MSc in Pharmaceutical Engineering

Technology Transfer, A Risk Management Approach

Eye Drops Case Study

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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. [1-9]

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. [1-9]

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.

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

1.Introduction

The global market is increasingly competitive and it is necessary to adopt business strategies such as Technology Transfer. 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. [1,2]

Technology Transfer 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. 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. [1-3]

Technology Transfer also incorporates documentation transfer and demonstration of the ability to effectively execute critical elements from the Receiving Unit. 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. [4-6]

Technology Transfer can be classified as horizontal or vertical depending on the scope in

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which it occurs. Thus, vertical Technology Transfer refers to the transfer process from Research and Development to large-scale production of the product. On the other hand, horizontal TT refers to the process of transfer from one market to another, which is usually a less developed one. [1-6]

Technology Transfer is increasingly present in the pharmaceutical activity and can occur for several reasons, including: Scale-up, the need for additional capacity, corporate mergers and consolidations, business strategies for relocating units in different regions of the world and the developer of technology does not have sufficient resources for manufacturing. [7,8]

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 (e.g.: through research grants), benefiting both parties involved. Technology Transfer 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. 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. [2-8] The ultimate beneficiary of a successful transfer 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. [8,9]

Typically, a Technology Transfer begins with a formal written agreement between Sending Unit and Receiving Unit to ensure that this partnership leads to a successful and efficient completion of the transfer process, i.e. that Receiving Unit successfully produces a safe, effective and quality product. 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 Sending Unit to audit the activities performed by the Receiving Unit or its agreed subcontractors. In addition to the contract, it is also necessary to make a Technology Transfer 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. [1,2,7]

Upon approval of the Technology Transfer Proposal, a Technology Transfer implementation plan is required to guide the transfer process, expectations and possible changes that may occur during implementation. This plan is based on proposal and aims to describe the elements involved in the implementation of process transfer as well as track the progress of the project. This plan should be Good Manufacturing Practices 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. 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. [1,7]

In the end it will be necessary to organize all the necessary information so that the Receiving Unit 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. 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 Receiving Unit resources and operations to identify potential gaps or misalignments that may require future modifications. [1,2,7,9]

For a successful Technology Transfer 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. This 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. [2,7] Therefore, this process can be simplified in 5 main steps: Process Development, Facility Fit Assessment, Team Selection, Execution and Qualification. [1-9]

As stated above, the responsibilities of each of the parties involved must be clear and well defined before the execution of the Technology Transfer. Before the process, the Sending Unit is responsible for assessing the legal, suitability and competence of the Receiving Unit to successfully conduct the outsourcing activities. It is also responsible for ensuring, by contract, that GMP principles and guidelines are met. [1,2,7,9]

The Sending Unit must provide all necessary information and knowledge in order for the Receiving Unit to be able to properly perform operations in accordance with applicable regulations. So, the Sending Unit 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. On the other hand, the Receiving Unit should review the information provided by the Sending Unit 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). Finally, the Sending Unit should monitor and review the performance of the Receiving Unit and the identification and implementation of any needed improvement. [1-9]

A Technology Transfer process is considered successful when the analytical method, product or process is routinely reproduced by the Receiving Unit according to predefined criteria. [4-7] Apart from documentation (a critical part of the project), the success of a transfer will also depend on the ability and performance of the individuals who are part of Sending and Receiving Unit. Each team member must understand his or her role and responsibility within the project. The success criteria are: Communication (clear, efficient and continuous), Certainty (to increase certainty and decrease the associated risk, there must be transparency and effective knowledge transfer throughout this process), Challenges (Throughout this process different obstacles arise that may hinder or even prevent a successful transfer, namely: legal and economic implications, information and materials movement restrictions, lack of cooperation between the parties involved and failure to comply with the regulatory requirements), Capacity (regarding the capabilities of Sending Unit and Receiving Unit, these should be similar, i.e. facilities and equipment should operate in accordance with similar operating principles) and Commitment (a strong commitment translates into increased Technology Transfer capacity and therefore a successful transfer). [1,2]
Regulatory factors must also be taken into account, as the pharmaceutical industry is highly regulated. In addition to the factors mentioned above, there are other business factors that may also influence the success of a Technology Transfer, namely: capacity/volume, time frames, cost, equipment and facility capabilities. But sometimes there are obstacles that can hinder or even prevent a successful Technology Transfer, such as: Incomplete Documentation, insufficient process knowledge, high costs, reduced production rates and increased number of atypicals. 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 Receiving Unit to identify and communicate these obstacles to the Sending Unit in order to ensure continuous knowledge management and thus contribute to the development of the control strategy. [1-9]

2. Manufacturing Process Validation

Before the product is placed on the market and to complete the Technology Transfer 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, this validation should demonstrate that the process is robust and that the product quality is assured prior to its release to the market. [10,11]

Manufacturing Process Validation shall be performed in accordance with GMP and the documentation should be properly archived and available in case of an inspection. Documentation

associated with process validation 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. [10-12]

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. [7,10,12]

It should also be noted that each product must have a batch master record and an associated Manufacturing Process Validation protocol. If applicable, the batch master record must be updated according to the validation results. [7]

2.1. Process Validation of Eye Drops Solution

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.

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). Moreover, it is also qualitatively constituted by API (anticholinergic), 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.

2.1.1. Manufacturing Process

The validation process started with the weighing of raw materials in a Class A room, 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). 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. 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.

Prior to sterilizing filtration through a 0.22 µm membrane filter, the integrity of the filter was determined by the bubble point method. Appropriate pressure value in both tests was greater than 31.0Psi (acceptance criteria). In addition to integrity analysis, preservative adsorption control on the pre-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.

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 filters. 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. And 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.

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 1**. and the main equipment used for the manufacturing and analysis of eye drops solution, it is described in **Table 1.**

Table 1. – 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

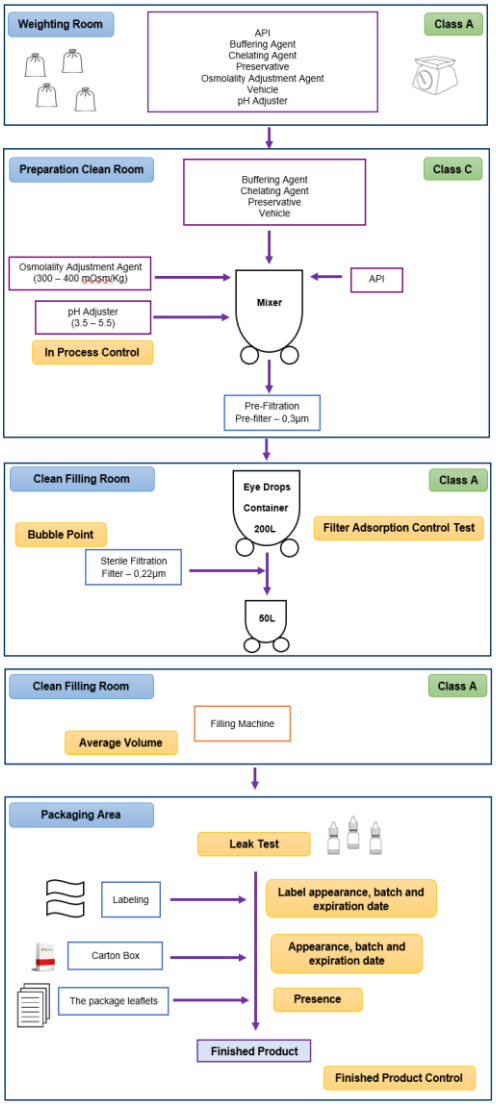

Figure 1. – Flow diagram of the manufacturing process.

3. Validation Results and Discussion

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

Table 2. – 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 3. 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 3.** 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 (Density (Batch 1) = 1.005 g/m and Density (Batch 23) = 1.004 g/mL).

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.

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.** and **5.** respectively**.**

Table 3. - 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%		-

Table 4. – 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 5. – 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 5.** 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.

The obtained values are shown in the following control charts.

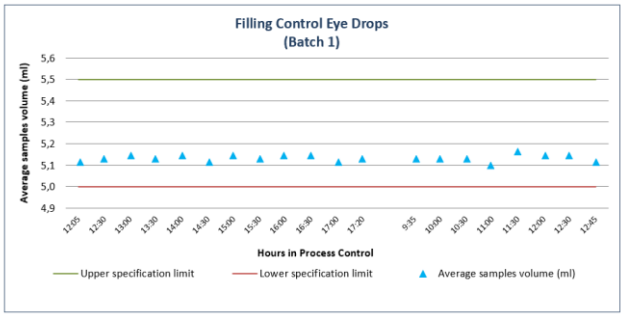

Figure 2. - Filling Control Results – Batch 1.

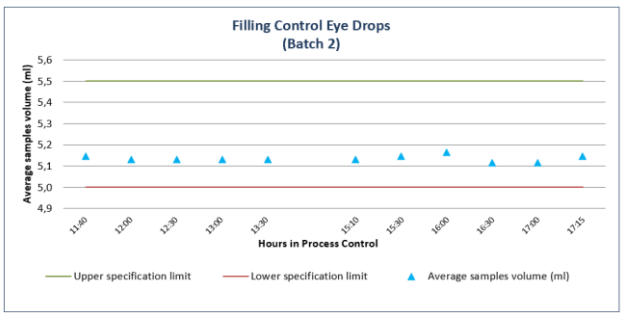

Figure 3. - Filling Control Results – Batch 2.

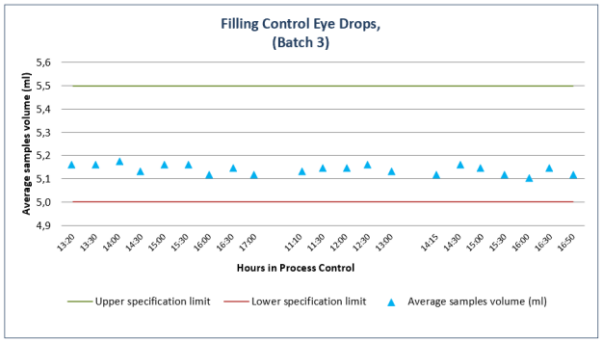

Figure 4. - Filling Control Results – Batch 3.

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 6. – 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 7.**, **8.** and **10**.

Table 7. - 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 8. - 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 9. - 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 Table **7.**, **8** and **9.** shows that the samples collected were clear and colorless as described in the specification. Regarding the pH of the solutions, they were within the previously defined limits (30-5.5 – 20-25ºC). The same result was found in the determination of osmolality, whose values were within the previously defined range of values. 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 were within the previously defined range of values

Finally, regarding the results of the sterility test, 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. 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 Technology Transfer, 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, like as: raw materials (storage conditions, weighting), equipment (sterilization, clean and compatibility with solution), velocity and time of the mixtures, holding time, sterilizing filtration (bubble point, filtration pressure and compatibility with solution), filter adsorption control, aseptic filling (air quality, temperature, pressure and filling velocity), leak test and packaging operation.

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). 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). 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 5.**).

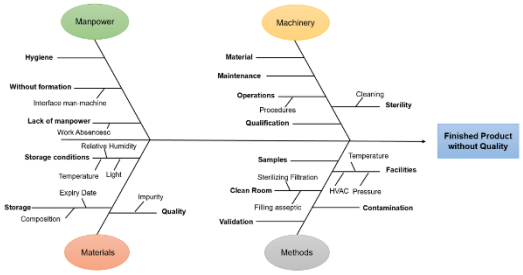

Figure 5. - Ishikawa diagram.

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. 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). 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.

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). 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.

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. 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.

Conclusion

Nowadays, the pharmaceutical market is increasingly competitive and broad. Business strategies such as Technology Transfer 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. 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. Thus, a validation protocol was developed for scaling up an eye drops solution, with a 150L industrial scale batch.

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.

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.

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