation Master Plan (VMP).

In the following points, the tasks that has been carried out during this project for the qualification of an existing equipment are detailed.

4.3.1 Design Qualification of R-127 (DQ)

The documentation required to perform design qualification of R-127 with a short description is shown in the table 16.

Table 16. Description of the DQ documents

DQ documents	
User requirement (URS)	Document which verifies that the equipment (R-127) compiles all the requirements in present. It is a way to verify the actually condition of the equipment.
Risk Analysis of equipment	Risk analysis about facility in general. It includes the auxiliary components such as measuring devices.
DQ Report	Overview of Design Qualification with non-conformances or deviations of equipment.

Design qualification was partially performed and according to Validation Master Plan (VMP) the only tasks that remains to be carried out are URS, Risk Analysis and DQ report. These documents can be found in the Annex II (1a, 1b and 1c).

4.3.2 Installation Qualification of R-127 (IQ)

Basically, to perform properly a qualification of the installation process is necessary to have all the documentation related to the equipment in place and completed. [5] An overview of this required documentation is shown in table 17.

Table 17. Description of the IQ documents

IQ documents	
Technical datasheet	Datasheet of existing equipment. It includes all the details about equipment and facility.
As built Plan	Technical documentation of the equipment and its plan as built.
GMP requirements	Identification, logbook...
Calibration Plan	Documentation of the equipment calibration.
Preventive Maintenance Plan	The preventive maintenance of the equipment should detail in a document.
Documental Matrix	Document that compiles all the documentation related with the equipment.
IQ Report	A report of all the deviations of documentation required in IQ.

According to VMP, the activities that have been done in IQ of R-127 are:

- Documental Matrix.
- IQ Checkup
- Datasheet of R-127
- IQ Report

Firstly, documental matrix realized compiles all the documentation related to the equipment and GMP requirements as stated above. An exhausting search of all the documents has been made to collect the latest versions of all the documents. The reference of every document is included to make the search of them easier.

Secondly, the IQ Checkup includes the revision of general R-127 aspects such as the identification of the equipment and its auxiliaries (stirrer and heat exchanger among others), the mechanical linkages, the whole installation and measuring instruments. The revision of the inclusion of R-127 in Preventive Maintenance Plan and Calibrate Plan is also included in IQ checking.

Thirdly, the datasheet of R-127 has been done. All the aspects related to the equipment R-127 are described in it such as the year of manufacture, the technique specifications including the design parameters of the equipment and its accessories and safety features.

The whole documentation generated in this phase can be seen in Annex II (2a, 2b,2c and 2d).

4.3.3 Operational Qualification of R-127 (OQ)

The documentation required in order to perform the OQ, is shown in table 18:

Table 18. Description of OQ documents

OQ documents	
Vacuum and operational ranges tests	Tests that qualifies the operational ranges of the equipment.
Operating Procedure	Basic operating procedure of installation.
Cleaning Procedure	Basic cleaning procedure of installation.
OQ Report	Overview of Operational Qualification.

According to VMP, the operation procedure and cleaning procedure has been done. Both procedures were made as CAPA actions in risk assessment of the process, as previously seen. These documents have served to complete the OQ process.

The operational qualification of R-127 apart from creating the procedures, has been consisted in different tests in the reactor/vessel. The tests were realized to review the operational ranges related to volume and temperature. The OQ Report has been done as well. The documents are shown in Annex II (3a, 3b).

4.3.4 Performance Qualification of R-127 (PQ)

The main objective is to demonstrate that the R-127 is suitable to carry out the NaOH 32% GMP process. The performance qualification required the documents shown in the table 19.

Table 19. Description of PQ documents

PQ documents	
Evidence	Demonstration of the effectively process.
Conclusions	Conclusion of the validation of the process.
Follow-up	Supervision of Preventive Maintenance Plan, Calibration Plan and regular reviews of water, HVAC and SI should be effectuated and well-documented.

The PQ of R-127 has not been carried out in this current project because it develops in the final validation conclusions.

4.4 CLEANING VALIDATION

As mentioned in the introduction of the current project, the activities and GMP requirements related to cleaning process (mentioned in VMP as well) are described in Cleaning Validation Protocol (CVP).

To perform the cleaning validation of R-127, the responsibilities of the activities have been divided as follows: Production Department, Analytical Development, Technical Direction, Quality Control and Quality Assurance.

4.4.1 Worst Case

Considering the fact that it is a multiproduct plant, the validation of the cleaning process performed for each equipment supposes a huge effort. Therefore, the approach of worst case has been used to validate the cleaning process. Basically, the worst case is understood as the hardest substance to clean and a criterion is needed to choose this substance from all the products.

To determine the worst case, a risk analysis that takes into account the equipment and the substances which are obtained in has been performed. From each substance different parameters that could affect the cleaning of the equipment and the effect of a cross-contamination to the final drug have been considered.

The basis of the criterion established to group the manufacture products is summarised below.

1. **Solubility (S):** The solubility-rating is based on the solubility of the substances in solvents used to clean. It is described in table 20.

Table 20. Solubility criteria

Group	Descriptive term	Solubility [g/100 mL H_2O]
1	Extremely soluble	>100
2	Very soluble	10 – 100
3	Moderately soluble	1 – 10
4	Slightly soluble	0.1 – 1
5	Practically insoluble or insoluble	<0.1

2. **Security Information MSDS (Material Safety Data Sheet):** Information of therapeutic doses (Lethal doses, DL) applied in rats. It is shown in table 21.

Table 21. LD_{50} criteria

Group	Descriptive term	LD_{50} oral rat [mg/kg]
1	Practically nontoxic	>15000
1	Slightly toxic	5000 – 15000
2	Moderately toxic	500 – 5000
3	Very toxic	50 - 500
4	Extremely toxic	5 - 50
5	Super toxic	<5

3. **Hardest to clean (H):** evaluation of the cleaning difficulty of starting materials and equipment. It is shown in table 22.

Table 22. Cleaning difficulty criteria

Group	Cleaning difficulty
1	Extremely easy
2	Easy
3	Medium
4	Hard
5	Extremely hard

4. **Manufacturing periodicity (P):** the production frequency of each product considering that those which are hardest to clean and have low therapeutic dose. It is shown in table 23.

Table 23. Periodicity criteria

Group	Periodicity (manufacture per year)
1	< 1
2	1 – 2
3	3 – 4
4	5 – 6
5	< 6

Considering this criterion, the value of risk (R) of every product has been calculated as product of these four parameters:

$$R = S \times P \times H \times DL$$

The worst case was the product with the major value of risk. So, the result of the risk analysis of R-127 performed is shown in table 24:

Table 24. Risk Analysis to determine the worst case

Equipment: R-127 PRODUCT	SOLUBILITY(25ºC) [g/100 ml H_2O]	Solubility Group	Lethal Dose [LD_{50} rats, mg/kg]	LD_{50} Group	Difficulty	Use	Value
di-POTASSIUM HYDROGEN PHOSPHATE 3-HYDRATE	112	1	>5000	1	2	2	4
EDTA, DIPOTASSIUM SALT 2-HYDRATE	70	2	3000	2	2	2	16
COPPER (II) SULPHATE 5-HYDRATE	20	2	960	2	1	3	12
MAGNESIUM SULPHATE 7-HYDRATE	38	2	>5000	1	2	2	8
ZINC ACETATE 2-HYDRATE	43	2	794	2	2	2	16
POTASSIUM DIHYDROGEN PHOSPHATE	25	2	>5000	1	1	2	4
NICKEL PLATING BATH	miscible	1	105	3	2	2	12
ZINC CARBONATE BASIC	0	5	10000	1	3	2	30
POTASSIUM HYDROGEN PHTALATE	80	2	3200	2	3	2	24
TRI-SODIUM PHOSPHATE	14,5	2	6500	1	3	2	12
LEAD (II) NITRATE SOLT. 30 % w/w	597	1	93	3	3	2	18
POTASSIUM SODIUM TARTRATE 4-HYDRATE	100	2	5000	2	2	2	16
BARIUM HYDROXIDE 8-HYDRATE	7,2	3	550	2	3	2	36
SODIUM HYDROXIDE 32 % w/w GMP	miscible	1	2500	2	3	2	12
POTASSIUM CARBONATE	112	1	1870	2	2	2	8

The cleaning process validation should be performed for the equipment-product combination with major risk value. So, as can be seen in the table the worst case in R-127 is barium hydroxide 8-hydrate with a risk value of 36. The risk value of NaOH 32% w/w GMP is 12, which means that the cleaning procedure validation should be performed to barium hydroxide 8-hydrate.

Three consecutive batches of barium hydroxide 8-hydrate manufactured in R-127 had to be analysed. Because of that, the cleaning procedure validation is unattainable of the current project.

4.4.2 Sampling methods

Cleaning procedure has been suggested (Annex I) to perform the cleaning of vessel (R-127) and this procedure has to be validated. To verify the effectiveness of the proposed procedure, the sampling methods are used. These sampling methods include rinse and swab – these methods are described in CVP as well. The description of these methods is shown in table 25:

Table 25. Description of the sampling methods [7]

Sampling Method	Description
Rinse	It consists on using a liquid to a large surface area and take a sample to test the amount of product residues and cleaning agents' residues. These residues can be assumed to be equal to the amount of residue in the last wash or rinse solvent portion. To sum up, the rinsing waters are analyzed.
Swab	The swab sample consists on soaking a swab with solvent and wiping it over a determinate product contact surface of an equipment.

In case of vessel R-127, according to CVP, the sampling method used should be rinsed because swabbing is impracticable. The sampling is recorded in sampling sheets to collect all the results and draw conclusions of the validation when three successful results are gathered.

4.4.3 Acceptance limits

In cleaning validation must be demonstrated that the cleaning procedure applied for an equipment reduces the quantity of residues to an established acceptance levels. [7] To guarantee the effectiveness of the cleaning procedures a criterion is applied. The criterion established is based on having at most 10 ppm of A in B. Being B the next product produced and A the previous product manufactured. The acceptance limits are shown in *Table 26*.

Table 26. Acceptance limits

Parameter	Acceptance limit
10 ppm criterion	There will be no more than 10 ppm of A in B.
Endotoxin content in rinsing water	< 0.25 IU/mL
Visual Inspection Criterion	The equipment will be exempt of residues after visual inspection. To perform the visual inspection, instructions of hardest points of clean are provided.
Recovery factor	Percentage of recovery product to clean per cleaning operation. If determining through experience is not possible, is assigned a value of 80%.
Safety factor	Is used to assure that the next processes doesn't become contaminated. Usually, its value is 1%.

4.4.4 Cleaning Holding Time (CHT) and Dirty Holding Time (DHT)

Cleaning Holding Time (CHT) and the Dirty Holding Time (DHT) are an important part during the cleaning procedures validation and are object of validation as well. [7] These two terms are understood as follows in the table 27:

Table 27. Description of CHT and DHT [7]

Term	Description
Cleaning Holding Time (CHT)	Maximum period of time that an equipment is considered clean.
Dirty Holding Time (DHT)	Maximum period of time that an equipment can be unclean without effect on the validation of the cleaning procedure.

The CHT needs to be demonstrated out of this project due to a stop of 15 days is required (summer vacations). However, for similar equipment has been demonstrated that during the performance of the PL-RINOX cleaning process, the cleaning status of the equipment was granted for 21 days. Micro testing is performed at the beginning and at the end of the covered period. For the DHT, it has not been stated for any equipment and nowadays the DHT validation protocol is being stated. It will be performed out of this project.

4.5 WATER SYSTEM QUALIFICATION

According to guideline of CMPM/CVPM, the quality of water suitable for the quality of products manufactured in production plant is Potable water, however, water specifications have been established based on Purified Water (standards established by European Pharmacopeia, Ph. Eur.) so as not to affect the quality of the final product. In the table 28 is shown such quality of water is required:

Table 28. Quality of water used in production plan

Parameter	Specification	Analysis Method
Appearance	Clear and colorless	Ph. Eur.
Conductivity (20 ºC)	Max. 50 µS/cm (25ºC)	Ph. Eur.
Nitrate (NO_3)	Max. 0.00002%	Ph. Eur.
Heavy metals (in Pb)	Max. 0.00001%	Ph. Eur.
Turbidity	Standard I	Ph. Eur.
Acidity or Alkalinity	Passes test	Ph. Eur.
Subst. reducing $KMnO_4$	Passes test	Ph. Eur.
Chloride (Cl)	Passes test	Ph. Eur.
Sulfate (SO_4)	Passes test	Ph. Eur.
Ammonium (NH_4)	Max. 0.2 ppm	Ph. Eur.
Calcium and Magnesium	Passes test	Ph. Eur.
Residue after evaporation	Max. 0.0010%	Ph. Eur.
Total Aerobic Microorganisms (TAMC)	Max. 100 cfu/mL	Ph. Eur.

The water system qualification follows the instructions defined in Water Process Control Plan. According to that, the water system qualification consists in two parts: Initial qualification and the control periodicity.

In initial qualification the points of use should be defined. A list of all points of use was elaborated, which contained the code of point and its location. The codification is performed in

the following way: UP-XY (being XY different numbers to identify each point). So, R-127 is encoded following this rule.

The next step in water qualification is the control periodicity. To achieve the control of parameters mentioned in water specifications, activities of sampling have been set as follows:

1. **Initial qualification:** A sample of each point must be taken for the first four weeks and, during the first year, a monthly analysis should be taken place.
2. **Sampling Frequency Reduced:** once all results from the initial qualification agree with the established specifications, a reduced sampling of each use point is stated. It has been established a monthly control of different points of use. By the end of the year, each deionized water use point is controlled three times. If there is a point of use out of specification a study is performed to determine the root cause and solve the issue.

The sampling routine pretends to demonstrate that there is a control of water through the measure of different parameters in order to guarantee that water is within the specifications described above.

Special attention is given to Total Aerobic Microorganisms Count (TAMC) establishing an alert level in 80 cfu/mL. So, below 80 cfu/mL the sanitation plan must be carried out (which is defined in WPCP).

The qualification of water system has been proposed as part of the current project, but it has been delayed due to the incorporation of new facilities with new points of use. According to the WPCP, when a new deionized water use plan is modified or new, the whole water system needs to be re-qualified. Therefore, the water use point used for the R-127 will be qualified when the new facilities are built (expected time: by the end of 2018).

These modifications enforce to restructure the sampling plans which means that the whole water system qualification leads to a longer duration of the current project.

4.6 PPQ IMPLEMENTATION

The validation conclusions of the process of manufacturing NaOH 32% w/w solution GMP has not been performed yet due to the fact that a manufacturing of one batch of 2 IBCs and another of 3 IBCs are pending to be manufactured.

In fact, according to the validation protocol, the conclusions are expected to be performed and approved by the end of December 2018.

The current batches involved into the validation process are shown in the table 29:

Table 29. Batches involved to the validation

Batch Identification	Batch Size (Nº of IBC)
81001	2
81182	2
80960	3
81181	3
81243	4
81733	4
82049	4

4.7 PRODUCT QUALITY REVIEW

In the stage of continued verification there are some tools to compile the product data. One of the most commonly used to have all the information about the process and the product is Product Quality Review (PQR).

The PQR might include different parts related to the process/product but the most relevant ones are described in the following list: [8]

1. Name of the product and batch size.
2. The consistency of NaOH 32% GMP production process.
3. Critical in-process parameters. Trends in product data.
4. Final product specifications.
5. Operating times.
6. Deviation or non-conformances.

The task that has been carried out in this last stage of process validation, is the implementation of PQR to study the robustness of the NaOH 32% GMP manufacturing process

(the complete PQR of NaOH 32% GMP can found in CD enclosed). So, the main parts mentioned that should have a PQR of one product has been applied on the NaOH 32% GMP from the product data generated in a group of different batches. In particular, the whole batches that have been analysed to perform the PQR and its size are shown in table 30:

Table 30. Batches analysed to perform the PQR

Batch identification	Batch Size Number of IBC	Batch identification	Batch Size Number of IBC
80476	2	80083	4
81001	2	80469	4
81182	2	81243	4
79109	3	81733	4
79125	3	82049	4
80960	3	82076	4
81181	3	-	-

The data processing to perform a PQR to study and analyse the process/product – the consistency of the process and the trends, for example – can be in many ways but the control charts are the most commonly used. The objective is to represent the data and draw conclusions.

4.7.1 Consistency of the process

Firstly, the consistency of the process has been determined by the evaluation of the product final weight obtained (kg of NaOH 32% GMP) of every batch and its yield. The analysis for PQR of NaOH 32% GMP is divided according to the batch size.

Every batch has an interval of final product weight expected and depends on the batch size. The values of the interval form boundaries are called upper and lower limits. These limits are calculated considering the yield of 90% for lower limit and 100% to the upper limit. The upper and lower limits of different batch sizes are shown in the table 8.

The data generated from batches leaves information about the process/product. To analyze the consistency of the process, the information needed comes from the process data. Its data is recorded from Master Batch Record (MBR).

The process parameters that have been analyzed are weigh and yield, as mentioned above. All the data has been organized as shown in the table 31:

Table 31. Process data of each batch

Batch identification	Batch Size (Nº of IBC)	NaOH 50% [kg]	Deionized water [kg]	Total raw materials[kg]	NaOH 32% [kg]	Yield [%]
80476	2	1881	1013	2894	2726	94.18
81001	2	1778	990	2768	2674	96.60
81182	2	1800	1020	2820	2721	96.49
79109	3	2820	1370	4190	4050	96.66
79125	3	2730	1700	4430	4050	91.42
80960	3	2627	1480	4107	4068	99.06
81181	3	2761	1530	4291	4068	94.80
80083	4	3590	1975	5565	5421	97.41
80469	4	3596	1975	5571	5379	96.55
81243	4	3497	1975	5472	5444	99.48
81733	4	3750	1975	5725	5439	95.01
82049	4	3770	2025	5795	5431	93.72
82076	4	3830	1975	5805	5423	93.42

According to the manufacturing process, a yield close to 100% should be expected due to the fact that, theoretically, no product losses are generated. However, according to the data obtained, the yield is within 90% and 100%. The difference between the yields obtained in each batch is in the percentage of product loss during the process. The values calculated of product loss (%) are shown in the table 32:

Table 32. Percentage of product loss

Batch identification	Nº of IBC	Product loss [%]
80476	2	5.82
81001	2	3.40
81182	2	3.51
79109	3	3.34
79125	3	8.58
80960	3	0.94
81181	3	5.20
80083	4	2.59
80469	4	3.45
81243	4	0.52
81733	4	4.99
82049	4	6.28
82076	4	6.58

In the current manufacturing process of solution of NaOH 32% w/w GMP, is understood as product lost as a combination of remnants and wastes of production process

$$Product\ lost = Remnants\ (1) + Wastes\ of\ production\ process(2)$$

1) Remnants of the final solution of NaOH 32% GMP

The causes of the high values of product lost lies in remnants of final product that remains in reactor. Therefore, the discussion internally of what are the causes of that is proposed. The possible causes of product loss are stated below:

- Raw materials stated on the MBR are not correctly defined.
- A water charging unit is not in correct status.
- Manual charging of sodium hydroxide 50% starting material from IBC to reactor.

Consequently, if a remnant of product stays in the reactor because IBCs are completed, this material is re-classified to an ISO product, so it is not considered a GMP material. To get a clear idea, a diagram is shown in figure 8:

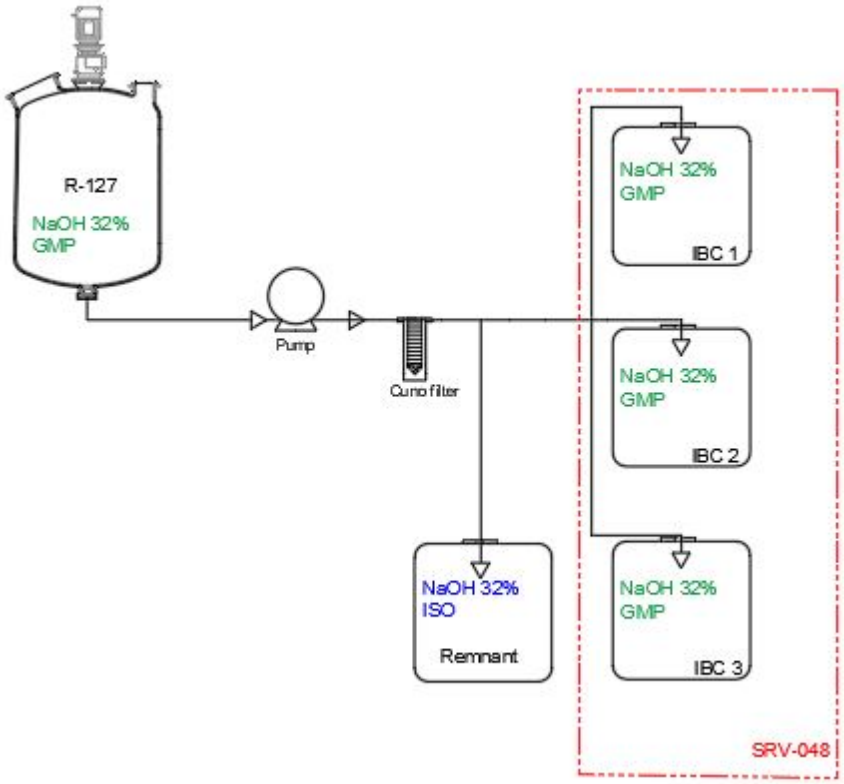


Figure 8. Explanatory scheme

2) Wastes in the production process.

To set an example, the final product that remains in hoses or Cuno filter and the raw materials that stayed in IBCs when they are discharged. All of them are considered wastes in the production process.

Therefore, for the current production process which is under GMP conditions, this combination of remnant and wastes of production process are considered wasted product.

On the bases of the above and with the information evaluated during the study of the consistency of the process, this project some suggested improvements appear in:

1. As mentioned in Risk Analysis, an installation of cell charge to know exactly the quantity of raw materials added at the beginning of the process and during it.
2. The implementation of remnants control that have to be stored at the end of the process. It allows to calculate exactly the percentage of product loss during the whole process.

4.7.2 Critical in process controls

PQR should have a part which compiles critical in process controls. Critical process parameters are understood as these parameters that can affect the quality of the product. [8] In order to have a process under control to comply the product specifications, a follow-up of these critical parameters during the process is needed. When these parameters are controlled during the manufacturing process, the detectability of an out-of specification product and the possibility of rectifying become easier.

In the study of the NaOH 32% GMP solution, the critical parameters have been selected and evaluated. The critical in-process parameters of the process are:

- **Initial and final temperature of NaOH 50% (charging):** The temperature of this starting material is carried out in the first stage of the process (solution). The temperature is tested before and after its addition to deionized water. These temperatures should be within the interval: room temperature - 80ºC for safety purposes.
- **Temperature of NaOH 32% GMP:** The temperature of NaOH 32% solution is tested during the process. Its measure is performed to know when is possible to discharge the solution safely. It should be within the interval: 20ºC – 30 ºC.
- **Assay of NaOH 32%:** The adjustment of final solution conforms to an assay between 31,7%-32,3%. The number of samples that has been taken to adjust the assay is recorded with the quantity of starting materials that have had to be added to adjust correctly.

Critical parameters are provided from MBR. Personnel recorded all the values in this dossier. The product data obtained in every batch that PQR compiles is shown in table 33.

Table 33. Product data of each batch

Batch identification	Number of IBC	$T_{o\ NaOH\ 50\%}$ [ºC]	$T_{NaOH\ 50\%}$ [ºC]	$T_{o\ NaOH\ 32\%}$ [ºC]	Assay [%]	Na_2CO_3 [%]
79109	3	23	50	28	31.93	-
79125	3	23	51	28	32.04	-
80083	4	25	50	30	31.97	-
80469	4	25	40	30	31.93	-
80476	2	22	45	31	32.04	-
80960	3	20	50	29	32.05	0.17
81001	2	25	52	23	31.97	0.17
81181	3	18	45	29	32.13	0.17
81182	2	24	42	28	32.17	0.17
81243	4	23	42	25	31.78	0.17
81733	4	20	47	20	31.89	0.17
82049	4	25	42	42	31.99	0.17
82076	4	23	33	33	31.94	0.17

As part of controlling the process, the percentage of carbonate in solution is also currently measured as part of a CAPA action. The percentage must be under 0.5 % to be conforming. The measurement of carbonate was stated due to a deviation observed during the process validation.

Critical in-process parameters have huge importance to demonstrate that the process is under control. So, the data gathering during the process provides the product's traceability according to the GMP requirements.

4.7.3 Final Product Specifications

Apart from critical in process parameters, it should be a control recorded of the final product specifications in every batch released. As can be seen in Annex III (Table 1), the product agrees with the final product specifications and the general trend of all batches is similar- all of them have very similar results.

4.7.4 Process times

One of the PQR parts is the process times. In MBR the times are also recorded. So, the cooling times obtained of different batches are shown in table 34:

Table 34. Cooling time recorded

Batch identification	Number of IBC	Total degree [ºC]	Total time [min]
80476	2	14	75
81001	2	29	660
81182	2	14	90
79109	3	22	120
79125	3	23	120
80960	3	24	720
81181	3	16	105
80083	4	20	525
80469	4	10	615
81243	4	17	960
81733	4	27	705

Therefore, a collection of phase time data allows to study different relations such as the influence of batch size and cooling time of the solution. The total degree is the difference between the solution initial temperature and the final one (when a sample is taken to determinate the assay). Batches 82049 and 82076 don't have the temperature recorded and for

this reason the cooling time has been unable to be calculated – both batches have been removed from table 34.

Nevertheless, the other batches bring information to determine the possible trend of cooling time. As it can be seen in the previous table, when batch size increases the cooling time is longer. Despite this, no general conclusions can be drawn from the data due to the inconsistency of the time values obtained. The main problem is that more than one of the values of the time data are very large. For example, in batch size of two IBC, there is a value of time of 660 minutes (of batch 81001). This result is not in keeping with the other values obtained for the same batch size. The same goes for batches 80960 and 81243.

The same happens with the total time of the manufacturing process. As can be seen in PQR NaOH 32% (in the CD enclosed), the time of the different stages was recorded, and with the data obtained it was expected that the process had a duration of 12.5 hours, but in fact it took about two days to achieve the complete process.

The causes of this incoherence are attributed to the influence of the following variables:

- The manual work is always a handicap and one of the main issues that causes the prolongation of work time.
- The cooling time is affected by the combination of room temperature and the condition of the current cooling system (is necessary to mention that this system is seriously deteriorated).
- The laboratory doesn't work a full day and is possible that some hours were included in results due to the waiting for the laboratory reply. All these facts contributed to the accumulation of this cooling time that is not real.
- At the weekend the process is stopped but the time is recorded.

Some improvements have been suggested in the following paragraphs, related to the factors mentioned above:

- The investment in a new cooling system and a project to monitor equipment data.
- The solution and assay adjustment steps, which are in the first stage of manufacturing process of NaOH 32% w/w GMP solution, took the longest time of the production

process. Because of this fact, improvements related with concentration of NaOH 50% and batch size have been suggested in order to reduce this time:

1. NaOH 50% raw material content: The assay specification guarantee of this raw material is stated as Min. 47%. However, this concentration can vary from each batch purchased. Due to this fact, the quantities of raw materials should be different for all batches depending on the NaOH 50% initial concentration. The improvement suggested includes the exact raw material needed to obtain a solution with an assay value of 31,5 - 32,5%.
2. Batch size: Although nowadays the trend is to follow the philosophy of "make to order" (manufacturing according to the customer needs), it can be concluded that the best option is the establishment of only one batch size of 4 IBCs due to timing issues during the manufacturing process. The highest cost can be attributable to the first stage, so it is better to produce a 4 IBC batch size for the same production time. This decision from the commercial perspective is unfeasible, but in this case, an agreement between Customer and Company has been stated. The Customer brings to the Company a demand planning of NaOH 32% GMP for 2018 and 2019. Therefore, a 4 IBCs batches are able to be planned. Anyway, the 2 and 3 IBCs manufacturing processes will also be validated to have more degrees of freedom in case of non-planned Customer request.

4.7.5 Non-conformances

PQR should have a review of all non-conformances or deviations of batches. In PQR of NaOH 32% GMP a section is dedicated to a specific overview of deviations. The number of deviation, the failure batch, the causes of non-conformance, the CAPA actions applied and the effectiveness of them are described. The tables are shown in Annex III (Table 2,3,4 and 5).

5. CONCLUSIONS AND RECOMMENDATIONS

- The Quality Risk Management has been implemented to the production process of NaOH 32% GMP through the performance of a Risk Analysis. Created cleaning and operating procedures due to the results of this analysis, have been together with the suggestion of new improvements to make the process more controlled and reliable.
- The qualification of the equipment involved in the manufacturing process of solution of NaOH 32% w/w GMP has been taken place during this project. Specially, the documentation required in stages of DQ, IQ and OQ has been carried out according to VMP. Therefore, the stages of qualification have been completed with the exception of PQ, because this will be stated on the validation conclusions.
- The cleaning validation is still incomplete due to two facts: the cleaning procedure has not been tested yet because the worst case has not been manufactured during the project period and DHT and CHT studies have not been evaluated because of the lack of time. They are planned to be performed during the summer of 2018.

Through the performance of the project, some recommendations have been obtained:

- The water system re-qualification has been proposed due to the incorporation of the equipment involved in the manufacturing process of NaOH 32% GMP (R-127). So, a plan has been designed in order to re-start the qualification as soon as possible.
- It has been applied the tool of PQR in the production process of NaOH 32% GMP. From this part, it can be recommended the following improvements:

- From the point of view of product specifications, a revision of the lead specification in NaOH 50% should be done.
- The time data compiled has been provided a trend of the duration of the complete production process, but to determine a batch time is necessary to implement new resources and invest on ways to have the process time under control.
- The investment in a cooling water system.
- The implementation of a control of remnants of final product.
- The monitoring of the variables involved in the process to have better process control and reduce the time of production.

All these activities have been part of the current process validation. Nevertheless, there are more tasks that need to be carried out in order to complete the whole validation process:

- The manufacturing of two more batches of NaOH 32% GMP: 2 IBCs and 3 IBS.
- The validation of the cleaning procedures and the DHT and CHT studies.
- The water system qualification including all the points mentioned during the current project.
- Stablishing the PQ according to the conformity of the validation batches (no equipment issues observed).

6. REFERENCES AND NOTES

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7. Active Pharmaceutical Ingredients Committee (APIC), *Guidance on aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants*, May 2014.

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9. Food and Drug Administration (FDA), *Data Integrity and Compliance with cGMP*, Guidance for Industry, April 2016.

7. ACRONYMS

ALCOA	Attributable Legible Contemporaneous Original Accurate
CAPA	Corrective and Preventive Actions
cGMP	current Good Manufacturing Practices
CHT	Cleaning Holding Time
CMPM	Committee for Proprietary Medicinal Products
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CVP	Cleaning Validation Protocol
CVPM	Committee for Veterinary Medicinal Products
DHT	Dirty Holding Time
DOE	Design of Experiment
DQ	Design Qualification
EMEA	The European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
IBC	Intermediate bulk container
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQ	Installation Qualification
MBR	Master Batch Record
OQ	Operational Qualification
PPQ	Process Performance Qualification

PQ	Performance Qualification
PQR	Product Quality Review
QbD	Quality by Design
VMP	Validation Master Plan

ANNEXES

ANNEX I: PROCEDURES

1. Cuno Filter Cleaning Procedure (PL-FILTC V01)

MÉTODO DE LIMPIEZA
DE FILTRO CUNO

PL-FILTC
V01

CONFECCION/REVISADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico Producción		
Xavi García	Director Producción		
Ángel Nogales	Jefe Planta		
Jordi Ferrando	Técnico Quality Assurance		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
PL-FILTC V01		Primera versión método de limpieza para filtro cuno.

	Doc nº:	PL-FILTC V01
	Sustituye:	-
	MÉTODO DE LIMPIEZA DE FILTRO CUNO	

PROCEDIMIENTO

Este procedimiento es especializado para la solución de NaOH 32% GMP p/p:

1. Previamente a la limpieza del filtro cuno, pasar agua desionizada por el circuito durante unos 2 o 3 minutos. Para ello, conectar mediante la conexión camlock la manguera destinada para la sosa (la cual debe estar conectada al R-127) con la manguera de agua desionizada.
2. Seguidamente, llenar una arqueta con agua desionizada. Dicha arqueta tiene una capacidad de 200L, llenar con la suficiente agua para realizar la limpieza del circuito.
3. Introducir la manguera destinada a NaOH dentro de la arqueta.
4. Desmontar retenedor del filtro cuno con precaución.
5. Retirar el filtro cuno y desecharlo.
6. Limpiar con agua desionizada el interior y exterior del retenedor del filtro.
7. Roscar de nuevo el retenedor (sin filtro cuno en el interior).
8. La manguera final debe estar dentro de un depósito destinado a la limpieza de la sosa. Las aguas de lavado deben llenar dicho depósito.
9. Poner en marcha la bomba. Dejar pasar agua desionizada durante 1 minuto minutos por todo el circuito.
10. Tomar una muestra del agua de lavado sacando con precaución la manguera de dentro del depósito de aguas de limpieza colocado anteriormente. Llevarla al laboratorio.
11. Parar la bomba.
12. Esperar aprobación del laboratorio. En caso de no conformidad, volver a repetir dicho proceso desde el paso 9, procurando que en la arqueta inicial haya la suficiente agua para realizar el lavado.

2. Stainless steel reactors' instructions (P-OP-I07_I11)

INSTRUCCIÓN DE USO
REACTORES DE INOXIDABLE

P-OP-I07_I11
V01

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
V01		Emitido para aprobación

	Doc nº:	P-OP-07_I11 V01
	Sustituye:	-
	INSTRUCCIÓN DE USO REACTORES INOXIDABLE *STAINLESS STEEL REACTORS' INSTRUCTION*	

1. INTRODUCCIÓN

En los reactores de acero inoxidable se llevan a cabo las fases de síntesis, disolución, concentración y cristalización. Todos ellos disponen de un agitador, una válvula de fondo y de un serpentín por el cual circula agua de refrigeración para enfriar o bien vapor para calentar. Además, los reactores de síntesis están provistos de una salida lateral para la toma de muestras.

2. OBJETIVO

Establecer procedimiento de puesta en marcha, funcionamiento y parada de reactores de acero inoxidable.

3. ALCANCE

El procedimiento es aplicable a reactores de inoxidable (reactores de síntesis y cristalizadores).

4. PROCEDIMIENTO

4.1 Revisión del estado del equipo

Previamente a la puesta en marcha del equipo, es necesario realizar una inspección visual del equipo para verificar que:

1. La limpieza interior y exterior del reactor se ha realizado correctamente y que, por lo tanto, no existen restos del producto anterior en el reactor.
2. La válvula de fondo del reactor está cerrada.
3. La llave de toma de muestras está cerrada, si aplica.
4. La posición de las llaves del sistema de calefacción/refrigeración están en correcta posición.
5. El panel de control y la sonda de temperatura funciona correctamente.

4.2 Puesta en marcha

4.2.1 Carga de materias primas

En los reactores de inoxidable es posible cargar materia prima sólida y líquida. Siempre que se adicione el sólido después del líquido, poner la agitación en marcha antes de su adición. En general se debe encender el equipo a través del interruptor marcha/paro del panel de control, mover el selector del agitador y seguidamente encender el agua de refrigeración. Los siguientes pasos para seguir:

1. Adición de materia líquida:
    a) Colocar el contenedor IBC con la materia prima próximo al reactor que se desea cargar.
    b) Para proceder a cargar, serán necesarias dos mangueras y una bomba. Conectar el extremo a la salida del contenedor IBC de materia prima y conectar su otro extremo en la bomba. Un extremo de la segunda manguera se conectará en el reactor a cargar y el otro se conectará a la salida de la bomba. Todas las conexiones deben ser cam-lock.
    c) Abrir válvula del contenedor IBC.
    d) Encender la bomba.
    e) Parar la bomba una vez se haya vaciado la cantidad requerida del contenedor IBC.
2. Adición de materia sólida:
    a) Colocar los sacos de materia prima en un lugar próximo del reactor a cargar.
    b) Limpiar los sacos con la ayuda de un trapo si se observa suciedad en ellos.
    c) Abrir la boca de hombre.
    d) Apoyar el saco con materia prima en la boca de hombre. Cortar el saco con la ayuda de una navaja y verter el sólido en el interior del reactor.
    e) Colocar el saco vacío en una bolsa para su posterior prensado.
    f) Cerrar la boca de hombre una vez finalizada la adición.

4.2.2 Sistema de calefacción/refrigeración

Para realizar el calentamiento (concentración) o refrigeración (cristalización) del reactor se debe hacer uso del sistema de calefacción/refrigeración. Se encuentra junto al reactor y puede observarse un ejemplo en la *Figura 1*, siendo análogo para todos los reactores inoxidables.

Para calentar:

1. Asegurarse que el agua circula por el condensador.
2. Cerrar la llave de entrada de agua de refrigeración (3).
3. Cerrar la salida de agua de refrigeración (4).
4. Abrir el bypass (agua-agua) (5).
5. Cerrar retorno vapor (2).
6. Lentamente abrir la entrada de vapor (1).
7. Cuando el tubo del bypass (agua-agua) esté muy caliente, abrir retorno de vapor (2).
8. Cerrar bypass (agua-agua) (5).
9. Regular el vapor con (1).

Para enfriar:

1. Cerrar la entrada de vapor (1).
2. Dejar abierta la llave de salida de vapor (2).
3. Asegurarse de que no hay presión a través del manómetro situado en la parte superior del reactor.
4. Cerrar el retorno de vapor (2).
5. Abrir el bypass (agua-agua) (5) y abrir el agua (3).
6. Comprobar que entra agua por el bypass (agua-agua).
7. Abrir la salida de agua de refrigeración (4).
8. Cerrar el bypass (agua-agua) (5).
9. Regular la entrada de agua (3) a caudal mínimo. Dicho caudal mínimo será correcto cuando se note que por la salida de agua (4) circula agua caliente. En caso contrario, repetir el procedimiento descrito desde el punto 2 de este apartado.

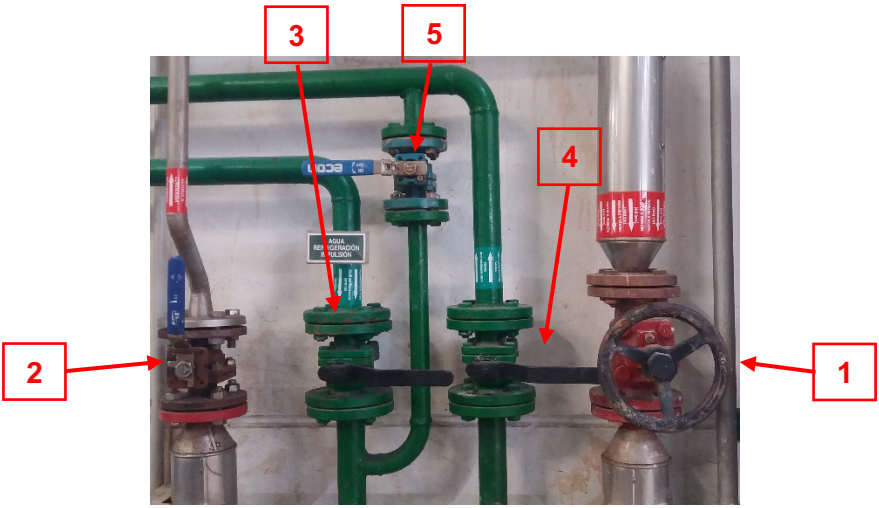

Figura 1. Sistema de llaves calefacción/refrigeración

4.2.3 Controles en proceso

4.2.3.1 Ajuste de la densidad

Para realizar un análisis de la densidad de líquidos es necesario seguir los siguientes pasos:

1. Extraer una muestra líquida del reactor.
2. Colocar la muestra en una probeta de 250 mL.
3. Preparar el densímetro y comprobar que esté en buen estado.
4. Realizar el análisis según indica en el MBR. Para realizar el análisis correctamente el densímetro debe ser de la escala adecuada (dicha escala viene indicada en el dossier), en caso de que:

a. El densímetro se hunda completamente: la escala es incorrecta, debe ser inferior.

b. El densímetro flota y el líquido queda fuera de la escala: la escala debe ser superior.

5. Leer la densidad que marca la escala justo en el punto de la superficie de la disolución. El punto de intersección es el que marca el menisco de la superficie de la disolución en la escala del densímetro.

4.2.3.2 Control del pH

El ajuste del pH es posible realizarlo con papel indicador o con pH- metro. En la tabla adjunta se muestran los pasos para ambos casos:

Papel indicador	pH-metro
1. Tomar una muestra y colocarla en un vaso de precipitados de 250mL (diluir la muestra si así lo indica el MBR).	1. Calibrar el pH-metro al inicio de cada jornada.
2. Cortar una tira de unos 2 cm de longitud de papel indicador de tres colores.	2. Tomar una muestra y colocarla en un vaso de precipitados de 250mL (diluir la muestra si así lo indica el MBR). Medir el pH. Comparar el valor con el que se indica en la ficha de fabricación.
3. Introducir un extremo dentro del vaso de precipitados con la muestra (1 – 2 segundos).	3. Si es inferior añadir más álcali. Si es superior, añadir más ácido. Dejar reaccionar durante 10 minutos después de cada adición. Una vez ajustado, dejar agitar durante 10 minutos más.
4. Comparar el color con la escala que aparece en la envoltura del papel indicador.	4. Volver a tomar muestra y medir de nuevo el pH. Anotar si está dentro de especificación.
5. Anotar el resultado en el MBR	5. Se considera ajustado el pH cuando 2 medidas consecutivas de 2 muestras diferentes extraídas con una diferencia de 10 minutos están dentro del valor especificado.

Una vez realizado el ajuste del pH, limpiar los utensilios requeridos para la toma de muestra y la medición con abundante agua desionizada.

4.2.4 Controles de laboratorio

Los controles de laboratorio se deben realizar cuando lo indique el MBR. Para ello se deben seguir los siguientes pasos:

a. Tomar la muestra que se desee analizar.

b. En la muestra se debe indicar la siguiente información:

- Producto
- Orden de Fabricación

- Fase
- Parámetro para controlar

c. Llevar la muestra correctamente identificada junto con el MBR al Laboratorio.

d. Anotar en la "Hoja de Control de Equipos" que la muestra está en el laboratorio.

e. Una vez se haya realizado el control, las acciones a realizar serán indicadas por Laboratorio. Dichas acciones serán anotadas por Laboratorio en la "Hoja de control de Laboratorio" de la OF correspondiente.

4.3 Parada

IMPORTANTE: Nunca se debe parar el agitador si hay producto cristalizado en el reactor.

Una vez descargado el reactor y asegurándose que no queda producto sólido en el fondo parar la agitación y proceder a la limpieza según el procedimiento PL_RINOX.

5. MANTENIMIENTO

Realizar Mantenimiento Preventivo según indicado en la plataforma de Mantenimiento de Intranet.

6. PRECAUCIONES, RIESGOS Y EPIs

6.1 Precauciones

Para todo proceso relacionado con los reactores inoxidables se deben tomar las precauciones generales siguientes:

- Procurar abrir la boca de hombre del reactor únicamente para la adición de sólidos o durante el muestreo para el control.
- Comprobar que la conexión a Scrubber/condensador esté abierta.

Para procesos más concretos las precauciones a tomar se muestran en la siguiente tabla:

Operación	Síntesis, concentración y cristalización
Proceso	**Precaución**
Carga de materias primas	Adición de materias primas lentamente.
	Cerrar correctamente la boca de hombre.
	No llenar el reactor más del 90% de su capacidad.
	Comprobar que las mangueras y conexiones cam-lock están en buen estado. Revisar especialmente que el producto no gotee.
	En la adición de producto sólido, evitar la generación de polvo.
	Durante la adición es posible observar un aumento de temperatura, tomar las precauciones para evitar salpicaduras/quemaduras.
	Tener especial cuidado al finalizar la adición de materias primas, Vaciar al máximo el producto acumulado antes de desconectarlas.
	Procurar que la válvula de fondo esté cerrada.
Sistema de Refrigeración Calefacción	Comprobar que las llaves del condensador están abiertas antes de poner en marcha el sistema.
	Abrir las llaves lentamente.
	Al refrigerar, abrir la llave de salida de agua previamente.
Agitación	Si la agitación se detiene con producto en el interior del reactor, no poner en marcha. Avisar al responsable inmediatamente.
Extracción de muestras y análisis de densidad	Esperar a que el contenido del reactor sea homogéneo.
	Para muestras líquidas, no debe haber producto sin disolver.
	La temperatura de la muestra puede ser superior a los 100ºC. Precaución ante quemaduras.
	Analizar inmediatamente la muestra una vez extraída.
	Es posible que el producto se cristalice al enfriar.
Ajuste del pH	No introducir el electrodo de pH directamente en soluciones calientes, debe ser a temperatura ambiente.
	No introducir el electrodo dentro del reactor.

6.2 Riesgos y EPIs

Los riesgos atribuidos a las fases realizables en los reactores inoxidables se muestran a continuación:

Riesgo	Causante
Quemaduras por temperatura y contacto con substancias químicas	Calentamiento del producto.
	Concentración/cristalización
	Manipulación del sistema de calefacción/refrigeración
	Salpicadura de producto
Sobreesfuerzo	Manipulación de cargas

En la tabla adjunta se muestran los EPIs necesarios:

EPIs	**Uso**
BOTAS DE SEGURIDAD	Siempre
PANTALÓN Y CAMISA ANTIÁCIDOS	Siempre
GAFAS DE PROTECCIÓN	Siempre
GUANTES DE NEOPRENO	Siempre
GAFAS ESTANCAS	Durante adición/descarga de producto líquido.
MÁSCARA INTEGRAL	Emergencias/ vapores irritantes y/o nocivos.
MÁSCARA BUCO-NASAL	Según instrucción de riesgos y seguridad de cada producto.
GUANTES DE PROTECCIÓN TÉRMICA	Manipulación de elementos calientes.

3. R-127 Cleaning procedure: PL-RINOX V02

MÉTODO DE LIMPIEZA DE REACTORES DE INOXIDABLE

PL-RINOX V02

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
PL-RINOX.00		Emitido para aprobación

PROCEDIMIENTO:

1. Vaciar completamente el equipo. Durante la limpieza del equipo, la manguera de descarga del reactor estará conectada en todo momento, de modo que quedará limpia juntamente con el resto del equipo.
2. Eliminar el producto de las paredes, fondo y agitador con abundante agua desmineralizada.
3. Llenar el reactor con agua desmineralizada, primero llenando 1/3 del reactor a través de la tubería de carga de 1" y luego hasta el total por la línea de carga de 2". Añadir 10 litros de ácido nítrico 60-65%. Poner la agitación en marcha, y calentar hasta una temperatura entre 60-80 ºC. Mantener la agitación y la calefacción durante 1 hora.
4. Parar la agitación y vaciar el contenido del reactor.
5. Enjuagar las paredes del reactor, el agitador y la cúpula del reactor con agua desmineralizada durante 15 minutos, manteniendo la válvula de fondo abierta.
6. Con la válvula de fondo cerrada, añadir agua desmineralizada hasta que toque la agitación al interior del reactor. Poner en marcha el agitador. Calentar a ebullición, y hervir durante 30 minutos.
7. Enfriar y vaciar el contenido del reactor.
8. Enjuagar las paredes del reactor, el agitador y la cúpula del reactor con agua desmineralizada, durante 15 minutos.
9. **Inspección visual:** Terminada la operación de limpieza se efectúa una inspección visual del estado del equipo el cual deberá mostrar las superficies sin manchas del producto. En caso contrario se abrirá una desviación.

4. IBC Cleaning Procedure: PL-RIKU

MÉTODO DE LIMPIEZA DE LOS CONTENEDORES RIKUTEC

PL-RIKU V01

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
PL-RIKU V01		Primera versión método de limpieza para los contenidores Rikutec.

	Doc nº:	PL-RIKU V01
	Sustituye:	**-**
	MÉTODO DE LIMPIEZA DE LOS CONTENEDORES RIKUTEC	

PROCEDIMIENTO:

1. Desenroscar el tapón negro (parte central del contenedor). Quitar la goma interior y limpiar con agua desionizada el tapón. Con un paño húmedo limpiar la rosca exterior de la boca central del contenedor. Poner una goma interior nueva.

2. Limpiar el interior del contenedor con abundante agua desionizada y aspirarla mediante vacío. Intentar aspirar todas las motas que hayan podido quedar en el fondo del contenedor.

3. Una vez lavado el interior del contenedor realizar una observación visual de que el interior del contenedor ha quedado limpio y sin partículas. Si no es así volver a repetir el paso 2.

4. Una vez el interior del contenedor está limpio limpiar la parte externa del contenedor con un paño húmedo. Registrar la limpieza en la guía de fabricación.

IMPORTANTE: No utilizar papel para la limpieza de los contenedores.

ANNEX II: EQUIPMENT QUALIFICATION DOCUMENTS

1. Design Qualification (DQ)
    a. User requirements, URS:

	REQUERIMIENTOS DE USUARIO R-127	Código: URS-R-127 Fecha: 04/04/2018

EQUIPO R-127	
CÓDIGO EQUIPO:	R-127
DESCRIPCIÓN:	Reactor de síntesis de acero inoxidable (4000 L)
USOS:	Síntesis/Cristalización/Concentración

REQUERIMIENTOS DE USUARIO	
REACTOR R-127	**¿Requerimiento disponible?**
Capacidad nominal	4000 L
Material de construcción	Acero inoxidable
Tipo de fondo	Klöpper
Boca de Hombre	Sí
Válvula de descarga	Sí
Válvula Toma muestras	Sí
Foco de iluminación	Sí
Sonda temperatura	Sí
Posibilidad de trabajar a presión	No
Conexión de energías	Sí
CIRCUITOS EXTERNOS	
Circuito de calefacción/refrigeración	Sí
Disponibilidad de agua de refrigeración	Sí
Disponibilidad de vapor	Sí
INTERCAMBIADOR DE CALOR	
Tipo de intercambiador de calor	Placas
Tipo de flujo	Paralelo
Fluido refrigerante	Agua refrigeración

SISTEMA DE AGITACIÓN	
Sistema de agitación	Sí
Tipo de agitador	Turbina
Tipo de cierre del agitador	Cierre mecánico
ELEMENTOS DE SEGURIDAD	
Manómetro (válvula de seguridad)	Sí
Semáforo para descarga	Sí
Disco de ruptura	Sí

FIRMAS Y APROBACIONES

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David Carreras	Quality Assurance		

b. Risk Analysis

Can be seen in CD enclosed.

c. DQ Report

	Doc nº:	DQ-R127 V01
	Sustituye:	**-**
	INFORME CUALIFICACIÓN DE DISEÑO ***DQ REPORT***	

Equipo	**R-127**

Cualificación de diseño

El equipo analizado es un equipo existente que forma parte de una instalación que está actualmente en funcionamiento. Las actividades realizadas para llevar a cabo la cualificación del equipo R-127 son acordes a las redactados en el Plan Maestro de Validación (VMP). En su momento no se siguió una cualificación del diseño desde el inicio por lo que este informe únicamente certifica que el equipo en cuestión ha sido sometido a un análisis de riesgo según su relevancia GMP y que dispone de todos los requerimientos previstos. Dicha información, de acuerdo con el Plan Maestro de Validación, pueden hallarse en los siguientes documentos:

1. Requerimientos de usuario (URS) con referencia de documento URS-R127. Documento que recoge y verifica que el equipo existente posee los requerimientos necesarios en la actualidad.
2. Análisis de riesgos con referencia de documento RA-R127. Dicho documento analiza los riesgos del equipo referidos a cuestiones de documentación e instalación existente del equipo.

Deficiencias

No se han detectado carencias que impliquen la definición de nuevos requerimientos de usuario que obliguen a iniciar un nuevo proceso de cualificación de diseño.

Conclusiones

El informe de cualificación del diseño queda así concluido constatando que el equipo ha estado operando según los requerimientos expresados en el documento URS y que será objeto de cualificación de la instalación y de operación. Con su adaptación a equipos y/o servicios existentes según se prevé en el Plan Maestro de Validación.

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HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
V01		Ejemplar para aprobación.

2. Installation Qualification (IQ)

a. Documental Matrix

	MATRIZ DOCUMENTAL	Revisión: MD-R127 Fecha: Abril 2018

Documento	**Requerido (S/N)**	**Realizado (S/N)**	**Referencia del documento**
Protocolo de Cualificación	S	S	Incluido en QA-011
Análisis de Riesgos	S	S	RA-R127
Requerimiento de Usuario	S	S	URS-R127
P&ID y Layout	S	S	Ver documentación técnica
Plano Constructivo	S	S	Ver documentación técnica
Esquema Eléctrico	N	N	-
Documentación Técnica	S	S	Documentación Fabricante
FAT: Pruebas en Constructor	N	N	-
SAT: Pruebas Puesta en Marcha	N	N	-
Procedimiento operativo	S	S	P-OP-07_I11
Plan de Mantenimiento	S	S	Ver Plan de Mantenimiento
Plan Calibración	S	S	Ver Plan de Mantenimiento
Inspección de seguridad (SHE)	S	S	Ver Plan de Mantenimiento
Certificación de Materiales	S	S	GKH140395A
Limpieza del equipo	S	S	PL-RINOX
Formación del Personal	S	S	P-OP-07_I11 y PL-RINOX
Cualificación Suministrador	N	N	-
Logbook equipo	S	S	Control informatizado

FIRMAS Y APROBACIONES

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APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

b. IQ Checkup

	IQ CHEQUEO	Revisión: IQC-R127 Fecha: 20/04/2018

CUALIFICACIÓN INSTALACIÓN IQ-CHEQUEO		
Equipo	**R-127**	
Prueba	**Observaciones**	**Resultados**
Identificación del equipo	Identificación existente y visible en la parte superior del reactor.	OK
Identificación del equipo en el panel de control	Identificación sencilla del interruptor marcha/paro, del selector de agitación y de la sonda de temperatura.	OK
Identificación del intercambiador de calor	Identificación existente y visible en una placa en el centro de la placa exterior del intercambiador. Datos perfectamente legibles.	OK
Identificación del agitador	Identificación existente y visible a través de una placa en el motor del agitador.	OK
Instalación	Presenta un golpe en la parte inferior exterior.	OK
Instalación eléctrica	El semáforo descarga funciona.	OK
Instrumentos auxiliares del equipo	En buen estado y en funcionamiento.	OK
Instrumentos de medida	Sonda de temperatura funciona correctamente.	OK
Instrucciones de uso y mantenimiento	Documentación existente	OK
Logbook	Existente	OK

FIRMAS Y APROBACIONES

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c. Datasheet R-127

	ESPECIFICACIONES TÉCNICAS R-127	Revisión: IQF-R127 Fecha: 25/04/2018

FICHA TÉCNICA DEL EQUIPO R-127

ESPECIFICACIÓN DEL EQUIPO	
Código equipo	R-127
Descripción	Reactor de síntesis / Vessel
Ubicación	-
Fabricante	Indústrias AJA de Lliça, S.L
Número de fabricación	1376
Fecha de fabricación	Junio 2015
Fecha de compra	2015

ESPECIFICACIONES TÉCNICAS DEL EQUIPO	
Dimensionado R-127	
Diámetro exterior del cuerpo	1616 mm
Diámetro interior cuerpo	1600 mm
Longitud con refuerzo	2702 mm
Longitud sin refuerzo	2000 mm
Tipo de fondo	Klöpper
Tipo de sujeción	Plataforma
Material	Acero inoxidable
Material en contacto con el producto	AISI 316L
Variables de diseño R-127	
Código diseño	AD-MERKBLÄTTER (CatII Módulo H)
Presión de prueba	Estanqueidad
Presión de diseño	Vacío
Temperatura de diseño	120 ºC
Tratamiento térmico	No
Coeficiente de soldadura	0,85
Margen de corrosión	0 mm
Volumen total	4,9 m^3
Fluido	Proceso
Aislamiento	No
Peso vacío	1640 kg
Peso lleno de agua	6690 kg
Circuito de calefacción/refrigeración: serpentín	
Tipo de sistema	Serpentín de media caña
Diámetro exterior	76 mm
Espesor	3 mm
Espaciado entre centros de media caña	120 mm
Material	Acero inoxidable
Altura de cuerpo	1620 mm

Variables de diseño del serpentín de media caña	
Presión de prueba	10,8 bar
Presión de diseño	6 bar
Temperatura de diseño	150 ºC
Tratamiento térmico	No
Coeficiente de soldadura	0,85
Margen de corrosión	0 mm
Volumen total	0,15 m^3
Fluido	Vapor
Aislamiento	Por otros
Intercambiador de calor	
Código	IP3601B35PX10
Número de fabricación	S25117
Fecha de fabricación	25/01/2016
Tipo de intercambiador	Placas
Tipo de flujo	Paralelo
Fluido	Agua
Capacidad	4,76 L
Tipo de placas	Desmontables
Número de placas	35
Material de las placas	Acero inoxidable AISI-316
Material de la junta	Junta en EPDM-PRX
Conexión	Rosca gas macho 2”1/2
Temperatura de diseño	140 ºC
Presión de diseño	8 bar
Presión de prueba	12 bar
Área de la placa	0,125 m^2
Área de intercambio total	4,125 m^2
Agitación	
Marca	Pimecsa
Número de fabricación	12978
Fecha de fabricación	06/2015
Tipo de agitador	Turbina
Material agitador	Acero inoxidable
Potencia	5,5 kW
Velocidad de agitación	128 rpm
Sistema de estanqueidad	Motor con cierre mecánico

Elementos de seguridad	
Disco de ruptura	No
Manómetro en serpentín	Sí
Sonda de temperatura auxiliar	No
Accesorios	
Llave de toma de muestras	Sí
Válvula de fondo	Sí
Sonda de temperatura	Sí
Iluminación a interior del reactor	Sí
Mirilla	DN-125
Boca de hombre	Sí

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

d. IQ Report

	Doc nº:	IQ-R127 V01
	Sustituye:	**-**
	INFORME CUALIFICACIÓN DE LA INSTALACIÓN ***IQ REPORT***	

Equipo	**R-127**

Cualificación de la instalación

La cualificación de la instalación se ha llevado a cabo para el equipo existente y codificado como R-127. Dicha cualificación se ha realizado de acuerdo con las actividades propuestas en el Plan Maestro de Validación las cuáles son:

- Realización de una Matriz Documental (MD-R127) dónde se recoge toda la documentación referente al equipo (GMP y otros aspectos) y sus respectivas referencias.
- IQ Chequeo (IQC-R127): Verificación in-situ de los aspectos relevantes de la instalación incluyendo una revisión de los Planes de Mantenimiento Preventivo y Planes de Calibración si se requiere. La actividad es documentada correctamente.
- Ficha IQ (IQF-R127): Redacción de una ficha del equipo con sus respectivas características. A través de dichos documentos se ha podido verificar que el equipo cumple con:
  - La documentación requerida del equipo está actualizada y correctamente archivada y codificada. En este requerimiento se incluyen los manuales del equipo, la documentación técnica y los certificados de materiales, calidad, pruebas hidráulicas y conformidad CE.
  - La existencia de procedimientos específicos del equipo, así como manuales de operación, procedimientos de limpieza, planes de mantenimiento y formación de personal.
  - La correcta caracterización del equipo, dónde se incluye la identificación del equipo (codificación) y la identificación de los elementos auxiliares.
  - La verificación de la correcta instalación del equipo mediante la comprobación de que el equipo cumple con los requerimientos de instalación propuestos por el fabricante. En este punto se revisa la instalación eléctrica, la instalación mecánica y el correcto estado de conservación y limpieza del equipo y entorno.
  - La calibración de los equipos auxiliares es correcta.

En base a la información obtenida durante el periodo de cualificación de la instalación, el resultado indica que cumple con las especificaciones y requerimientos indicados.

Deficiencias
No se detecta ninguna deficiencia/desviación que implique la apertura de una posible acción correctiva/preventiva y su posterior cualificación.
Conclusiones
El informe de cualificación de la instalación IQ queda así concluido constatando que el equipo está instalado de acuerdo con las especificaciones indicadas y que está en condiciones de pasar al estadio siguiente de cualificación operacional (OQ).

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
V01		Ejemplar para aprobación.

3. Operation Qualification

a. Operational tests

	CUALIFICACIÓN OPERACIONAL PRUEBAS OQ	Revisión: OQT R-127 Fecha: 28/04/2018

Prueba	**Criterio de aceptación**	**Resultado**	**Observaciones**
Volumen mínimo de operación: Llenar con agua hasta la mitad de las palas/agitador y medir el volumen.	Reportar resultado	Turbina inf.: 460 L Pala media: 2.000 L Boca de hombre: 4.860L	
Volumen máximo de operación: Llenar con agua hasta la boca de hombre, medir el volumen y aplicar un factor de seguridad de 85%.	Reportar resultado	Vtotal = 4860 L Vcorregido = 4130 L	
Temperatura máxima +100 ±5ºC: Llenar con agua desionizada: volumen mínimo, enfriar hasta la temperatura mínima y mantener 30 min. Reportar la temperatura.	T≥100ºC	t_1= 0 min T_1 = 30 ºC t_2 = 30 min T_2 = 100ºC t_3= 45 min T_3 = 100 ºC	
Temperatura mínima: 25ºC ±5ºC: Llenar con agua desionizada: a volumen mínimo enfriar hasta la temperatura mínima y mantener 30 minutos. Reportar la temperatura.	T ≤ 30 ºC	t_1= 0 min T_1 = 25 ºC t_2 = 30 min T_2 = 25 ºC t_3= 45 min T_3 = 25 ºC	
Condensador: Llenar con agua desionizada. Calentar hasta ebullición y destilar unos 50 litros. Destilar sobre probeta de 100 mL. Reportar los resultados.	Sin requerimiento	q_1=77 L/h q_2= 73 L/h q_3= 77 L/h qmig = 76 L/h	
Estanqueidad: Se observa la ausencia de fugas.	Reportar resultado	No presenta fugas	

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

b. OQ Report

	Doc nº:	OQ-R127 V01
	Sustituye:	**-**
	INFORME CUALIFICACIÓN OPERACIONAL *OQ REPORT*	

Equipo	**R-127**

Cualificación operacional

El equipo analizado es el reactor de inoxidable R-127. La cualificación operacional se ha llevado a cabo siguiendo las actividades propuestas en el Plan Maestro de Validación. Se han realizado pruebas y reportado los resultados para verificar el correcto modo de operación del equipo. Dichas pruebas han sido documentadas en el documento de pruebas OQ con referencia OQT-R127.

Deficiencias

NO se han detectado deficiencias/desviaciones que impliquen la apertura de acciones correctivas/preventivas y su posterior cualificación.

Conclusiones

El informe de cualificación operacional OQ queda así concluido constatando que el equipo está instalado de acuerdo con las especificaciones indicadas. En este punto se considera el equipo cualificado y apto para trabajar en condiciones reales de proceso. En la integración de este equipo en un programa de validación de proceso, se concluirá su cualificación de funcionamiento o PQ en función de los resultados que se obtengan.

FIRMAS Y APROBACIONES

REDACTADO	CARGO	FECHA	FIRMA
Clara Galisteo	Técnico de producción		
REVISADO	CARGO		
Francesc García-Donas	Responsable Producción		
Xavier García	Director Producción		
APROBADO	CARGO	FECHA	FIRMA
David Carreras	Quality Assurance		

HISTORIAL DEL DOCUMENTO

REVISIÓN	FECHA	COMENTARIO
V01		Ejemplar para aprobación.

ANNEX III: TABLES

Table 1. Table of Product Final Specifications recorded of every batch.

	Specification	Identification A	Identification B	Assay	Appearance of solution	Sodium Carbonate	Chloride	Sulphate	Heavy metals (as Pb)	Iron
	Guarantee	Passes test	Passes test	31,5 - 32,5	Passes test	Max. 0,5	Max. 50	Max. 50	Max. 5	Max. 3
	Units	-	-	%	-	%	ppm	ppm	ppm	ppm
Validation Batches	79109	Passes test	Passes test	32,0	Passes test	0,02	< 50	< 50	< 5	< 3
	79125	Passes test	Passes test	32,1	Passes test	0,02	< 50	< 50	< 5	< 3
	80083	Passes test	Passes test	31,9	Passes test	0,20	< 50	< 50	< 5	< 3
	80469	Passes test	Passes test	32,0	Passes test	0,20	< 50	< 50	< 5	< 3
	80476	Passes test	Passes test	32,0	Passes test	0,20	< 50	< 50	< 5	< 3
	80960	Passes test	Passes test	32,1	Passes test	0,20	< 50	< 50	< 5	< 3
	81001	Passes test	Passes test	32,0	Passes test	0,20	< 50	< 50	< 5	< 3
	81161	Passes test	Passes test	32,1	Passes test	0,20	< 50	< 50	< 5	< 3
	81182	Passes test	Passes test	32,1	Passes test	0,20	< 50	< 50	< 5	< 3
	81243	Passes test	Passes test	31,8	Passes test	0,20	< 50	< 50	< 5	< 3
	81733	Passes test	Passes test	31,8	Passes test	0,30	< 50	< 50	< 5	< 3
	82049	Passes test	Passes test	32,0	Passes test	0,20	< 50	< 50	< 5	< 3
	82076	Passes test	Passes test	31,9	Passes test	0,30	< 50	< 50	< 5	< 3
	Average (x)	-	-	32,0	-	0,2	-	-	-	-
	Standard deviation (σ)	-	-	0,11	-	0,08	-	-	-	-
	x - 2σ	-	-	31,8	-	0,0	-	-	-	-
	x + 2σ	-	-	32,2	-	0,4	-	-	-	-

Table 2. Deviation 1

Deviation 1	
Product	Sodium hydroxide 32% w/w GMP
Batches affected	80321
Origin	Internal
Non-conformance identification	OOS-QC-19/2017
Initial date	10/10/2017
Final date	25/10/2017
Kg Affected	5.400

Causes of non-conformance

The product was in reactor more than fifty days. When solution of NaOH remains some time inside the reactor, tends to be carbonated because of carbon dioxide. This batch is out of specification.

Corrective and preventive actions (CAPA)

1) Batch rejected.

2) Modification of the MBR and include carbonate content as a Critical In Process parameter to be controlled before performing the filtration and packaging step. Maximum content of 0.5% as is stated on the final product specifications).

Results and effectiveness of CAPA

There has been no recurrence on the non-conformance since the CAPA was implemented.

Table 3. Deviation 2

Deviation 2	
Product	Sodium hydroxide 32% w/w GMP
Batches affected	80959
Origin	Internal
Non-conformance identification	12 (GMP)
Initial date	19/12/2017
Final date	20/02/2018
Kg Affected	4.050

Causes of non-conformance

The product was manufactured according to regulations of ISO instead of GMP. In addition, the compliment of Data Integrity in MBR was incomplete. These causes leading to reject the product completely.

Corrective and preventive actions (CAPA)

1) Informing the operators involved in the manufacturing of the batch affected about how to proceed following rules of GMP.

2) Quality Assurance needs to perform a Data Integrity training to all Manufacturing Plant operators.

Results and effectiveness of CAPA

CAPAs 1 and2 implemented. No deviations during the final review of the MBR are observed from Quality Assurance. For that reason, the effectiveness of the training performed is demonstrated.

Table 4. Deviation 3

Deviation 3	
Product	Sodium hydroxide 32% w/w GMP
Batches affected	81182, 81181, 81001, 81243
Origin	Customer Complaint
Non-conformance identification	1283
Initial date	15/02/2018
Final date	Pending to be closed
Kg Affected	9.450

Causes of non-conformance

There were individual foreign particles in different IBCs. It could be possible because IBC are re-used and when the black screw caps are manipulated, foreign particles (Carbonate + degraded gasket) can easily be introduced inside the IBC.

Corrective and preventive actions (CAPA)

1) Cleaning IBCs (new and returned) before use. A Cleaning procedure of the IBCs will be stated. On this cleaning procedure, the changing of the gasket from the black screw cap will also be stated. The cleaning performance and check will be included in the Master Batch Records.

2) For the new deliveries, the Viton material of the black screw cap gasket will be changed by EPDM material.

3) Study of the stability of the following solutions:

- NaOH 32% Batch 81181 (filtered solution)

Results and effectiveness of CAPA

CAPAs 1 and 2 are already implemented. New production batches has been delivered to the customer and they found the product correct.

Data for the first month of the stability of the filtered batch 81181 is correct: clear and colorless, CAPA 3 will be finished by the end of June.

Table 5. Deviation 4

Deviation 4	
Product	Sodium hydroxide 32% w/w GMP
Batches affected	81733
Origin	Internal
Non-conformance identification	14 (GMP)
Initial date	08/03/2018
Final date	16/05/2018
Kg Affected	4.050

Causes of non-conformance

Some carbonate particles are observed over the final product.

Corrective and preventive actions (CAPA)

1) Reprocess of batch 81733. The filtration needs to be done and registered with a new MBR.

2) Cleaning procedure PL-RIKU needs to be modified to include the cleaning of the black screw cap to avoid contamination of sodium carbonate due to the sodium hydroxide carbonation.

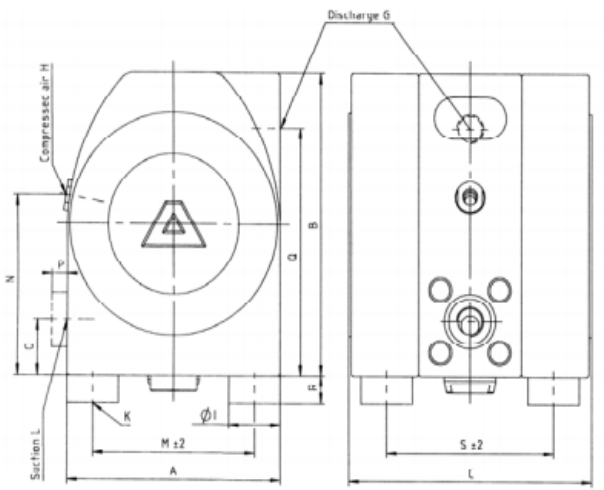
Results and effectiveness of CAPA

CAPAs 1 and 2 implemented. Batch 81733 is released, and two more batches are produced performing the updated procedure PL-RIKU without observing any deviation.

ANNEX IV. SPECIFICATIONS OF PUMP AND CUNO FILTER

a. Pneumatic Pump Data Sheet

PNEUMATIC PUMP	
Specifications of pump	
Material	Teflon
Diaphragm	Yes
Capacity	3,4 m^3/h
Length	166 mm
Width	189 mm
Height	240 mm
Nominal port size	½"
Air connection	R 1/4
Max. Particle size of solids for pumps with ball valves	4 mm
Suction lift dry, mWC	3 ft
Suction lift wet, mWC	9,5 ft
Max. Driving and operating pressure	7 bar
Max. Operating temperature	70 °C



b. Cuno Filter Data Sheet

CUNO FILTER	
Specifications of Cuno Filter	
Fineness	1 μm
Material	Polypropylene
Length	250 mm (10")
Consistent with	Strong acids, concentrated alkali, oxidizing agents, reducing agents, electroplating and other chemical products in aqueous solutions.
Not recommended to	Hydrocarbons such hexane, naphtha and others.
Maximum operating temperature	+ 80ºC