Technology Transfer, A Risk Management Approach

Eye Drops Case Study

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Preface

The work presented in this thesis was performed at Faculty of Pharmacy, University of Lisbon (Lisbon, Portugal) and Laboratório Edol (Linda-a-Velha, Portugal), during the period February-August 2019, under the supervision of Professor Rui Loureiro, PhD. The thesis was co-supervised at Instituto Superior Técnico by Professor Carlos Henriques, PhD.

The information in Chapter 3 and 4 was complemented by the experience of the student in the company Laboratório Edol – Produtos Farmacêuticos, S.A.

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“If you want to go fast, go alone; If you want to go far, go together”. – African Proverb.

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“Some men see things as they are and ask ‘why?’,
Others dream things that never were and ask, ‘why not?’.”
George Bernard Shaw

I dedicated this thesis
to the most important person in my life: my husband.
Thank you for helping me to realize my dream.
Thank you for “flying” with me.

Declaration

I declare that this document is an original work of my own authorship and that it fulfills all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.

Abstract

Nowadays, the business area of pharmaceutical companies is increasingly broad, which means that companies have to adapt and adopt new strategies, such as partnerships, exports, research of new products, increase of production scale, among others. [4,7,8,10]

Thus, the objective of the development of this thesis was to contribute to the increase of knowledge of technology transfer in the pharmaceutical industry, more specifically in Laboratório Edol, through the description of transfer planning and associated documentation (contract, proposal, implementation plan and package), of the main project phases (process development, facility fit assessment, team selection, execution and qualification) as well as identifying success criteria (communication, certainty, challenges, capacity and commitment), of the main barriers (incomplete documentation, insufficient process knowledge, high costs) and the responsibilities of the parties involved in technology transfer. [4,13,27,28,35]

In addition, a 150L industrial scale batch scale up manufacturing validation protocol was developed which included: the various manufacturing steps, main equipment used, the critical steps, the sampling process and the acceptance criteria. The results obtained from the 3 validation lots showed that the 150L eye drop production is validated.

In the end, a risk management of this production was also done, in order to identify the most critical steps and the difficulties that may arise when the transfer of this manufacturing process to the new facilities. [46]

***Keywords*:** *Technology Transfer, Manufacturing Process Validation, Risk Management.*

Resumo

Atualmente, a área de negócios das empresas farmacêuticas é cada vez mais abrangente, o que implica que as empresas têm de se adaptar e adotar novas estratégias, tais como parcerias, exportação, pesquisa de novos produtos, aumento da escala de produção, entre outras. [4,7,8,10]

Desta forma, o objetivo do desenvolvimento desta tese passou por contribuir para o aumento de conhecimento da transferência de tecnologia na indústria farmacêutica, mais concretamente no Laboratório Edol, através da descrição do planeamento da transferência e documentação associada (contrato, proposta, plano de implementação e pacote), das principais fases do projeto (desenvolvimento do processo, avaliação das instalações, equipa de transferência, execução e qualificação) bem como a identificação de critérios de sucesso (comunicação, certeza, desafios, capacidade e compromisso), das principais barreiras (documentação incompleta, conhecimento insuficiente do processo, custos elevados) e das responsabilidades das partes envolvidas na transferência de tecnologia. [4,13,27,28,35]

Além disso foi desenvolvido um protocolo de validação do aumento de escala de produção de colírio com um lote industrial de 150 L que incluiu: os passos de fabrico, principais equipamentos utilizados, os passos críticos, o processo de recolha de amostras e os critérios de aceitação. Os resultados obtidos dos 3 lotes de validação mostraram que a produção de colírio de 150 L encontra-se validada.

No fim, foi ainda feito uma análise de risco desta produção, de modo a identificar as etapas mais críticas (filtração esterilizante e enchimento asséptico) e uma avaliação das dificuldades que podem surgir aquando da transferência deste processo de fabrico para as novas instalações. [46]

Palavras-chave: *Transferência de Tecnologia, Validação do Processo de Fabrico, Gestão de Risco.*

Abbreviations

API – Active Pharmaceutical Ingredient

CPP – Critical Process Parameter

CPV – Continuous Process Verification

CQA – Critical Quality Attribute

EMA - European Medicines Agency

EU - European Union

FDA - Food and Drug Administration

GMP - Good Manufacturing Practices

HEPA – High-Efficiency Particulate Air

HPLC – High-Performance Liquid Chromatography

HVAC – Heating, Ventilation and Air Conditioning

ICH - International Council for Harmonization

MPV – Manufacturing Process Validation

PQR – Product Quality Review

QRM – Quality Risk Management

R&D – Research and Development

RU – Receiving Unit

SOP – Standard Operating Procedures

SU – Sending Unit

TPV – Traditional Process Validation

TT – Technology Transfer

TTD – Technology Transfer Dossier

TTP – Technology Transfer Proposal

VMP – Validation Master Plan

WHO - World Health Organization

Glossary

Calibration – It is a set of operations that demonstrate in a documented manner that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. [51,52]

Critical Process Parameter (CPP) – It is a process parameter that must be monitored and controlled because its variability impacts a critical quality attribute. This monitoring ensures that the process is produced with the desired quality. [54]

Critical Quality Attribute (CQA) – It´s a chemical, physical or biological characteristic or property that should be within an approved limit, range or distribution to ensure the desired product quality. [54]

Intellectual Property – It´s information, ideas and knowledge. It´s divided into two categories: Industrial Property (patents, trademarks, industrial designs) and Copyright (poems, novels, films, music). [53]

Intellectual Property Rights – They are specific legal rights which protect the creators or owners of Intellectual Property. These rights are outlined in Article 27 of the Universal Declaration of Human Rights. [53]

Patent – It´s as exclusive right granted for an invention (a product or a process) for a limited period, generally 20 years. A patent provides owners protection for their inventions. [53]

Qualification – A set of activities that documentally verify and evidence that a system or equipment that has been designed is installed and operating in accordance with predefined specifications and in a reproducible manner. [52]

Quality Risk Management – It is a systematic process for the assessment, control, communication and risk review for the product quality of pharmaceutical formulations throughout its life cycle. It´s a process that supports science-based and practical decisions when integrated into quality system. It´s a key part of technology transfer project and it can facilitate better and more informed decisions. [46]

Robustness – It´s the ability of a process to demonstrate acceptable quality and performance, while tolerating variability in inputs. [51,52]

Validation – It is the demonstration that control of critical process steps results in products with reproducible properties or that causes a reproducible event. [36, 52]

Contents

List of Figures

List of Tables

Chapter 1 – Introduction

1.1. Aim of this thesis

The aim of this thesis is to contribute for an improvement on Technology Transfer (TT) and Manufacturing Process Validation (MPV) in pharmaceutical industries. The main goal is to elaborate a checklist with attributes and conditions which must be present, to support the decisions regarding the transfer process. This type of process is most commonly used in multiproduct pharmaceutical industries. Furthermore, it will describe a manufacturing process validation for industrial scale batches about the eye drops solution.

1.2. Outline

The elaboration of this work will be done in multiple phases.

Initially, a literature review, based on scientific articles and published documents by various organizations, such as, European Medicines Agency (EMA), World Health Organization (WHO), Food and Drug Administration (FDA) and International Council for Harmonization (ICH) about TT and PV, will be performed

Posteriorly, the process transfer and validation for special cases, such as sterile medication and dermal products, will be described. Furthermore, the Critical Process Parameters (CPPs) as well as identifying possible failures/risks during the different stages of the process, will be also described

Finally, a real case scenario about manufacturing process validation for industrial scale batches in accordance with Good Manufacturing Practices (GMP) will be presented

1.3. Technology Transfer Drivers

Nowadays, economic growth is global as well as services development and new competitive markets, especially in the area of pharmacy industry. Increased average life expectancy, development and research into new therapeutic practices as well as increased buying power have all contributed to increased drug consumption in recent years.

However, despite the progress made, it is estimated that about 2 billion people worldwide don´t have access to the necessary medicines, even "lifesaving" medicines. In order to minimize the problem of access to various medicines and improve public health, technology transfer can be a good strategy for local drug production, especially in developing countries.

In the next chapters the implementation of the manufacturing process as well as the transfer of associated the reasons and the success criteria will be described in more detail. The conflict between the sales to affordable medicines and the pharmaceutical industries business priorities, such as profit and the right to produce or not a drug, depending on the financial return, will also be described.

Chapter 2 – Literature Review

2.1. Technology Transfer

2.1.1. Definition and Classification

TT is a process that follows the entire life cycle of a product and can be described as a process of transferring intellectual property (copyrights, know-how, patents, etc.) to an appropriate, responsible and authorized party (Receiving Unit - RU). It consists of the transfer of product documented knowledge, process or analytical method and experience gained from laboratory development (laboratory scale) to product commercialization (industrial scale). The transition of this knowledge provides the basis for the manufacturing process, critical step control strategies, validation process and continuous improvement. Examples of knowledge to be transferred include:

- Scientific and operational information;
- Product Quality Attributes (Critical Quality Attribute – CQA and material attributes);
- Unit Operations;
- Health, Safety and Environmental requirements;
- Learning points from previous collaborative activities;
- Control strategy;
- Implication tor the use of tools (e.g. calibration of models);
- Continuous improvement ideas and plans.

TT also incorporates documentation transfer and demonstration of the ability to effectively execute critical elements from the RU. [1-6]

This transfer process can occur in different cases, namely: between private sector firms at the same or at different countries, government labs to private labs or from academia to private sector firms. [7,8,9]

TT can be classified as horizontal or vertical depending on the scope in which it occurs. Thus, vertical TT refers to the transfer process from Research and Development (R&D) to large-scale production of the product. Usually this type of transfer involves management of intellectual property rights. [7] On the other hand, horizontal TT refers to the process of transfer from one market to another, which is usually a less developed one. Sometimes this type of transfer requires some process modifications or even in the final product, in order to produce a product with the requirements and criteria accepted by the regulatory authorities in the destination market. In addition, often factory or even weather conditions are different from the original process which may require process / product updates. [2,4,5,6,7]

2.1.2. Reasons to Technology Transfer

TT is increasingly present in the pharmaceutical activity and can occur for several reasons, including:

- Scale-up – due to the transition from laboratory development to production and subsequent commercialization;
- The need for additional capacity, in order to respond to market needs;
- Corporate mergers and consolidations;
- Business strategies for relocating units in different regions of the world (economic advantages in different regions of the world: cheaper labor costs, tax exemption, greater control of the global market;
- The developer of technology does not have sufficient resources for manufacturing (local and large-scale production equipment) and / or for product commercialization (marketing and distribution channels).;

Regardless of what is the main goal, good documented TT planning and success criteria are required for all scenarios. These may vary depending on TT goal / reason. [4,7,8,9,10]

2.1.3. The Importance of Technology Transfer

For there to be a breakthrough in knowledge and technology development, is necessary to have cooperation and collaboration between various entities, namely between university researchers and industry. This type of collaboration often results in licensing and sponsored research opportunities (eg: through research grants), benefiting both parties involved. [11-13]

TT helps complement academic research and ensures that the university's intellectual property interests and rights are protected. Thus, the university may issue a license for conditional use of the technology in question. [13,14]

Successful transfer and technology development help promote the institution, since it will increase recognition and reputation as a potential site for development and innovation. In addition, the university can use the revenues from licensing to support other researches, to improve conditions in the institution and help stimulating local economic development. On the other hand, industry partners benefit from reduced costs during the research and development phase. [14-33]

The ultimate beneficiary of a successful TT are the people, which benefits not only from products coming to the market but also from the creation of new jobs related with development (sale of raw materials), manufacturing (sale of equipment, factory workers) and selling products. [11,13,14,26,33,34]

2.1.4. Planning Considerations

Typically, a TT begins with a formal written agreement between Sending Unit (SU) and RU to ensure that this partnership leads to a successful and efficient completion of the transfer process, i.e. that RU successfully produces a safe, effective and quality product. [4,13,27,28,35] The established contract must clearly describe the responsibilities of each party, specifically who performs each step along the transfer process: knowledge management, purchasing materials, conducting production and quality controls

(including in-process controls). In addition, the contract must allow SU to audit the activities performed by the RU or its agreed subcontractors. [27,35]

According to European Union Commission Regulation nº. 316/2014 of 21 March, TT agreements may occur if each party's individual share in the relevant markets does not exceed 30% for non-competitors and 20% if they are competitors. Moreover, such agreements should not contain serious anti-competitive restrictions and should aim to improve production and/or distribution, thereby ensuring benefits for the final consumer. [28]

In addition to the contract, it is also necessary to make a TT proposal, which should describe the purpose and scope of the project, which team members as well as their roles and responsibilities within the project, the time required for each stage, the success criteria as well as the likelihood and severity of the associated risks. This document aims to ensure that the elements involved from both the SU and the RU understand the project and that they agree with the strategy adopted and the defined deadlines. In the end, the SU and the RU should revise the document and at the end, if all parties are in agreement, they should approve the document. [4,13,28,29,30,31]

Note that sometimes the TT contract and proposal may be the same document, depending on the complexity of the TT project. [4,37]

Upon approval of the Technology Transfer Proposal (TTP) a TT implementation plan is required to guide the transfer process, expectations and possible changes that may occur during implementation. This plan is based on TTP and aims to describe the elements involved in the implementation of TT as well as track the progress of the project. It thus provides more detailed information on the various elements (functions, qualifications), key execution activities, risk identification and assessment results, fault analysis and mitigation actions. It should also contain up-to-date schedules, resources, budgets, key assumptions, regulatory strategies, and success criteria. [4,13,27,31]

This plan should be GMP compliant and should start as soon as possible, allowing to anticipate problems and faster response to anomalies, thus avoiding possible delays at different stages. When necessary, the project manager can adjust the schedule without moving the key milestones. [13,17]

Together with the Technology Transfer Plan it is necessary to establish a timeline between a successful TT and the various associated tasks. **Figure 2.1.** describes the main elements in managing a TT and the timeline relationship between them. [4]

It should be noted that each TT process is unique and therefore there is no generic and absolute plan covering all cases. [4,13,27]

The Technology Transfer Plan should not be a fixed document and should be continuously reviewed and updated. Whenever there are changes that impact the process budget, timeline for major milestones or assumptions/risks, these should always be incorporated and approved by the parties involved in the process. [27]

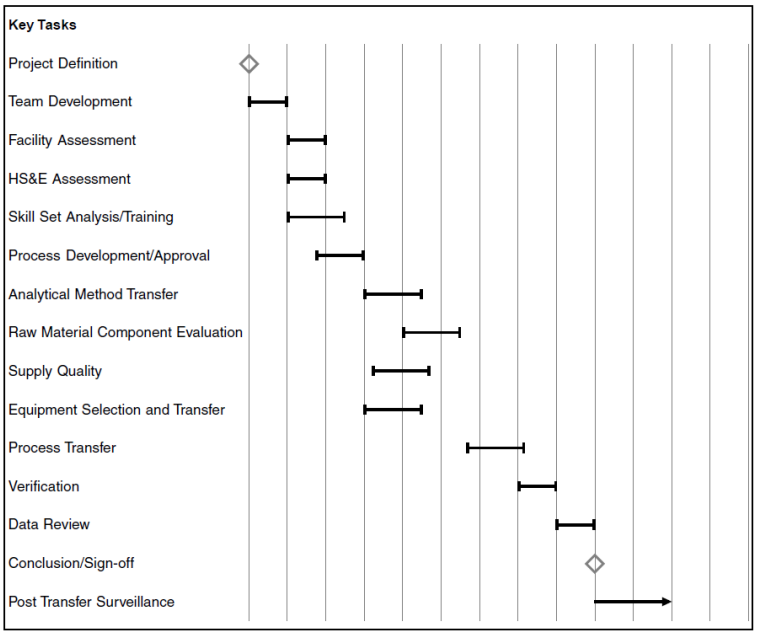


Figure 2.1 - The main elements in managing a Technology Transfer. [4]

In the end it will be necessary to organize all the necessary information so that the RU can use it and become self-sufficient in carrying out an analytical method or manufacturing process - The technology transfer package. The information provided should be easily accessible and should ensure an easy understanding of the process. [16,27]

Basic requirements for the technology transfer package can include:

- Business requirements;
- Product specific requirements (CQAs, control strategy);
- Facilities capabilities assessment;
- Process flow diagrams, unit operations, material attributes and parameters;
- Detailed historical data (including justification any process changes);
- Risk assessments;
- The control strategy (identified CPPs and CQAs);

In addition to the above requirements for the technology transfer package, more requirements may be incorporated as TT progresses. [16,27,35]

The technology transfer package should be used by both units and can be used as a basis for risk assessments. These assessments should compare process or procedure history with RU resources and operations to identify potential gaps or misalignments that may require future modifications. [27,35]

2.1.4.1. Project Phases

For a successful TT to take place, a good planning of the various steps, as well as the presence of qualified, trained and experienced personnel working within a quality system are required.

Furthermore, it is necessary that the various stages, especially the development, production and quality control stages are properly documented. [13,17]

The TT process is a very complex and multi-directional process that involves the cooperation of many individuals, from basic researchers to manufacturing specialists to marketing people. [17,27,34]

The TT process can be simplified in 5 main steps: Process Development, Facility Fit Assessment, Team Selection, Execution and Qualification. [13,34]

Step 1 – Process Development

The TT process begins during small-scale process and product development long before final manufacturing facilities are selected. During the process development it is necessary to take into account the resources for unit operations, production environments, quality attributes, process parameters and the constitution of the manufacturing process team (pharmacists, operators, maintenance team, cleaning team). [33,34]

Furthermore, it is necessary to consider different parameters that may interfere with the success of a TT before starting the scale-up, namely: costs, reliability, innovation and product quality. [13,27,34]

This step also defines the best manufacturing method based on data provided by R&D through the Technology Transfer Dossier (TTD), i.e. a document containing all drug product information:

- Master formula card - contains product name, packaging details, storage conditions, safety precautions, raw material details along with approved suppliers and a brief description of the manufacturing;
- Master packaging card - provides packaging information, including the type of material used, stability profile and expired date;
- Master formula - describes the formulation as well as the various steps of the manufacturing instruction as well as the required environmental conditions;
- Standard test procedures and specifications - provides information on Active Pharmaceutical Ingredient (API) profiles and excipients, finished product requirements and their release. [34]

It should be noted that the earlier the discussion and integration of risk management and risk reduction, the more effective the development process becomes. [4,13]

During this step it is advisable to seek legal advice to deal with intellectual property or other possible issues that may cause delay to the development stage. [4,13]

Step 2 – Process/Facility Fit Assessment

The second step comprises assessing the fit of both the product process and the facilities to which it will be transferred and manufactured. Equipment constraints, manufacturing details, space constraints as well as facility flexibility should be carefully assessed and shared among the development and manufacturing team to optimize TT. [13,27,34]

When adjusting the process to manufacturing facilities, a commitment between SU and RU is required to maintain a robust process and subsequently obtain a quality product. It is also necessary to analyse the regulatory impact, especially if process adaptation requires changes to the facility's control

strategy. In addition, environmental/safety and health representatives should be consulted in order to assess potential problems that may arise in the manufacturing process, e.g. wastewater treatment. [27,32,34]

Step 3 – Process Transfer Team Selection and Define Deliverables

The success of a TT depends on many factors, especially people. For this reason, the TT team must be multifunctional and must be composed of specialized members from SU and RU. Everyone involved should be aware of GMP principles and should receive initial and ongoing training depending on their role. [4,13,27,32]

Team members are selected to provide technical knowledge of manufacturing process requirements, including CQAs, plant and equipment capacities and limitations, process performance history, regulation, etc. Each team member thus has a specific role and responsibilities during the transfer process. [13,17,34]

In addition to the overall team, a core team that has all the knowledge about the TT process is needed and actively follows all stages of the transfer - The core technology transfer team. Typically, this team is made up of individual's representatives of the different segments of the business. The table **2.1**. describes its elements as well as the associated functions. [13,27,32,34,35]

Table 2.1. – Elements of the core technology transfer plan and their functions. [32-35]

Elements	Function
The Project Manager	The overall coordination, responsibility and communication progress to the management. His authority may be delegated as appropriate.
Regulatory Affairs	Coordination of the appropriate regulatory filings, advice on the timing of approval, filing documentation contents and response to the regulatory inquiries.
Engineering	Project coordination associated with equipment acquisition, construction control, installation and qualification.
The Material management	Coordination of strategic planning, resource allocation and supple chain activities. Analysis and advice on the most favorable production strategy taking into account business partnership and internal capacity.
The Manufacturing operations	Receiving location of production activities and to represent the originating site.
Research and Development	To direct and train the production trials at the receiving site and support in solving technical problems.

After selecting the overall team, it is important for a full-member meeting to explain the various steps of the transfer, providing an overview of the process and adaptation of the facilities/equipment, and even initiate some important technical discussions. Also, it will be presented the Technology Transfer Plan, i.e. TT objectives, deadlines, schedules, responsibilities of each team, etc. This type of meeting helps

to increase cooperation and fellowship among the various elements, contributing to the success of TT. Usually this meeting takes place at the RU premises. [13,17,27,34]

The transfer team should meet frequently to assess progress as well as the previously set deadlines. [4,13]

Post-transfer activities may sometimes require support for regulatory inspections or transfer-related issues, thus involving either SU or RU members to assist and support regulatory activities, documentation or participating in site inspections. [11,32,34]

Step 4 – Execution (Monitor/Progress)

The TT execution phase corresponds to the implementation of the Technology Transfer Plan. The new process is transferred to the RU by integrating process requirements into business processes, associated process and operational documentation. [32,34,35]

This process transfer also includes failure and risk analysis and identification, as well as resolution previously agreed upon the transfer team, including:

- Process descriptions for each unit operation;
- Process and operating control strategies (risk management tools);
- Process and equipment risk assessments. [4,13,27]

Following risk identification, TT execution may include facility modifications identified in risk identification analysis, full scale manufacturing equipment testing to ensure proper operation, including mixing studies, cleaning, etc. [13,27,34]

Before starting large-scale production, it is advisable to perform the process on a small scale to demonstrate that the adopted model is valid and produces products within the stated specifications (semi-industrial lots - PV). These small-scale models can also be used for process training, for additional process development work, and can also be used to help solve problems that can be observed in early large-scale executions, thus providing more control over some parameters. [13,25,27,32,34]

The operational experience of the RU team ensures successful integration of process requirements and enables manufacturing batch registration and operating instructions that result in a successful manufacturing process. In addition, the TT team closely monitors process execution and results as well as operational observations during the first batch manufacturing process of the new process. The results provide a prediction about the success of the TT in question and information on possible changes/adjustments of the manufacturing process. [13,37,34]

The implementation phase of the TT process also included the development and approval of documentation and / or electronic systems that will later be used to execute the process in the UK. This documentation included: batch records, Standard Operating Procedures (SOPs), etc. There should therefore be a structure agreed upon by SU and RU that defines the review and approval of manufacturing documents as well as the tracking and management of different versions throughout the process. [4,13,27,32,34,35]

After approval of the receive location it is essential to formally document the lessons learned and corrective actions implemented. It is also vital to continue to exchange information on manufacturing

process performance, deviations and possible changes in order to contribute to continuous improvement of the manufacturing process. [13,37,32,33,34,35]

Step 5 – Qualification

Upon successful completion of the technology transfer execution phase, the project will move to the analytical procedure / process qualification phase. This phase corresponds to the RU technology demonstration and the comparison of the process and product generated to ensure that it aligns with expectations. [4,13,27,34]

Please note that the qualification protocol implementation should only be done after the protocol has been reviewed and approved by all appropriate departments. Any deviations from the protocol must be done in accordance with the established quality procedures. [33,34]

This phase should also involve a documented report on the completion of the evaluation of the data obtained as well as the identification of mitigation plans needed to address any issues observed during qualification. If the analytical procedure/process qualification does not meet the acceptance criteria, an investigation should be made into the possible failure and attempt to resolve the issue before repeating the exercise. [13,37,33,34,35]

The final actions of the TT process correspond to a review of the whole process, i.e. assessment of how each transfer step occurred, whether deadlines were met, communication and teamwork were effective, if adjustments made to procedures resulted in improvement, etc. The knowledge gathered from this review should be shared by the teams involved in the TT process. [13,27,34]

Finally, before declaring that a TT has been successful, it is necessary to verify whether any corrective action is required. [13,27]

2.1.4.2. Sending Unit and Receiving Unit Responsibilities

As stated above, the responsibilities of each of the parties involved must be clear and well defined before the execution of the TT. Before the TT process, the SU is responsible for assessing the legal, suitability and competence of the RU to successfully conduct the outsourcing activities. It is also responsible for ensuring, by contract, that GMP principles and guidelines are met. [27,35]

The SU must provide all necessary information and knowledge in order for the RU to be able to properly perform operations in accordance with applicable regulations. So, the SU should provide a list of equipment (makes, models, capacity), qualification and validation documentation (manuals, maintenance logs, calibration logs, drawings, procedures), criteria and information on hazards and critical steps associated with product, process or method. This information will serve as the basis for a Quality Risk Management (QRM) at the RU. On the other hand, the RU should review the information provided by the SU and make a side-by-side comparison of equipment in terms of their functionality, makes, models, qualification status, minimum and maximum capacity, critical operating parameters, critical equipment components (e.g. screens, filters, temperature and pressure sensors). [4,7,13,27]

Besides that, SU should assess the suitability preparedness of the RU before transfer, namely equipment, support services (e.g. quality control procedures, documentation, equipment qualification,

water for pharmaceutical production and waste management) and premises (layout, construction, finishing of buildings, emergency planning (e.g. in case of gas and fire, risks of processes (e.g. reactions, exposure limits and explosion risk) and services with impact on the product, process or method to be transferred – water, compressed air and HVAC (Heating, Ventilation and Air Conditioning)). [4,13,27]

The RU must demonstrate that it is able to perform the various operations described in the contract effectively and has the proper conditions, such as: facilities, equipment, knowledge, experience and specialized and competent persons. It should be noted that the RU must not subcontract to third parties work entrusted to it without prior evaluation and approval by the SU, or make unauthorized changes to or outside the terms of the contract. The RU must understand and accept that outsourcing activities may be subject to inspection by the competent authorities. [13,27]

Finally, the SU should monitor and review the performance of the RU and the identification and implementation of any needed improvement. [27,35]

2.1.5. Success Criteria

A TT process is considered successful when the analytical method, product or process is routinely reproduced by the RU according to predefined criteria. [4-7] Apart from documentation (a critical part of the project), the success of a TT will also depend on the ability and performance of the individuals who are part of SU and RU. Each team member must understand his or her role and responsibility within the project. [6,8,10]

Communication

Communication between SU and RU must be made clear, efficient and continuous throughout the TT process. It should be done in both directions in order to increase efficiency in solving problems that may arise throughout the process and to contribute to increased cooperation between the parties involved. Open communication on technical issues should always be done before and during the planning and execution of the transfer.

Certainty

Uncertainty about the TT process results in an increased level of risk for both the SU and the RU and may undermine the process in question. Thus, to increase certainty and decrease the associated risk, there must be transparency and effective knowledge transfer throughout the TT process. Any lack of transparency can lead to inefficient technology transfer.

Challenges

Throughout the TT process different obstacles arise that may hinder or even prevent a successful transfer, namely: legal and economic implications (intellectual property rights, conflict of interest and confidentiality, royalties and pricing), information and materials movement restrictions, lack of cooperation between the parties involved, failure to comply with the regulatory requirements of the SU, RU or destination countries, and the lack of properly trained personnel for this purpose.

Capacity

All TT stakeholders must be fully aware and perform their duties and fulfill their obligations effectively and expeditiously. Regarding the capabilities of SU and RU, these should be similar, i.e. facilities and equipment should operate in accordance with similar operating principles.

Commitment

For a TT to be successful there must be a strong and real commitment between the parties involved. There must be good and clear communication about the technology to be transferred in order to build and strengthen a favorable environment, thus leading to increased certainty and reduced risk. A strong commitment translates into increased TT capacity and therefore a successful transfer. [4,8]

Regulatory factors must also be taken into account, as the pharmaceutical industry is highly regulated. From a regulatory standpoint, the main factors for a successful TT are:

- The presence of product, process and/or method acceptance criteria or clear clearly and well defined from the beginning of development stage.
- Suitable installations as well as equipment/instrumentation for the TT in question;
- Trained and specialized personnel in different areas (Analytical, Quality, R&D, etc.);
- The presence of protocols and standard operating procedures agreed upon by SU and RU;
- Data obtained during the experiment are properly documented and prove that the product, process or method can be successfully reproduced by RU. [11-15]

In addition to the factors mentioned above, there are other business factors that may also influence the success of a TT, namely: a) Capacity/Volume; b) Time frames; C) Cost; D) Equipment and facility capabilities; E) Regulatory Requirements. Each company defines the relative importance of each of these factors in TT. [4,10]

At the end of the TT process, both SU and RU must demonstrate through a document that regulatory requirements and business needs have been met to be able to conclude that TT has been successfully executed. [4,7,8]

2.1.6. Barriers of Technology Transfer

Sometimes there are obstacles that can hinder or even prevent a successful TT, such as:

- Incomplete Documentation;
- Insufficient process knowledge;
- High costs – qualified labour, equipment purchase, high rates of batch rejections;
- Inefficient or incomplete Process Validation;
- Reduced production rates;
- Increased number of atypicals – product defects, elegance issues;
- Not being capable of handling variations of process controls, operators, raw materials;
- Delayed regulatory approval and/or product launch.

All of these obstacles contribute to a decrease in process reliability as well as an increased likelihood of getting a product out of intended specifications. It is therefore necessary for the RU to identify and communicate these obstacles to the SU in order to ensure continuous knowledge management and thus contribute to the development of the control strategy. [33,34]

2.1.7. New business

The global market is increasingly competitive and it is necessary to adopt business strategies such as TT. Before starting the transfer process, it is necessary to assess whether it will benefit both parties involved, what are the risks associated, whether they imply special needs, etc. In order to facilitate the decision-making process, a checklist has been prepared with the conditions to be assessed before starting the transfer process. This information can be consulted in table **2.2.** and **2.3.** [4,7,13,27]

Table 2.2. - Checklist for Evaluation at Technology Transfer by Sending Unit. [4,7,13,27]

Requirements
☑ 1. **Manufacturer Evaluation**
1.1. Credibility
1.2. Tecnical Knowledge
1.3. Tecnical expertise and experience
1.4. Flexibility to align on differences in requirements
1.5. Regulatory Factors
☑ 2. **Project team**
2.1. Experience level
2.2. Training
2.3. Functions
☑ 3. **Facilities capabilities assessment;**
3.1. Localization
3.2. Layout (emergency planning)
3.3. Construction
3.4. Equipments (qualification status, minimum and maximum capacity)
3.5. Quality Control Laboratory
3.6. Service with impact on the product (water, compressed air and HVAC)

Table 2.3. - Checklist for Evaluation at Technology Transfer by Receiving Unit. [4,7,13,27]

Requirements	
☑ 1. **Process Evaluation** 1.1. Complete Documentation 1.2. Transparent process 1.3. Batch size and number of batches 1.4. Process flow diagrams 1.5. Unit operations 1.6. Critical steps 1.7. Material attributes and parameters 1.8. Acceptance criteria 1.9. Risk assessments (operator exposure, environment) 1.10. Regulatory Factors 1.11. Detailed historical data (justification any process changes) ☑ 2. **Raw materials** 2.1. Physical and chemical characteristics 2.2. Identification test 2.3. Toxicity 2.4. Stability 2.5. Storage conditions 2.6. Cost ☑ 3. **Equipment and Facilities Assessment** 3.1. Capacity 3.2. Functionality 3.3. Qualification status 3.4. Model 3.5. Material of construction 3.6. Procedures (operation, cleaning) 3.7. Critical equipment components (screens, filters, temperature and pressure sensors)	☑ 4. **Cleaning procedure** 4.1. Detergents (specific) 4.2. Cleaning methods 4.3. Decontamination procedures 4.4. Critical steps 4.5. Acceptance criteria 4.6. Risk assessments ☑ 5. **Project Team** 5.1. Experience level 5.2. Training 5.3. Functions 5.4. Total number ☑ 6. **Business factors** 6.1. Cost 6.2. Time frames 6.3. Regulatory Requirements 6.4. Royalties and Intellectual property rights 6.5. Profit 6.6. Economic Strategic 6.7. Additional Costs (new equipment, adaptations facilities)

The tables **2.2.** and **2.3.** describe the key points that should be evaluated before moving forward with a TT. Therefore, when choosing its business partner, the SU should assess RU's credibility with suppliers, customers and other business partners, the level of TT knowledge and experience as well as the results obtained from other TT processes. Furthermore, you should evaluate the project team, namely which roles will they have within the project, qualifications and level of experience for this type of projects.

Also evaluate the manufacturing facilities, taking into account the location (if you have good access, if you are in a country with tax benefits), the construction of the factory (for example if the walls, ceiling and floor are made of easy-to-clean materials and equipment (if they are qualified, if they are suitable for the process in question), the layout, taking into account the changing rooms, emergency exits and services with impact on the product (what is the water production process, if it meets the regulatory criteria, etc.). [4,7,13,27]

Regarding the RU, it must take several aspects into consideration before accepting a TT, including the transfer process (if the documentation is completed and written transparently, what batch size will be manufactured, what unit operations, the critical steps and acceptance criteria), the raw materials (if they require special storage conditions, if they are toxic to the operator and / or the environment, what is their cost), the equipment (if the equipment is sufficient in capacity and number and suit the process in question) and cleaning procedures (what type of detergent will be used, if the product to be manufactured will be difficult to remove, if the cleaning process avoids cross contamination) . [4,7,13,27]

Furthermore, the RU should also evaluate project team members regarding the level of experience, functions and total number of elements (assess whether more people need to be hired), the business factors, if the TT deadline is acceptable and if this partnership is strategically favorable). [4,7,13,27]

Following this assessment by both parties, the TT process may continue or not based on the conclusions each party has reached. [4,7,13,27]

Chapter 3 – Manufacturing Process Validation

Before the product is placed on the market and to complete the TT process, the manufacturing process must be validated, i.e. demonstrate that the manufacturing process in question is suitable for the proposed goal, which meets with the predefined requirements and produces a product with the required quality. Thus, the MPV should demonstrate that the process is robust and that the product quality is assured prior to its release to the market. [27,35,36,37,38]

In addition, the MPV can also be applied in other situations, such as: API supplier change, batch size increase, facility change, etc. [38]

3.1. Definition

The Process Validation can be defined as a documented verification or evidence that a specific process, method or system reproducibly produces a result that meets predetermined acceptance criteria. The objective of validation is to ensure that all processes, systems and procedures that may affect the quality of the API, excipients and finished product, operate reliably and reproducibly. [27,36,37]

MPV shall be performed in accordance with GMP and the documentation should be properly archived and available in case of an inspection. Documentation associated with MPV is essential for effective communication in complex, time consuming and multidisciplinary projects and allows the gained knowledge about a product/process to be accessible and understandable to others involved in the process. [27,37,38]

Batch size should be defined according to the process and based on the characteristics of the product. The batches manufactured in the scope of a manufacturing process validation should have the same size as the batch intended to be manufactured and placed to the market. [27,37,38]

All validation activities should be well planned and should take into account the life cycle of both the facilities and equipment as well as the process and product in question. Therefore, an annual MVP plan should be prepared, identifying the products, type of validation, scope (revalidation, batch size change/addition, new products, etc.), batch size, number of batches and estimated execution date. All changes made to the annual plan shall be recorded and duly justified. Furthermore, all the generated documents during this process must be approved by authorized personnel defined in the pharmaceutical quality system. [27,36]

It should also be noted that each product must have a batch master record and an associated MPV protocol. If applicable, the batch master record must be updated according to the validation results. [36,38]

3.2. Validation Master Plan

As noted above, all validation activities should be carefully planned. The key elements of the validation program must be defined and documented in the Validation Master Plan (VMP). [27]

The VMP is a document that gathers various information about the MPV, including the means, the validation status of the systems and references to other documents. It also contains the identification of the people involved in the validation process, their roles and responsibilities within the project as well as the signatures of the various people responsible for its approval, including the technical direction. This document should be written briefly, concisely and clearly so that everyone involved in the validation can understand it. If necessary, it may also contain lists, tables, flow charts, graphs, etc. [27,36,38]

Since the VMP is a live document and can be consulted at any time, its content must be kept up to date. Each revision must be properly coded (by number) and dated. [27]

3.3. Validation Methods

Manufacturing process validation is performed at an early stage by the Traditional Process Validation – TPV (section 3.3.1.) method, however there is also the possibility of implementing Continuous Process Verification – CPV (section 3.3.2.) in situations where there is already enough knowledge and understanding of both product and process through historical data and manufacturing experience. In some cases, both methods may be implemented. – Hybrid approach (section 3.3.3.). However, regardless of the used method, the process should be robust and ensure that the finished product has the required quality. [27,36,38]

3.3.1. Traditional Process Validation

TPV is defined as the manufacture of a defined number of batches under routine conditions in order to confirm the reproducibility of the process. Usually, this type of validation is performed when the pharmaceutical development and/or process development is concluded, after scale-up to production scale and before of the finished product commercialization. [27,38]

Therefore, a manufacturing process validation protocol should be developed (section 3.4.), where the manufacturing process, the tests to be performed, the CPPs, CQAs and the respective acceptance criteria are described. [27,36]

According to GMP, it is considered acceptable to manufacture at least 3 consecutive batches under routine conditions to validate the process. However, the number of batches to be manufactured should also be defined based on process variability, process/product complexity, the knowledge acquired during development as well as the manufacturer's general knowledge and experience. Furthermore, the number of batches to be manufactured must be sufficient to demonstrate that the process has the capacity to produce a product with the required quality. [27]

The process validation scheme must be contained in the marketing authorization dossier and should at least contain the following information:

Table 3.1. - Checklist of Traditional Process Validation. [27]

Requirements
☑ 1. Objective
☑ 2. Short description of process - composition of product, flowchart, main equipments;
☑ 3. Acceptance criteria – in process controls proposed;
☑ 4. Finished product release specification;
☑ 5. Analytical methods;
☑ 6. Sampling plan – when, where and how the samples are taken;
☑ 7. Additional testing intended to be carried out;
☑ 8. Methods for recording and evaluation of results;
☑ 9. Proposed timeframe;
☑ 10. Responsibility
☑ 11. References

Once the validation is concluded, the respective manufacturing process validation report must be elaborated. (section 3.4.). [27,36]

3.3.2. Continuous Process Verification

According to GMP, for products where it has been scientifically proven during their development that control strategy provides a high degree of product assurance, CPV can be used as an alternative to TPV. Therefore, a real-time approach that verifies and demonstrates that the process operates within predefined parameters and consistently produces a product with the required quality, must be performed. This type of approach provides more information and knowledge about the process and thus facilitates process improvements. [27,36,38]

For a CPV, companies must initially define the process monitoring scheme, namely:

- Details of at-line, in-line or on-line monitoring including number of samples, size of samples, parameters tested and frequency of monitoring;
- Analytical Methods;
- Acceptance criteria;
- Information/data including statistical models or tools used to determine that this approach supports the ability of the process and controls to produce reproducible product at commercial scale;
- Details of design space (if it has been developed). [27]

After obtaining the data, it will be necessary to assess if the product is in a validated state or if any further intervention is required. [38]

3.3.3. Hybrid Approach

When there is a strong knowledge of the process and the product from the manufacturing experience and batch data history, a hybrid approach can be used, i.e. TPV is used for initial validation and then CPV is for later validations. [38]

3.4. Process Validation Protocol

Successful PV requires a written plan that describes how validation will be conducted, containing the detail of the manufacturing process (including flowchart and critical steps to control), the parameters to be tested, production and quality control equipments, definition of CPPs and CQAs as well as acceptance criteria based on development data or process knowledge, (**Annex I**). [27,36]

The following table indicates the minimum criteria that should be met in a process validation protocol.

Table 3.2. - Checklist of Process Validation Protocol. [27,36]

Requirements
☑ 1. Objective
☑ 2. Introduction
☑ 3. Composition of product
☑ 4. Manufacturing Process
4.1. Flowchart
4.2. Main Equipments
4.3. Critical Steps to Control
☑ 5. Acceptance criteria
☑ 6. Validation Plan
6.1. Preparation of product
6.2. Holding time validation of product
☑ 7. Further Information
☑ 8. Registration of Information
☑ 9. Responsibility
☑ 10. References
☑ 11. Versions control

All the significant changes to the approved protocol, must be properly described, justified and documented. Furthermore, if the change may have impact in the product quality, a risk assessment must be performed in order before they are implemented. [27]

3.5. Process Validation Report

Once the validation process is concluded, a manufacturing process validation report must be elaborated based on the obtained data. In addition to all the data obtained during the validation process, this report shall also contain the references of the used procedures, qualitative and quantitative composition of each raw material used by each validation batch, the main equipments used and their qualification status, as well as any deviations that may have occurred. A conclusion taking into account the predefined acceptance criteria must be included (**Annex II**). The Table **3.3**. summarizes the main criteria that a process validation report must contain [27]

Table 3.3. - Checklist of Process Validation Report. [27]

Requirements
☑ 1. Objective
☑ 2. Introduction
☑ 3. Composition of product
☑ 4. Manufacturing Process
☑ 5. Validation Results
5.1. Manufacturing Conditions (time, temperature)
5.2. In Process Control
5.3. Finished Product Control
☑ 6. Overall review
☑ 7. Conclusions
☑ 8. Registration of Information
☑ 9. Responsibility
☑ 10. References
☑ 11. Versions control

After the report has been prepared, must be reviewed by qualified persons to evaluate whether the obtained results are consistent across batches, demonstrating that the process is reproducible and robust, allowing the product in question to be placed in the market. [27,36,37,38,39,40,41]

However, if the results show significant deviations from the expectations, they should be investigated in order to determine the main cause and propose corrective actions. [27,42.43,44,45,46]

3.6. Product Quality Review

In order to ensure that the entire manufacturing process is currently controlled, that the products obtained continue to have the desired quality and that the process remains validated, it is required to have a report that gathers all information related with the manufacturing process. – Product Quality Review (PQR). [27,47]

The PQR elaboration contains various information about the manufacturing process including: information about the product (dosage, packaging, batch size); number of batches manufactured, released and rejected;, number of batches out of specification or with non-conformities; the yield of each batch manufactured; primary packaging materials suppliers and manufacture; analytical results (manufacturing conditions, IPC and FPC) and conclusion. [27,36,38,47] Table **3.4.** indicates the main topics that should be covered in this report.

Table 3.4. - Checklist of Product Quality Review. [47]

Requirements
☑ 1. Objective
☑ 2. General product information (name, composition, presentation)
☑ 3. Manufactured batches 3.1. Size(s)
3.2. Number of manufactured
3.3. Manufacturing data
☑ 4. Identification of critical parameters and acceptance criteria
☑ 5. Summary of the analytical results obtained for each batch manufactured (IPC and FPC)
☑ 6. Comparison of the review from previous PQRs;
☑ 7. Identification of issues or trends
☑ 8. Conclusions
☑ 9. Proposed actions
☑ 10. Responsibility (names, functions and signatures)
☑ 11. Versions control

This type of revision allows the manufacturer to verify the consistency of the process in question, the suitability of specifications to the raw materials, intermediate product and finished product and adverse trends. Upon completion of the review, if applicable, the manufacturer decides to take measures or corrective measures to promote continuous process and product improvement. [46,47]

3.7. Changes Control

Sometimes during TT and according to the data obtained by the MPV it is necessary to make changes in order to obtain a more robust and reproducible manufacturing process. Any changes that may affect product quality, efficacy and/or safety or process reproducibility must be documented, justified and evaluated before being implemented. The assessment therefore consists of ensuring in a documented manner that the changed process results in a product quality in accordance with the approved specifications. [27,36,46]

3.7.1. Risk Assessment

To evaluate the impact of a specific change, it requires a risk assessment before and after its implementation. The identified risks after implementation should have less impact than the risks before the implementation of the proposed change. [27,46]

Changes can be classified according to their impact on the quality, efficacy and safety of the process and/or product, (Table **3.5.**).

Table 3.5. – Change Classification. [27,46]

Classification	Definition	Examples
Critical	Changes that directly affect the quality, safety and/or efficacy of the product and/or the reproducibility of the product.	- Product composition changes; - Equipment changes with direct impact in the manufacturing process;
Major	Changes with a level of uncertainty or for which impact level cannot be estimated.	- New batch size addition; - Changes to approved analytical methods;
Minor	Changes without impact in the quality product.	- Label size change; - Similar component changes - with identical characteristics;

Based on the risk analysis result, it will be evaluated whether or not the modified process remains in the validated state. [27,38,46]

Chapter 4 – Manufacturing Process Validation Applied to Industrial Scale Batches

Laboratório Edol – Produtos Farmacêuticos, S.A. is a portuguese pharmaceutical company specializing in the areas of ophthalmology, dermatology, otorhinolaryngology and dermocosmetics. In recent years, due to the strong expansion in different areas and the increase in sales in different countries, the need to adopt strategies to meet market needs arises, namely the production of products by third parties, the construction of a new industrial hub for production, scale up production, etc.

Thus, it was developed a validation protocol for scaling up of an eye drops solution, with a 150 L industrial scale batch.

4.1. Process Validation of Eye Drops Solution

The eye drops are one of the main ophthalmology medicines and is characterized by being a sterile (absence of microorganisms) for topical use that can be applied directly to the eyes and / or eyelids. It is a product composed essentially of highly purified water (vehicle), specifically, water that is characterized by the absence of metals and organic matter, pyrogen-free and relatively sterile. Moreover, it is also qualitatively constituted by API, buffering agent, buffer chelating agent, preservative, osmolality adjustment agent (Sodium Chloride) and pH adjuster (Sodium Hydroxide and/or Hydrochloric Acid).

In order to demonstrate and verify that the increase in eye drop production translates into the manufacture of a quality product, a validation protocol has been developed. This protocol included the manufacturing process (main equipments, additional steps), critical steps, the sampling process (who, how and when), the acceptance criteria and was used to manufacture 3 validation batches.

4.1.1. Manufacturing Process

The validation process started with the weighing of raw materials in a Class A room (**Annex III**), with laminar air flow to minimize the risk of microbial load. In addition, in order to control the particulate matter, room temperature and humidity were also controlled. As such, only properly equipped personnel can enter the room (uniform, cap, shoe protection and mask).

It should be noted that only raw materials previously approved by quality control were used in the manufacturing process. They are usually in the warehouse approved area, duly identified by an additional label containing the product name, batch, internal number, approval date, retest date, and expiration date. In general, the tests performed on each raw material are tests of identity (infrared or ultraviolet absorption spectrum), purity (determination of heavy metals), quality (crystallinity), dosing (HPLC), among others.

At the end of the weighing process, the weight of each raw material was properly verified by the weighing area manager and a production supervisor.

Subsequently, the process of mixing all raw materials, except the API, was started in a blade reactor in a Class C room (**Annex III**). The API was added only after total dissolution of all the raw materials in water.

After the mixing process was completed, quality control samples were taken to determine if osmolality adjustment was required (as need to 300 – 400 mOsm/Kg) and pH (as need to 3 - 5.5). Only after adjusting these two parameters, two 200 mL samples were taken for microbiological control and 200 mL for physicochemical control from the top and from the bottom of the mixer (0h) and after 72h (the worst-case scenario of 72h waiting between the end of the preparation and the start the sterilizing filtration) – In Process Control. The tests performed in this step are in the next table.

Table 4.1. – Process Control and acceptance criteria for the evaluation of eye drops solution.

Step	Process Control	Acceptance Criteria
Holding Time Validation: 0 h	Appearance	Limpid and colourless
	pH	Between 3.0 – 5.5 (20 - 25ºC)
	Osmolality	Between 300 and 400 mOsm/Kg
	API Identification	Positive
	API Assay	Between 90 – 110%
	Preservative Identification	Positive
	Preservative Assay	Between 96 – 110%
	Bioburden	Absence
	Densidity	Around 1 g/mL
Holding Time Validation: 72 h (Before Sterilizing Filtration)	Appearance	Limpid and colourless
	pH	Between 3.0 – 5.5 (20 - 25ºC)
	Osmolality	Between 300 and 400 mOsm/Kg
	API Identification	Positive
	API Assay	Between 90 – 110%
	Preservative Identification	Positive
	Preservative Assay	Between 96 – 110%
	Bioburden	Absence

Prior to sterilizing filtration through a 0.22 µm membrane filter, the integrity of the filter was determined by the bubble point method. This test consists of applying an air pressure to the upstream side of the hydrophilic filter whose pores were full of water. The pressure was then gradually increased until bubbles passed through the filter and were detected in the downstream liquid. Before finishing the sterilizing filtration, the bubble point was determined again. Appropriate pressure value in both tests was greater than 31.0Psi (acceptance criteria).

In addition to integrity analysis, preservative adsorption control on the filter was also performed. Thus, the solution was gradually filtered and samples of 30 mL at the end of the 3rd L, 5th L and 8th L in order to dose the preservative in question. When preservative concentration was within the approved

specifications (95 – 110%), the remaining solution was filtered and the initially used volume was discarded.

It should be noted that both the prefilter and the filter used were initially subjected to heat sterilization (160ºC for 20-30 minutes).

Subsequently, the eye drops were aseptically filled in a Class A room, where air quality was determined by controlling relative humidity, temperature and using HEPA (High-Efficiency Particulate Air) filters. These filters have a tight loop and allow for removal of dust, microbes and particles with a size equal to or greater than 0.3 µm. In addition, positive pressure was maintained in relation to the surrounding areas so that air would circulate from inside the room to the outside, reducing the possibility of air and consequently product contamination.

Prior to the start of filling, 10 units of completely empty vials were weighed (to determine the average weight of the vials) and 12 units of fully filled vials were also used to adjust the weight.

During the filling, a control of the filling volume was made by the previously determined density and by the average weight of 5 vials every 30 minutes. Subsequently, in line leak test was performed in order to identify any level of leakage.

During secondary packaging, labeling (label appearance, batch and expiration date), carton box (expiration date, batch, appearance) and the presence of the package leaflet were checked by analysing 5 samples every 30 minutes until the end of the filling process.

At the end, an evaluation of the finished product was made by sampling at the beginning, middle and end of the filling/packaging process according to the following scheme:

For the 1st Batch - 195 samples of finished product were collected: 20 from the beginning, 20 from the middle and 20 from the end for analytical and microbiological control and 135 samples for stability tests.

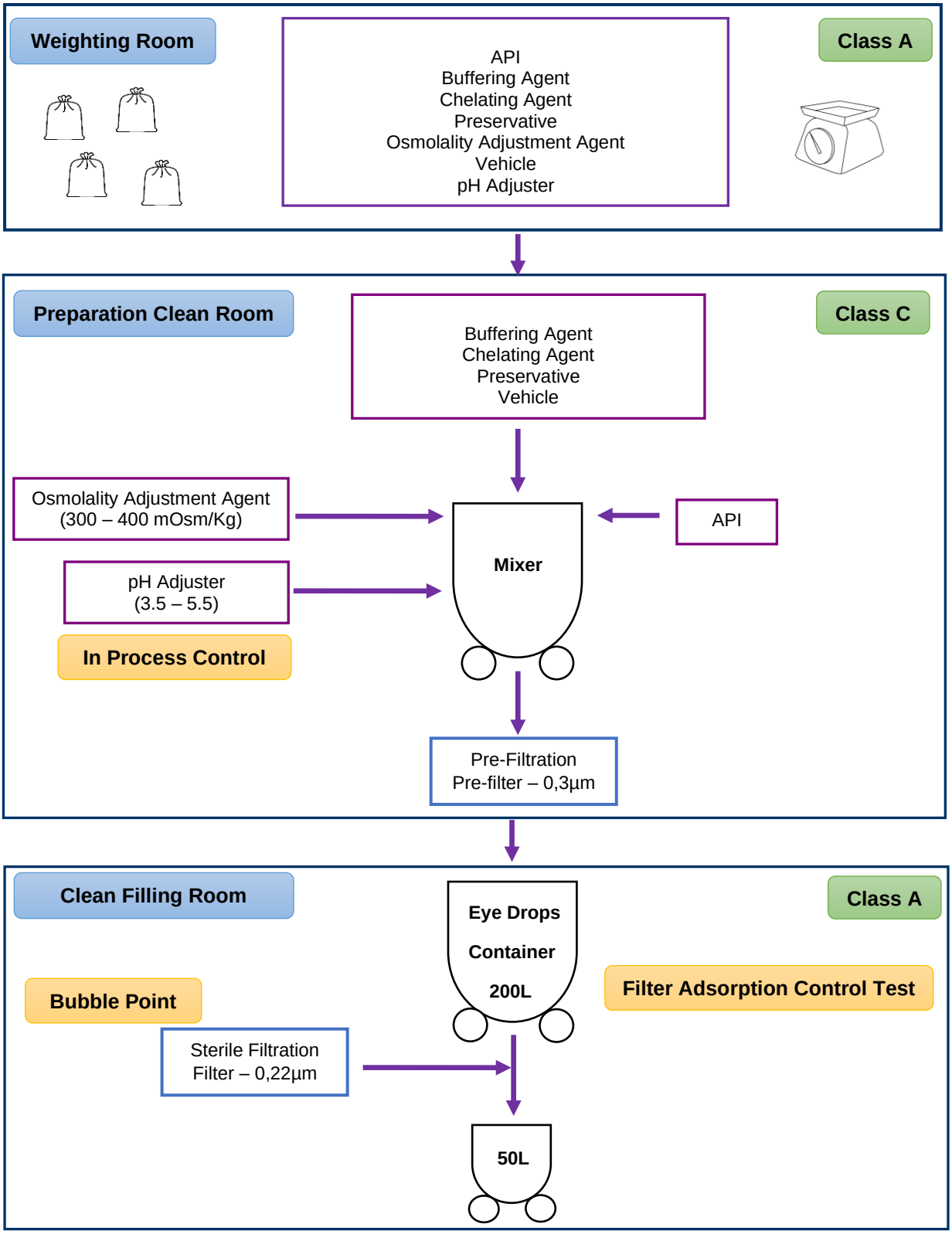
For the 2nd and 3rd Batch - 90 samples of finished product were collected: 20 from the beginning, 20 from the middle and 20 from the end for analytical and microbiological control and 30 samples for stability tests. Table **4.2.** describes the tests performed on the finished product as well as the respective acceptance criteria (**Annex IV**).

Table 4.2. – Finished Product Quality Control.

Step	Process Control	Acceptance Criteria
Finished Product	Appearance	Limpid and colourless
	pH	Between 3.0 – 5.5 (20 - 25ºC)
	Osmolality	Between 300 and 400 mOsm/Kg
	Filling Volume	5.0 – 5.5 mL
	API Identification	Positive
	API Assay	Between 90 – 110%
	Preservative Identification	Positive
	Preservative Assay	Between 96 – 110%
	Sterility Test	Absence of growth

At the end of the 3 validation batches, a report was elaborated with the obtained data to determine if the scaling up was successful.

The manufacturing process of eye drops, solution, is schematically described in the flowchart presented in Figure **4.1.**. Furthermore the main equipment used for the manufacturing and analysis of eye drops solution, it is described in table **4.3.**.



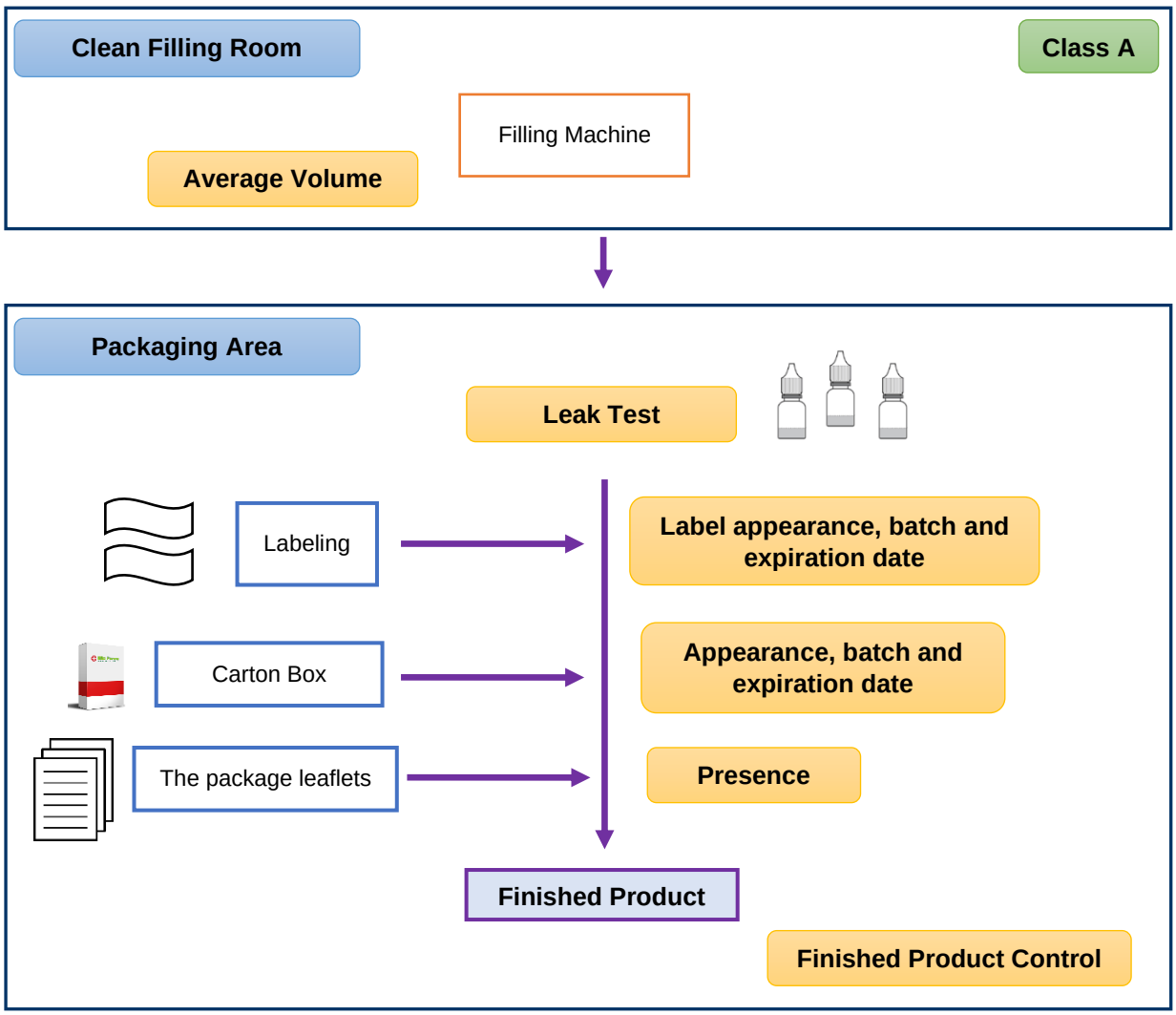


Figure 4.1. – Flow diagram of the manufacturing process.

Table 4.3. – Main Equipments.

Equipment	Function
Mixer	To mix liquids and solids
Filling and encapsulating	To fill vials with solution and closure
Sealing test	To identify any level of leakage
Labelling machine	To apply labels on vials
Cartoners	Carton box formation, vial and the package leaflets insertion and box closure
Weighting	To determine weight
Grouper	To group the carton boxes
HPLC	To identification and determination the API and Preservative
pH meter	To determination pH of solution
Osmometer	To determination osmolality of solution

4.1.2. Validation Results

After manufacturing 3 validation batches (Batch 1, Batch 2 and Batch 3), the data obtained at each step of the validation process were collected in order to validate the manufacturing process of eye drops solution.

Table **4.4.** describes the quantities of units manufactured as well as the respective yield obtained in each validation batch.

Table 4.4. – Manufactured units and Yield obtained at each batch.

Batch	Manufactured units	Yield
Batch 1	25744	85.8 %
Batch 2	25899	86.3 %
Batch 3	25597	85.3 %

In the table analysis it is possible to verify that the obtained yield was consistent in the 3 validation lots, although the yield is low due to the rejection of 8 L performed during the filter adsorption control.

Table **4.5.** describes the results obtained from the samples taken from the mixer after the end of the preparation and before the start of the sterilizing filtration (after 0h and 72h waiting time - the worst-case scenario) – In Process Control.

In the analysis of table **4.5.** it is possible to verify that in the 3 validation batches the solution was clear and colourless in both samples collected from the top and bottom of the mixer. It is also possible to observe that both pH and osmolality values were within the approved specifications. Regarding API and preservative identification, all HPLC tests were positive for both products. Furthermore, the HPLC assay value of these substances was within the specification range either after the end of mixing (0h) or after waiting 72 hours.

Finally, in the analysis of Bioburden, it was found that there was no microbiological growth in both 0h and 72h.

It should be noted that at this stage the density of the solution was also determined, which was later used to control the filling weight.

Thus, taking into account the obtained results, it is possible to verify that the solution is compliant and that the holding time of 72h has been validated, specifically, there is a 3-day interval between manufacture and aseptic filling (e.g. manufacture in Friday and fill on Monday) without risk of microbiological development.

Table 4.5. – Holding Time Validation of Eye Drops Solution.

	Appearance	pH	Osmolality	API Identification	API Assay	Preservative Identification	Preservative Assay	Density	Bioburden
Specifications	Limpid and colourless	3.0 – 5.5. (20-25ºC)	300 – 400 mOsm/Kg	Positive (HPLC)	90 – 110% (HPLC)	Positive (HPLC)	96 – 110% (HPLC)	Around 1 g/mL	Absence of growth
Batch 1 (0h) Top	Conforms	5.28 (24.7ºC)	317	Positive	103.5%	Positive	99.5%	1.0049	Conforms
Batch 1 (0h) Bottom	Conforms	5.29 (24.9ºC)	315	Positive	103.3%	Positive	99.5%	1.0049	Conforms
Batch 1 (72h) Top	Conforms	5.28 (24.7ºC)	320	Positive	101.7%	Positive	100.6%	1.0058	Conforms
Batch 1 (72h) Bottom	Conforms	5.29 (24.9ºC)	321	Positive	100.9%	Positive	100.5%	1.0054	Conforms
Batch 2 (0h) Top	Conforms	5.38 (22.2ºC)	320	Positive	101.9%	Positive	101.8%	1.0042	Conforms
Batch 2 (0h) Bottom	Conforms	5.38 (23.1ºC)	318	Positive	102.2%	Positive	101.5%	1.0047	Conforms
Batch 2 (72h) Top	Conforms	5.30 (24.2ºC)	319	Positive	101.8%	Positive	102.0%	1.0046	Conforms
Batch 2 (72h) Bottom	Conforms	5.29 (24.3ºC)	319	Positive	101.2%	Positive	103.4%	1.0043	Conforms
Batch 3 (0h) Top	Conforms	5.43 (22.3ºC)	317	Positive	100.5%	Positive	98.6%	1.0044	Conforms
Batch 3 (0h) Bottom	Conforms	5.46 (21.7ºC)	315	Positive	101.7%	Positive	98.8%	1.0030	Conforms
Batch 3 (72h) Top	Conforms	5.33 (23.5ºC)	317	Positive	102.3%	Positive	100.4%	1.0043	Conforms
Batch 3 (72h) Bottom	Conforms	5.34 (23.7ºC)	318	Positive	101.0%	Positive	99.9%	1.0043	Conforms
Average	-	5.34	318	-	101.8%	-	100.5%	1,0046	-
Minimum	-	5.28	315	-	100.5%	-	98.6%		-
Maximum	-	5.46	321	-	103.5%	-	103.4%		-

For each batch, in the beginning and before the end of the sterilizing filtration it was necessary to verify the integrity of the filter through the bubble point (minimum bubble point value is ≥ 31.0 Psi). The preservative adsorption to the sterilizing filter control test was also performed and aimed to study the minimum amount of solution to be rejected to ensure that the filter did not retain more preservative. Aseptic filling only initiates when the preservative concentration (HPLC analysis) reached at least 95%. The results obtained in the bubble point test and the preservative filter adsorption control test are shown in the tables **4.6.** and **4.7.** respectively**.**

Table 4.6. – Bubble Point Determination.

Batch	Pressure (Psi) Before Filtration	Pressure (Psi) After Filtration
Batch 1	33.4	31.5
Batch 2	33.6	31.5
Batch 3	33.6	31.5

Table 4.7. – Filter Adsorption Control Test.

Litters Rejected	Batches		
	Preservative Assay (95-110%)		
	Batch 1	Batch 2	Batch 3
Before Filtration	100.6%	102.7%	100.1%
3rd	96.5%	96.7%	98.7%
5th	96.0%	102.0%	98.8%
8th	96.3%	102.3%	100.4%
Total Rejected	8 L	8 L	8 L

Regarding the bubble point results before and after sterilizing filtration, it was found that they were above specification, i.e. ≥ 31.0 Psi. Thus, the obtained results prove the integrity of the filters used in each validation batch.

The data obtained in table **4.7.** demonstrate that at the end of the 3rd rejected L, the preservative concentration is greater than 95% in the 3 validation batches. Thus, in the manufacture of future batches of eye drops, it is considered validated a minimum rejection of 3L of eye drops solution, before the filling process is started.

During the filling process it was evaluated whether the filling volume of the bottles was within specifications (5.0 - 5.5 mL). For this, during the aseptic filling process, 5 samples were taken every 30 minutes and the average volume was calculated taking into account the previously calculated density. (**Annex VI**).

The obtained values are shown in the following control charts.

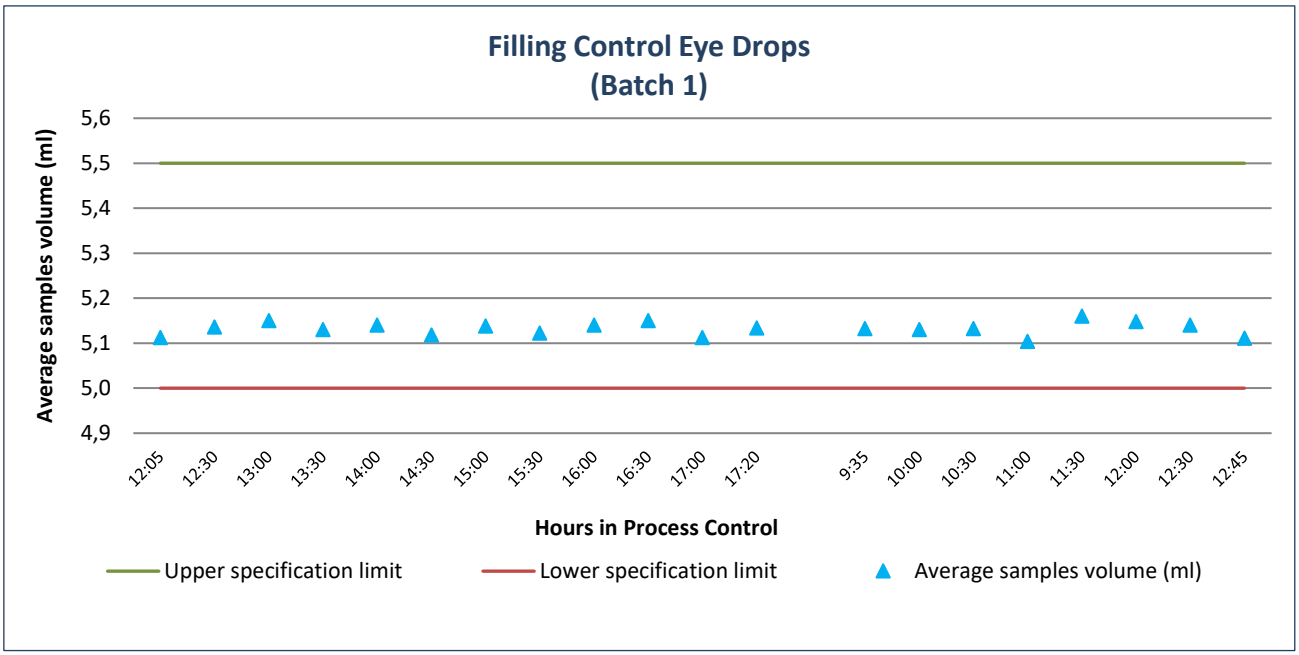


Figure 4.2. – Filling Control Results – Batch 1.

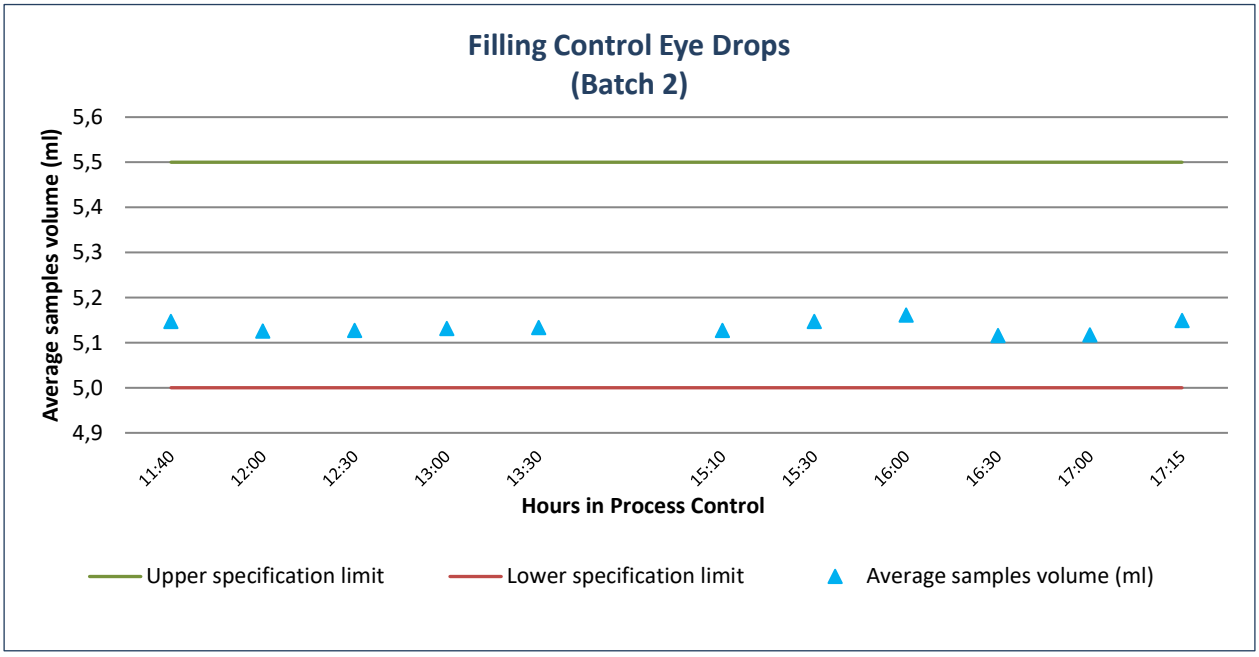


Figure 4.3. – Filling Control Results – Batch 2.

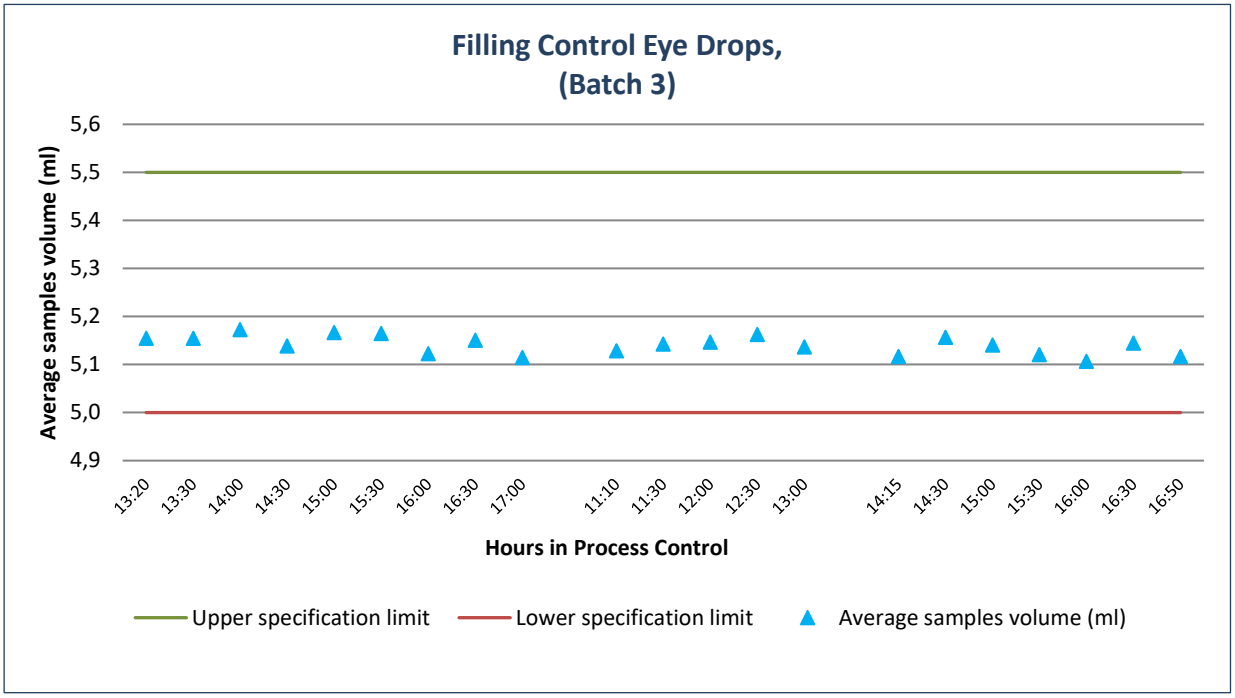


Figure 4.4. – Filling Control Results – Batch 3.

In the analysis of the 3 control charts, it is found that the average volume of the vials tends to be between 5.1 mL and 5.2 mL, i.e., within the approved limits.

Since this is a sterile product, the in-line leak test was performed on all the validation batches. The following table describes the number of bottles tested, the number of bottles rejected and percentage of bottles rejected for each batch manufactured.

Table 4.8. – Leak Test Results.

Batch	Number of bottles		Percentage of bottles rejected
	Tested	Rejected	
Batch 1	25811	57	0.2%
Batch 2	25964	52	0.2%
Batch 3	25650	43	0.2%

The low percentage of rejected bottles shows that the closure of the bottles was effective, since the bottles did not leak their contents.

After the filtration and filling/packaging process 20 start samples, 20 middle samples and 20 end process samples were collected.

The samples were subjected to analytical control of the following parameters: appearance, pH, osmolality, API identification and assay, preservative identification and assay and sterility test.

The obtained results from the finished product analysis of the 3 validation batches are described in the tables **4.9.**, **4.10.** and **4.11**.

Table 4.9. – Finished Product Results – Batch 1.

Tests	Appearance	pH	Osmolality	API Identification	API Assay	Preservative Identification	Preservative Assay	Filling Volume	Sterility Test
Specifications	Limpid and colourless	3.0 – 5.5. (20-25ºC)	300 – 400 mOsm/Kg	Positive (HPLC)	90 – 110% (HPLC)	Positive (HPLC)	96 – 110% (HPLC)	5.0 – 5.5 mL	Absence of growth
Beginning	Conforms	4.56 (24.5ºC)	356	Positive	100.0%	Positive	99.5%	5.13 mL	Conforms
Middle	Conforms	4.57 (24.2ºC)	357	Positive	98.9%	Positive	100.9%		Conforms
End	Conforms	4.56 (24.0ºC)	356	Positive	101.5%	Positive	102.0%		Conforms
Average	-	4.56	356	-	100.1%	-	100.8%	-	-
Minimum	-	4.56	356	-	98.9%	-	99.5%	-	-
Maximum	-	4.57	357	-	101.5%	-	102.0%	-	-

Table 4.10. – Finished Product Results – Batch 2.

Tests	Appearance	pH	Osmolality	API Identification	API Assay	Preservative Identification	Preservative Assay	Filling Volume	Sterility Test
Specifications	Limpid and colourless	3.0 – 5.5. (20-25ºC)	300 – 400 mOsm/Kg	Positive (HPLC)	90 – 110% (HPLC)	Positive (HPLC)	96 – 110% (HPLC)	5.0 – 5.5 mL	Absence of growth
Beginning	Conforms	4.75 (22.0ºC)	318	Positive	98.8%	Positive	98.6%	5.14 mL	Conforms
Middle	Conforms	4.75 (21.8ºC)	318	Positive	97.6%	Positive	99.6%		Conforms
End	Conforms	4.77 (21.8ºC)	318	Positive	97.8%	Positive	100.6%		Conforms
Average	-	4.76	318	-	98.1%	-	99.6%	-	-
Minimum	-	4.75	318	-	97.6%	-	98.6%	-	-
Maximum	-	4.77	318	-	98.8%	-	100.6%	-	-

Table 4.11. – Finished Product Results – Batch 3.

Tests	Appearance	pH	Osmolality	API Identification	API Assay	Preservative Identification	Preservative Assay	Filling Volume	Sterility Test
Specifications	Limpid and colourless	3.0 – 5.5. (20-25ºC)	300 – 400 mOsm/Kg	Positive (HPLC)	90 – 110% (HPLC)	Positive (HPLC)	96 – 110% (HPLC)	5.0 – 5.5 mL	Absence of growth
Beginning	Conforms	4.80 (22.2ºC)	318	Positive	101.9%	Positive	99.3%	5.14 mL	Conforms
Middle	Conforms	4.78 (22.1ºC)	319	Positive	103.1%	Positive	102.0%		Conforms
End	Conforms	4.80 (21.9ºC)	318	Positive	103.3%	Positive	102.3%		Conforms
Average	-	4.79	318	-	102.8%	-	101.2%	-	-
Minimum	-	4.78	318	-	101.9%	-	99.3%	-	-
Maximum	-	4.80	319	-	103.3%	-	102.3%	-	-

The analysis of Tables **4.9** shows that the samples collected were clear and colorless as described in the specification. Regarding the pH of the solution, it ranged from 4.56 - 4.57 (20 - 25° C), i.e. it was within the previously defined limits. The same result was found in the determination of osmolality, whose average value was 356 mOsm/kg.

Regarding the identification of API and preservative by HPLC, the results were positive in the samples collected at the beginning, middle and end of the filling process. The API and preservative assay had an average value of 100.1% and 100.8% respectively. These values are within the previously defined range of values.

Regarding the sterility test, all the samples collected from the beginning, middle and end of the filling process were sterile.

From the Batch 2 finished product data, it seems that the appearance of the solution was in accordance with the specifications. The mean pH and osmolality of the solution was 4.76 (20-25° C) and 318 mOsm/kg respectively, which were within the defined limits.

API and preservative identification were positive in samples collected from the beginning, middle and even the end of the packaging process. Regarding the assay of both substances, the values ranged from 98.1 - 98.8% for API and 98.6 - 100.6% for preservative. Thus, the values are as expected.

Finally, regarding the results of the sterility test, all the samples are sterile.

Table **4.11.** regarding the last validation shows that the solution was clear and colorless as specified. The same was true for the determination of pH and osmolality that were within the specified parameters.

Regarding the identification of API and preservative, the results were positive for both substances. The average API and preservative assay by HPLC were 102.8% and 101.2% respectively. The obtained results are within specifications.

Regarding the sterility test, the results were in accordance with the specification, i.e. all the samples are sterile.

Taking into account the results obtained from the 3 validation batches and once the obtained results are within the specifications, it can be concluded that the 150L eye drop production is validated.

4.1.3. Risk Management in Manufacturing Eye Drops.

Risk management in Eye Drops production aims to identify, manage and prevent possible failures / risks during the various stages of production of this drug. This information will help to identify critical steps and further assess the difficulties that may arise during TT, i.e. in the transition from this manufacturing method to other facilities.

To obtain a quality finished product it is necessary to identify the critical steps during the manufacturing process from raw materials (shelf life, storage conditions, special precautions are required) to packaging and labelling, where it is necessary to take into account various aspects from secondary packaging design (to ensure product authenticity, label readability) to bottle closure selection and label issuance (different versions of the same label need to be taken into consideration - potential confusion). [29]

Thus, the critical steps identified in the manufacturing process of this medicine are:

- Raw materials: storage conditions and weighting;
- Equipment: sterilization, clean and compatibility with solution;
- Velocity and time of the mixtures;
- Holding time: between the end mixture and sterilizing filtration;
- Sterilizing filtration: bubble point, filtration pressure and compatibility with solution;
- Filter adsorption control;
- Aseptic filling: air quality, temperature, pressure and filling velocity;
- Leak test;
- Packaging Operation. [46-53]

All these critical steps must be properly controlled, especially sterilizing filtration and aseptic filling (the most critical steps) to minimize the risk of contamination during the process, thus obtaining a quality finished product. Therefore, the operating procedures must be standardized and described in a simple and clear manner to avoid possible errors during the manufacturing process that may affect not only the quality of the product but also the safety of the operators themselves. In addition, operators should receive initial and continuous training and their performance should be continuously monitored (e.g. by counting viable microorganisms before entering clean rooms). [48-52]

In addition to the critical steps described above, there are other factors that may undermine the integrity of the end product, such as manufacturing facilities, air quality system (HEPA filter cleanliness, qualifications) and clean rooms (relative humidity control, temperature and pressure, cleaning method, type of detergent, frequency of cleaning). [48-56]

An Ishikawa Diagram was constructed in order to facilitate the understanding of the cause/effect relationship, namely of people, raw materials, equipment and processes that may interfere with the quality of the finished eye drop product. (Figure **4.4**). [46,48,49,50,51]

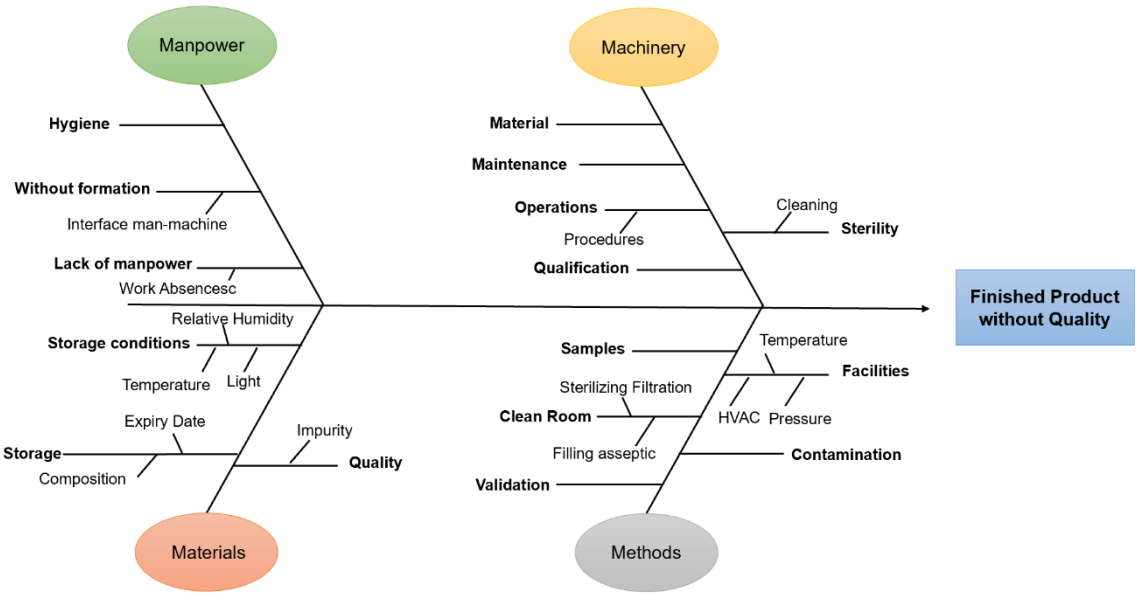


Figure 4.5. – Ishikawa diagram.

Regarding the people involved in production, there are several factors that can have a negative impact, including poor hygiene, lack of initial and continuing training and lack of labour (which may be due to unexpected work absences (e.g. disease) or even poor scale management). This type of cause can influence not only the quality but also the productivity of the company. [48-56]

Raw materials are associated with various risk factors such as quality (impurities out of specification), improper storage conditions (relative humidity, temperature and sun exposure), storage itself, as it is necessary to take into account stock rotation (shelf life), expiry date (shorter expiry date is first used) as well as material composition (if flammable, strong acid or base). [48,57,58,59,60,61]

The equipment has some critical points such as constituent material (which should not interfere with the product), maintenance (preventive or corrective) and operating conditions (instructions for use must be clear and objective and if necessary, must be accompanied by representative diagrams). It is also necessary that all equipment is qualified, namely, documented proof that the equipment operates as established. In addition, as it is a production of a sterile medicine, the equipment must be sterilized, especially those in direct contact with the product. [48,55,56,62]

For processes, these should be validated and the room classes for sterile filtration and primary packaging should be rooms with specific conditions to minimize microbial contamination (Rooms A/B). Installations where the processes take place must have adequate conditions, i.e. the temperature and relative humidity should prevent the proliferation of microorganisms and at the same time be comfortable for operators (should not cause perspiration). Air must be clean and aseptic provided by a HVAC system. In the event of a general power cut or even water cut, alternatives must be available to ensure the proper functioning of the facilities (e.g. the existence of electricity generators). [46,48,49,50]

Once critical steps have been identified, appropriate manufacturing controls should be established based on pharmaceutical development studies. For example, determination of clothing and footwear to be worn inside and outside the cleanroom, determination of cleanliness validation limits for both the room and the equipment itself that is in direct contact with the product. [29,31]

However, despite the different control methods, the results obtained may be outside of the defined specifications. It is necessary to identify possible causes (e.g. check the storage conditions of the raw materials or the intermediate product, the calibrations and status qualification of the equipment) and study corrective measures for this deviation. In addition, preventive measures should be studied to minimize the probability of this risk to occur. These measures may include making checklists of each employee's tasks (to avoid forgetting any critical step), stakeholders training, to handle the various devices that are involved in controlling environmental factors (e.g. hygrometer for measuring humidity), have spare parts in the warehouse (to don't cause delay in the manufacturing process time), among others. [46,48,49,50,52]

Implementing risk mitigation measures may introduce, however, new risks or even increase existing ones. Therefore, after the implementation of a preventive risk mitigation measure, a risk reassessment should be made: if it was effective, if the probability and/or the severity of the risk decreased and if it was well implemented. [46]

Chapter 5 – Conclusion and Future Work

Nowadays, the pharmaceutical market is increasingly competitive and broad. Business strategies such as TT need to be adopted. This can occur for several reasons, such as: scale-up, installation of additional capacity, corporate mergers and consolidations and business strategies for relocating units in different regions of the world.

Regardless of the main purpose of the process transfer, good documented planning (contract, proposal, implementation plan and package) of the various project phases is required: process development, facility fit assessment, team selection, execution and qualification.

In addition to the necessary documentation (a critical part of the project), the success of a TT will also depend on the ability and performance of the individuals who are part of SU and RU. Team members must understand their role and responsibility within the project. The success criteria of a TT include: communication (must be clear, efficient and continuous throughout the transfer process), certainty (there must be transparency in knowledge transfer), challenges (during TT there are a number of obstacles that may undermine the success), capacity (the capabilities of SU and RU, these should be similar) and commitment (there must be a strong commitment between both parties, which translates into increased TT capacity and therefore a successful transfer). However, obstacles often arise which may undermine the transfer process, in particular: incomplete documentation, insufficient process knowledge and high costs.

In order to complete the TT process, the manufacturing process must be validated, i.e. documented demonstration that the process results in the manufacture of a quality and reproducible product. All validation steps should be well planned and performed according to GMP regardless of the various types of validation (traditional, continuous verification and hybrid).

Successful PV requires a written plan that describes how validation will be conducted, containing the detail of the manufacturing process (including flowchart and critical steps to control), the parameters to be tested, production and quality control equipments, definition of CPPs and CQAs as well as acceptance criteria based on development data or process. At the end, a validation report should be prepared to assess the validation results against the acceptance criteria.

Laboratório Edol is a Portuguese pharmaceutical company specializing in the several areas, especially ophthalmology. Due to its strong growth and business expansion to other locations, the need to move to another production site as well as scale up production of various medicines was decided

Thus, a validation protocol was developed for scaling up an eye drops solution, with a 150L industrial scale batch. This protocol included the manufacturing process (additional steps, main equipment), critical steps, the sampling process (who, how and when) and the acceptance criteria that will be used to manufacture 3 validation lots.

The analytical results obtained from those industrial batches accord with the specifications, as presented in the manufacturing process validation protocol, indicating homogeneity between batches, as well as a good reproducibility of the manufacturing process.

The results from these three batches strongly suggest that the manufacturing process is able to consistently manufacture a product with the required quality.

Based on the above review it is determined that production remains in validated state and it is acceptable to begin commercial production.

Risk management in Eye Drops production aims to identify, manage and prevent possible failures/risks during the various stages of production of this medicine. This information will help to identify critical steps and further assess the difficulties that may arise during the transition from this manufacturing method to other facilities.

The critical steps identified in the manufacturing process of this product are: holding time (between the end mixture and sterilizing filtration), sterilizing filtration and aseptic filling. All these critical steps must be properly controlled, especially sterilizing filtration and aseptic filling to minimize the risk of contamination during the process, thus obtaining a quality finished product.

In the future, it will be necessary to continue to track production with this new batch size by collecting data such as: number of manufactured and discarded batches, yield, information on raw materials used, main equipment and their qualification status. A PQR should also be developed to check whether or not the production in question remains in a validated state.

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ANNEXES

Annex I – Template Manufacturing Process Validation Protocol for Industrial or Pilot Scale Batches

[*Logo*] [*Name of Company*]	[*Product Name*]	**Reference**	[*Code*]
		1st Version	[*Date*]
		Final Version	[*Date]*
[*Department*]		**Page**	1/2

Prepared By:	**Reviewed By:**	**Approved By:**
[*Quality Assurance*]	[*Production Technician*]	[*Qualified Person*]
	[*Quality Control Manager*]	[*Production Manager*]

1. Introduction

[*Summarize a short description about the validation process and a reference to the respective Master Batch Record*]

2. Objective

The present document is intended to demonstrate and standardize the data should be including in the validation of the manufacturing process, in accordance with GMP.

3. Composition

[*Quantitative composition and function of each raw material*]

4. Manufacturing Process

[*Describe the complete manufacturing process*]

4.1 Flowchart

[*Flow diagram of the manufacturing process*]

4.2 Main Equipments

[*Describe the main equipment used for the manufacturing, including name, brand, model, internal ID and status*]

4.3 Critical Steps to Control

[*Define the steps, process controls and specifications for the evaluation and obtainment of a finish product with required quality*]

Prepared By:	**Reviewed By:**	**Approved By:**
[*Quality Assurance*]	[*Production Technician*]	[*Qualified Person*]
	[*Quality Control Manager*]	[*Production Manager*]

5. Acceptance Criteria

[*Define the acceptance criteria for each parameter, in each one of the steps of the manufacturing process and reflect the reproducibility of the process*]

6. Validation Plan

[*Describe the manufacturing steps considered as potentially influent in the characteristics of the final product*]

7. Further Information

[*Indicate the number of the total batches, significant deviations from those expected, corrective actions proposed and others additional information*]

8. Registration of Information

[*Indicate to local, where all the obtained results during the validation process and all the observations should be registered*]

9. References

[*Indicate to bibliography, including guidelines and internal procedures*]

10. Versions control

[*Indicate version number, date and justification about new version*]

Annex II – Template Manufacturing Process Validation Report for Industrial or Pilot Scale Batches

[*Logo*] [*Name of Company*]	[*Product Name*]	**Reference**	[*Code*]
		1st Version	[*Date*]
		Final Version	[*Date]*
[*Department*]		**Page**	1/2

Prepared By:	**Reviewed By:**	**Approved By:**
[*Quality Assurance*]	[*Production Technician*]	[*Qualified Person*]
	[*Quality Control Manager*]	[*Production Manager*]

1. Introduction

[*Summarize a short description about the validation process, including batch size, number of batches and the analytical control. Reference to the respective Master Batch Record and Validation Protocol*]

2. Objective

The present document aims to validate the manufacturing process.

3. Composition

[*Qualitative and quantitative composition, product code, batch number and function of each raw material*]

4. Manufacturing Process

[*Describe the complete manufacturing process, including main equipments*]

5. Validation Results

[*Describe the data obtained in each step of the process validation*]

5.1. Manufacturing Conditions

[*Describe the controlled parameters and all the conditions of the manufacturing process*]

5.2. In Process Control

[*Describe the analytical control and the results obtained in the manufacturing process*]

5.3. Finished Product Control

[*Indicate the number of samples of finished product were collected and describe the analytical control and the results obtained*]

6. Overall review

[*Describe the principal results obtained, especially in the critical steps*]

7. Conclusions

[*Describe if the analytical results obtained indicate homogeneity between batches*]

8. Registration of Information

[*Indicate to local, where all the obtained results during the validation process and all the observations should be registered*]

9. References

[*Indicate to bibliography, including guidelines and internal procedures*]

10. Versions control

[*Indicate version number, date and justification about new version*]

Annex III – Clean Room and Clean Air Device Classification

Table A.III.T1 – Clean Room Classification. [17]

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Grade A: It is a high-risk operation zone (eg filling zone) containing laminar airflow systems, which provide homogeneous and unidirectional airflow at a velocity between 0.36 – 0.54 m/s.

Grade B: It is a zone for aseptic preparation and filling, this is the background environment for the grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

Annex IV – Finished Product Control

edol saúde que se vê	**Analytical Bulletin**	**Reference**	FPC – QC 001
		1st Version	02/02/2019
		Final Version	15/09/2019
Quality Control		**Page**	1/1

Prepared By:	**Reviewed By:**	**Approved By:**
[*Quality Assurance*]	[*Quality Control Manager]*	[*Qualified Person*]

Information			
Product	Eye Drops	**Analysis Date**	__/__/____
Código	_____	**Batch**	_____
Batch Size	150 L	**Expiry Date**	__/____
Requerente	Laboratório Edol, SA	**Manufacturing Date**	__/__/___
		Sample Size	_____

Tests	**Methods**	**Acceptance Criteria**	**Results**		**Operator**
			Conforms	Non-Conforms	
Appearance (*Ph. Eur. 2.2.1*)	Visual Method	Limpid and colourless	☐	☐	Date:__/__/____
Potentiometric determination of pH (*Ph. Eur. 2.2.3)*	pH meter	3.0 – 5.5 (20-25 ºC)	☐	☐	Date:__/__/____
Osmolality (*Ph. Eur. 2.9.35*)	Osmometer	300 – 400 mOsm/Kg	☐	☐	Date:__/__/____
API Assay (*Ph. Eur. 2.2.29)*	HPLC	90%-110%	☐	☐	Date:__/__/____
API Identification (*Ph. Eur. 2.2.29)*	HPLC	Positive	☐	☐	Date:__/__/____
Preservative Assay (*Ph. Eur. 2.2.29)*	HPLC	96% - 110%	☐	☐	Date:__/__/____
Preservative Identification *(Ph. Eur. 2.2.29)*	HPLC	Positive	☐	☐	Date:__/__/____
Sterility test (*Ph. Eur. 2.6.1*)	Culture Media	Absence of growth	☐	☐	Date:__/__/____

Final Result Approved ☐ Rejected ☐

Quality Control Manager _____ Date: __/__/____
Technical Director _____ Date: __/__/____

Annex V – Filling Control Results

Table A.V.T1 – Samples Volume – Batch 1.

Hours	Samples	
	Weight Average (g)	Volume Average[1] (g)
12:05	5.138	5.112
12:30	5.162	5.136
13:00	5.176	5.150
13:30	5.156	5.130
14:00	5.166	5.140
14:30	5.144	5.118
15:00	5.164	5.138
15:30	5.148	5.122
16:00	5.166	5.140
16:30	5.176	5.150
17:00	5.138	5.112
17:20	5.160	5.134
09:35	5.158	5.132
10:00	5.156	5.130
10:30	5.158	5.132
11:00	5.130	5.104
11:30	5.186	5.160
12:00	5.174	5.148
12:30	5.166	5.140
12:45	5.138	5.112

Table A.V.T2 – Samples Volume – Batch 2.

Hours	Samples	
	Weight Average (g)	Volume Average[2] (mL)
11:40	5.170	5.147
12:00	5.148	5.125
12:30	5.150	5.127
13:00	5.154	5.131
13:30	5.156	5.133
15:10	5.150	5.127
15:30	5.170	5.147
16:00	5.184	5.161
16:30	5.138	5.115
17:00	5.140	5.117
17:35	5.172	5.149

[1]Density = 1.005 mg/mL
[2]Density = 1.004 mg/mL

Table A.V.T3 – Samples Volume – Batch 3.

Hours	Samples	
	Weight Average (g)	**VolumeAverage[3] (mL)**
13:20	5.174	5.155
13:30	5.174	5.155
14:00	5.192	5.173
14:30	5.158	5.139
15:00	5.186	5.167
15:30	5.184	5.165
16:00	5.142	5.123
16:30	5.170	5.151
17:00	5.134	5.115
11:10	5.148	5.129
11:30	5.162	5.143
12:00	5.166	5.147
12:30	5.182	5.163
13:00	5.156	5.137
14:15	5.136	5.117
14:30	5.176	5.157
15:00	5.160	5.141
15:30	5.140	5.121
16:00	5.126	5.107
16:30	5.164	5.145
16:50	5.136	5.117

[3]Density = 1.004 mg/mL