TIAGO MIGUEL DA COSTA NOVAIS JERÓNIMO

QUALITY CONTROL OF PRIMARY PACKAGING IN THE PHARMACEUTICAL INDUSTRY

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JÚRI

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To my Family

Quality means doing it right even when no one is looking

Henry Ford

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For my school I'd to extend my gratitude to my advisor Dr. Nilmara Dias, for the orientation and the assistance during the making of this thesis. Another acknowledgment has to go to Professor Lurdes Gameiro that put me in contact with Hikma in the first place and that showed herself always available to answer any of my questions or difficulties.

A special thanks goes to all my friends and family that supported me throughout my journey during this internship as well as my master's degree.

ABSTRACT

This internship was conducted in Hikma, which is a pharmaceutical company located in Sintra, Portugal responsible for the production of injectables for the Portuguese and American market. To ensure that every single product supplied by the company follows the strict specifications imposed by the European Medicines Agency and the Food and Drug Administration, Hikma uses advanced and specialized equipment and laboratory techniques to test the quality and safety of not only the product itself but also its packaging.

For this internship, quality control tests were carried out on the primary packaging materials used for the injectables produced by Hikma. The types of primary packaging analysed consist of glass containers, rubber stoppers, flip-offs and twist-offs. As these are all very different types of primary packaging the analyses differ between each of them, in general each type has chemical and physical analysis except flip-offs and twist-offs that require exclusively physical analysis. Of course, this classification serves only to summarize the considerable number of analyses that need to be carried out for all types of primary packaging, as the physical and chemical analysis of each type differs depending on the specific primary packaging to be analysed, some of these analyses consist of the use of spectroscopy, titration and specialized equipment like a texture analyser. Throughout the internship more than 200 batches were analysed and all the analysis carried out were conform, meaning that they were all according to specification.

KEYWORDS: Pharmaceutical industry, Injectables, Quality control, Primary packaging, Chemical and Physical analyses.

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ABBREVIATIONS

AQL Acceptable quality limit, %

CTA Clinical trial application

EMA European medicines agency

EP European pharmacopeia

FDA Food and drug administration

GMP Good manufacturing practices

GLP Good laboratory practices

IND Investigational new drug

MAA Marketing authorization application

NDA New drug application

QA Quality assurance

QC Quality control

R&D Research and development

USP United states pharmacopeia

NMT Not more than

1. FRAMEWORK

This curricular internship was integrated in the 2nd year of master's degree in chemical and Biological Engineering in *Instituto Politécnico de Setúbal (IPS) / Escola Superior de Tecnologia do Barreiro (ESTBarreiro)* with the orientation of professor Nilmara Dias, with a final duration of 700 hours. The internship was developed in Hikma pharmaceutical, in the wet chemistry lab belonging to the quality control department supervised by engineer Daniela Guerreiro.

The wet chemistry lab concerns itself with quality control analysis of active and inactive pharmaceutical components as well as primary packaging of pharmaceutical drugs. As some equipment wasn't present in the wet chemistry lab, namely the hydraulic press, autoclave, and vacuum pump, as such the instrumental laboratory belonging to the same department was also used.

The work employed in this internship consisted of the realization of quality control analysis of primary packaging of pharmaceuticals like glass vials and ampoules, flip-offs, twist-offs and rubber stoppers.

Additionally, some analysis of the infrared spectrum of active components of pharmaceutical drugs were also realized. This was done to serve as a complement to the analysis of the primary packaging and to enrich the internship with an alternative method of infrared analysis to the one realized for rubber stoppers.

As such the equipment and materials provided in these laboratories were essential for the realization of this thesis in Hikma.

2. OBJECTIVES

This internship had as its main goals the analysis of primary packaging in the pharmaceutical industry with the purpose of determining their adherence to established specifications by the regulatory agencies responsible for the pharmaceutical sector. The more general goal of the internship was to integrate the intern in a professional environment, more specifically a quality control laboratory, as well as to develop autonomous qualities and teamwork and communication capacities.

3. CARACTERIZATION OF THE HOSTING INSTITUTION

The hosting institution for this internship, Hikma, is a pharmaceutical company that was founded in Jordan in 1978. Since its creation the company has expanded its operations to include manufacturing facilities, development, and research centers as well as commercial offices across the globe.[1]

Hikma's products include a wide array of generic and branded pharmaceutical products, with a focus on complex and difficult-to-manufacture pharmaceutical drugs. Globally, the company produces three types of medication, injectables, oral solids like pills and oral liquids like syrups. In Portugal, Hikma produces solely injectables which are then made available to hospitals in the country and, primarily, in the US. Some examples of illnesses treated by the company's products include cardiovascular disease, cancer, respiratory illnesses, and neurological disorders. [1]

For Hikma to reach its current state it couldn't depend solely on the variety or quality of its pharmaceutical drugs. One of the various core strengths of this company is its vertically integrated business model, this business model consists of the company's control over multiple stages of its production process and supply chain which, in this case, include the sourcing of raw materials and distribution of the final product.[1]

Of course, Hikma's relative swift growth can also be attributed to its numerous strategic acquisitions and partnerships, an example of a very lucrative acquisition would be the acquisition of Roxane Laboratories in 2015. Roxane Laboratories was a US-based manufacturer of generic pharmaceuticals, and its acquisition expanded Hikma's presence in the US market. Another factor responsible for the company's remarkable growth is its commitment to sustainability and corporate social responsibility. Not only has Hikma implemented several incentives to reduce its negative environmental impact, but it also established strong corporate governance framework, which includes a commitment to ethical business practices and transparent reporting. [1]

Overall, Hikma is a leader in the global pharmaceutical industry, with a strong and consistent track record of delivering high-quality medication to patients globally. The company's commitment to sustainable development, strategic partnerships and vertically integrated business model makes it an attractive partner for possible investors in the healthcare sector.

4. TIMELINE OF THE INTERNSHIP

Table 1 - Timeline of the internship in Hikma from april to august

	Weeks																			
Atividades	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Literature review																				
Training required to work in a quality control laboratory																				
Packaging quality control																				
Laboratory work/Result analysis																				
Report writing																				

5. THEORETICAL INTRODUCTION

5.1. PHARMACEUTICAL INDUSTRY

Every industry has specific goals that must be accomplished to ensure their success, and the pharmaceutical industry is no different. This industry has two main goals, firstly it is to ensure healthy competitiveness in the drug market, this competition ensures affordable prices for the medication society depends on. The second goal is to ensure the swift development of the industry's technology.[2]

Overall, these two goals of the pharmaceutical industry revolve around its responsibility for the manufacture, development, and research of new, safe, and effective drugs. A pharmaceutical drug is a substance that is capable of curing, preventing, or alleviating the symptoms of ailments or diseases. The Food and Drug Administration (FDA) defines pharmaceutical drug as "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."[3]

The pharmaceutical drugs present in the market need to undergo rigorous analysis to ensure high quality and safety standards as defined by the FDA and European Medicines Agency (EMA) authorities. To maintain the required quality and improve on it there must be considerable investment by pharmaceutical companies in Research and Development (R&D), quality control and in quality regulations.

5.1.1. PHARMACEUTICAL DRUG DEVELOPMENT

Drug development is a very lengthy process owing to the stringent regulation in effect in the pharmaceutical industry. To clarify this statement, on average, and as an optimistic estimate, the time it takes for a new drug to go from discovery to being on shelves in the nearest pharmacy is about 12 – 15 years. Time is not the only challenge, only 1 in 5000 drugs are approved to market by regulatory entities like FDA and EMA. [4]

This development can be divided into four stages, each with its own challenges and requirements for the pharmaceutical company that intends to develop a new drug. [5]

1.1.1.1 Discovery

The discovery stage gets initiated and ultimately ends in a laboratory. It starts with the discovery of several compounds that have a direct beneficial effect on human health or, alternatively, the compound can be harmful to dangerous microorganisms that would otherwise negatively affect human health. After this initial discovery what follows is extensive research and computational testing to evaluate the extent of the capabilities of the discovered compounds for their intended purpose.[5]

5.1.1.2. Preclinical research

Following the discovery phase is the preclinical research phase, where the compounds are assessed in experimental models made to simulate human physiology. In this stage it is also imperative that any toxicity to humans is fully ascertained as the next stage concerns human testing of the lead compound candidates. [5]

Once the compounds are fully characterized, the more promising compounds get selected for candidacy in the next stage, and assuming the tests performed on the compounds provide results in line with researcher's expectations, the developers of the compounds can proceed to an application for permission to advance to the clinical human trials of the compounds. [5]

This application varies depending on the regulatory agency it is sent to. An Investigational New Drug (IND) for the FDA, and a Clinical Trial Application (CTA) for EMA. These regulatory agencies then proceed to examine the application, if they are unsatisfied with any data, they can send the application back and request further testing, otherwise the compounds advance to the next stage.[5]

5.1.1.3. Clinical development

Phase I

It is in this phase that the first human trials begin. Usually around 80 healthy volunteers are selected, with the goal of determining the behavior of the compounds in the human body and determining if it corresponds to the data acquired on the preclinical research. It is also in this phase where toxicity, safe dosages and how long the compound is active in the human body are determined. [5]

Phase II

Assuming positive results in the previous phase, researchers can apply to proceed for phase II, where around 200 patients diagnosed with the illness/condition that the compound is meant to treat are selected. These patients will then make use of the compounds. In this phase not only safety but also efficacy is determined. [5]

Phase III

This is the last phase before the request for market approval for regulatory agencies in the pharmaceutical industry. In this phase, at least 1000 patients with the illness/condition that the compound is meant to treat are selected. The data acquired on the usage of the compounds by these 1000 patients must be enough for researchers to make safe conclusions on the safety and all side effects of the compound when exposed for lengthy periods of time.[5]

5.1.1.4. Market approval

After enough information is acquired in phase III, developers will begin requesting market approval with a New Drug Application (NDA) for FDA and/or Marketing Authorization Application (MAA) for EMA. These applications include not only all the data from the previous

phases compiled in what can reach hundreds of thousands of pages of documentation, but also an appeal from the principal investigator for the approval of the compound.[5]

Assuming a positive response from the regulatory agency then the compound or, as it is called now, the medicine is ready for market launch.[5]

Overall, it takes at least a decade for a compound to go from discovery to market launch, due to this long duration of time it is essential for pharmaceutical companies to not only expedite the process but also to ensure no setbacks in all the distinct phases through the use and application of quality control regulations. [5]

5.1.1. PACKAGING IN THE PHARMACEUTICAL INDUSTRY

As previously established in this thesis, the quality and safety of the drugs developed by pharmaceutical companies is crucial, and a critical factor that is always taken into consideration is the packaging. This is due to the fact that even if the drug being produced is of high quality, that becomes irrelevant if by the time the drug reaches the consumer it has already lost qualities that ensured its effectiveness and safety.

Essentially, pharmaceutical packaging is the process of enclosing pharmaceutical products in a package that provides protection, identification, and information to the consumer. The packaging must be designed to protect the product from contamination, damage, and tampering. It must also be easy to use and transport while providing accurate information about the product.[6]

There are various factors that can affect the chemical and physical properties of the product, these can be intrinsic if these are factors inherent to the product itself like hydrolysis or oxidation, or these can be extrinsic if these are outside forces acting on the product like temperatures or humidity. Typically, pharmaceutical packaging must consider both of these factors to ensure the quality of the product.[6]

5.1.2. GOOD MANUFACTURING PRACTICES AND GOOD LABORATORY PRACTICES

When it comes to quality control regulations, there are two main quality management systems that ensure safety and quality of drugs and other products, these are Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP).

The main difference between these two quality management systems is their scope, GMP encompasses all the manufacturing process while GLP encompasses all the testing and research phases. Due to this difference each quality management system applies to a specific phase in the drug development stages (**Figure 1 - Different drug development stages along with their respective quality management system**).

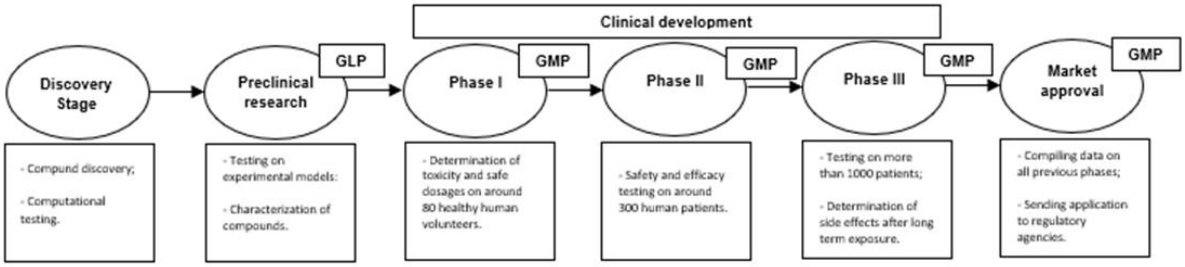

Figure 1 - Different drug development stages along with their respective quality management system (Adapted from source [7])

Good laboratory practices are a set of principles concerned with ensuring the safety and integrity of non-clinical laboratory studies. This control is achieved through the regulation of all conditions and variables involved in the non-clinical laboratory studies, for example, the regular calibration and maintenance of laboratory equipment as well as reliable bookkeeping of each equipment notebook, ensuring that each use of the equipment is registered with the signature of the individual that used it as well as the date of its use. [7]

As previously stated, Good Manufacturing Practices encompasses all the manufacturing process, and as such regulates the design, monitoring and operation of manufacturing processes and facilities. [7]

The main purpose of GMPs is to ensure that every individual and equipment involved in the manufacturing process is following the proper guidelines to ensure a safe and effective product. Every individual from the manufacturer to the packager to even the one responsible for the sanitization of the factory must follow these guidelines because everyone involved in the production process of the product is directly or indirectly responsible for the final quality of the finished product. [7]

These stringent regulations ensure the safety and reliability of the product in the eyes of the consumer by minimizing any contamination, mix-ups or any other errors occurring during the manufacturing process.

5.1.3. QUALITY CONTROL

Before trying to explain what quality control is, one should first elucidate what quality is. In the context of a manufactured product quality can have two distinct meanings. [8]

1 – Quality focused on meeting the requirements and needs of the customers. The purpose of heightening this quality is to increase customer satisfaction and, as a result, the manufacturers' income. This increase, however, requires investment which means an increase in the cost. This quality usually costs more for the manufacturer.

2 – Quality focused on the absence of inadequacies. This lack of errors means that there is no need to account for field failures, customer dissatisfaction, etc. The increase in this quality usually means a decrease in costs due to the lack of errors that would require rework.

Nowadays quality encompasses these two definitions, becoming a quality focused on eliminating deviations from specifications, meeting customer requirements and, more importantly, ensuring that the product is effective and safe to use. According to Juran, to achieve quality, three management processes are required, the so called “Juran trilogy”: [8]

- Quality planning
- Quality control
- Quality improvement

Quality planning refers to the quality goals to be met along with the customer needs and taking that into consideration, the development of specific manufacturing and quality processes required to meet those goals and needs. Quality control refers to the actual control being undertaken, comparing that data to the quality control goals, and finally acting on the potential difference. Quality improvement aims to improve quality control results through, for example, the introduction of new procedures for higher quality standards. [8]

As such quality control is a managerial process concerned with providing stability to the manufacturing process.

In the pharmaceutical industry, quality control concerns the improvement and constant development of specific analytical methods to test various chemical compounds. Analytical chemistry is the measurement, processing and registering of information obtained through analytical methods on any given chemical compound. Every single compound has distinctive characteristics, so each compound has a specific analytical method designed to identify and quantify it. The broad term “analytical method” can be narrowed down to two types of analysis, the qualitative analysis that is concerned with the identification process, and the quantitative analysis that is concerned with the determination of the mass or concentration of any given compound. [9]

5.1.4. QUALITY ASSURANCE

As previously stated, quality control and quality assurance are often used interchangeably, and this is not without cause as quality control and quality assurance have much in common. They are both concerned with the evaluation of performance, comparing this performance with established goals, and finally acting on the difference. When it comes to their differences, quality control focuses on the control over the process. During operations performance is evaluated and then compared to the established goals. The resulting information is processed and is then used in the operating process.[9]

The focus of quality assurance is to verify that control is being maintained. After operations performance is evaluated, the resulting information is processed and provided to the operating forces and necessary staff members.[9]

QA covers every variable that directly or indirectly affects the final quality of the product. It covers all the steps taken to ensure the reliability, quality, and safety of the product, which can be pharmaceutical or otherwise. As such QA incorporates GMPs in its scope. [9]

The guidelines and procedures followed in a quality control environment assist in minimizing errors and deviations but, of course, the occasional deviation is inevitable. These deviations must be dealt with post haste as, for example, in a pharmaceutical company, deviations can vary from negative impact on the brand to something far more significant – the loss of lives.[9]

5.1.5. DEVIATIONS IN A QUALITY CONTROL ENVIRONMENT

Every company operating on GMP guidelines must have proper deviation management. Deviation management is the process of identifying and correcting any and all deviations from proper procedure and/or standards.[10]

Giving a relevant example of proper deviation management, the vents ensuring the circulation of sterilized air on a sterilized production room have failed causing the potential contamination of various batches. Because proper deviation management procedures were being followed, this deviation was detected and the batches were removed before they could be sent to the market, ensuring no health risks to consumers and brand damage to the producer and distributor.

Of course, not all deviations are the same and each can be classified differently. There are different types of deviation according to their predictability:[10]

- Planned Deviations
- Unplanned Deviations

Planned Deviations

These deviations are pre-approved temporary deviations from existing protocol. These pre-approved deviations usually only last for a reduced number of batches and are typically employed to minimize damage caused by a problematic situation. Evidently these deviations are undertaken in such a way that their implementation will not affect the final quality of the product in any way shape or form. An example of such a planned deviation would be the reduced final batch size considering a reduced availability of raw materials.[10]

Unplanned Deviations

These deviations are unexpected deviations from existing protocol at any point of the manufacturing or quality assessment stage. These deviations can result from equipment failure or breakdown, power outages and human error. An example of this type of deviation would be the use of equipment out of calibration. These deviations can negatively impact the final quality of the product depending on how the deviation is classified. Unplanned deviations can be classified in four different ways:[10]

- Incidents
- Minor Deviations
- Major Deviations
- Critical Deviations

Incidents

An incident is essentially a deviation that does not impact the final quality of the product. An example of which would be workers in the production line not wearing proper apparel and/or equipment, or a misstep in procedure that nonetheless has no negative impact on the final quality of the product.[10]

Minor Deviations

Minor deviations have a minimal or negligible impact on the final quality of the product. An example of which would be the use of a balance outside its tolerance weight.[10]

Major Deviations

Major deviations have a moderate or major impact on the final quality of the product. An example of which would be the reception of raw materials in damaged packaging.[10]

Critical Deviations

Critical Deviations have a significant impact on the final quality of the product. An example of which would be the use of contaminated raw materials.[10]

Figure 2 - Flowchart of the typical deviation management proceduredemonstrates the typical deviation management process.

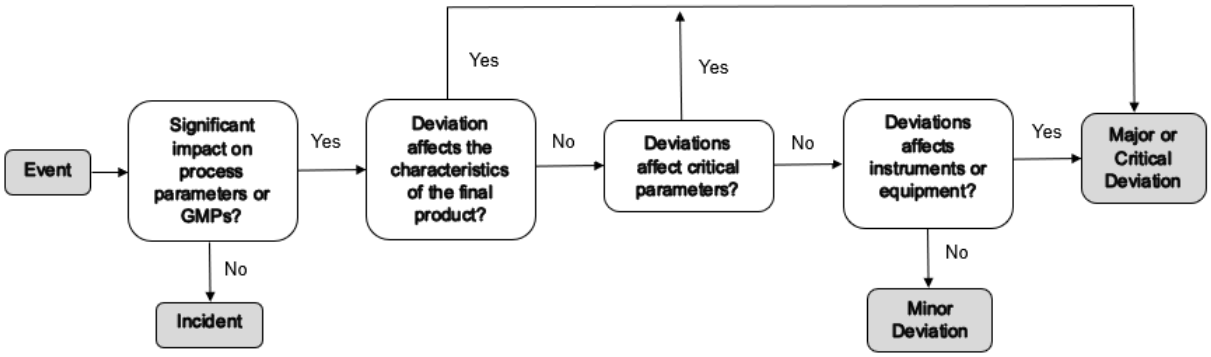

Figure 2 - Flowchart of the typical deviation management procedure (Adapted from source [10])

These are the classifications of different deviations, but what exactly is the procedure for when there is the occurrence of a deviation?

This procedure can be divided into four stages:

- Identification
- Reporting
- Investigation

- Documentation
- Implementation

Identification

In this stage there is the identification of the deviation, this identification can occur during the manufacturing process, quality control process or even after the product has entered the market. It's in this stage that a deviation will be classified according to the previously mentioned deviation classifications.[10]

Reporting

In this stage the deviation and all related data will usually be reported by the department in which the deviation has occurred. The maximum time frame for this stage is one day after the identification of the deviation in order to ensure a swift response by the company.[10]

Investigation

After identifying and reporting the deviation, the next stage is the determination of the cause of the deviation. This identification is undertaken on major and critical deviations since these deviations have a significant impact on product quality. [10], [11]

It's in this phase that a laboratory analytical event form is filled out with details regarding the event, including the cause as well as corrective measures to ensure that the event is an isolated incident.[10], [11]

Documentation

The next stage is the documentation of the deviation as well the resulting laboratory analytical event form to ensure a clear tracking. The necessity for the tracking of any data including deviations is the reason why pharmaceutical companies maintain an audit trail, which are the chronological records of any data acquired in the normal function of the typical pharmaceutical company.[10], [11]

Implementation

In this last phase the company ensures that no similar deviations will occur through the implementation of preventive and corrective measures.[10], [11]

5.2. QUALITY CONTROL IN PHARMACEUTICAL PACKAGING

This thesis has already established what quality control is in the pharmaceutical industry, but now it is essential to shed light on the quality control in place for the packaging of medication

in the pharmaceutical industry. Proper packaging is indispensable to maintain the quality of the drug. The packaging protects the drug not only from physical damage but also from biological and chemical degradation. A sizable portion of drugs on the market nowadays are extremely sensitive to adverse conditions and as such, proper drug packaging must be able to provide protection from light, water, and proximity to other sensitive substances.[12]

The packaging in the pharmaceutical industry can be divided into three categories:[12]

- Primary packaging
- Secondary packaging
- Tertiary packaging

Primary packaging is the "first line of defense", is the one that's in direct contact with the product, for a pharmaceutical drug and as such must provide physical and chemical protection to the drug itself. An example of primary packaging would be vials that contain injectables. Secondary packaging is the outer packaging and concerns itself with the protection of the primary packaging during its storage, transportation and distribution to the clients, an example of secondary packaging would be cartons or boxes. Tertiary packaging is used for bulk handling, warehouse storage and transport shipping, an example of which would be shipping containers. [12]

This thesis concerns itself with the analysis of the primary packaging of injectables, and this includes the chemical and physical analysis of glass containers like vials and ampoules, rubber stoppers, flip-offs and twist-offs.[12]

For all of the chemical analysis of the concerned primary packaging there is a need to prepare specific solutions for each chemical analysis. In a quality control lab, the preparation of solutions is very important as it can affect the accuracy and precision of the results obtained. In other words, the ability to prepare accurate solutions, reagents, and buffers will influence the outcome of the analysis.

5.2.1. ANALYSIS OF GLASS CONTAINERS

In the pharmaceutical industry, glass containers are used as primary packaging, meaning that they are in direct contact with the pharmaceutical drug, making it essential to perform an extensive list of analysis to ensure they are up to the standards set by the regulatory agencies.

There are two different glass containers used and analyzed in Hikma, glass ampoules and glass vials. Both of these containers have advantages and disadvantages for their uses, glass ampoules are entirely made of and sealed in glass and so are excellent for the preservation of the pharmaceutical component, however because to open the ampoule there is a need to break the opening there is a risk of contamination by micro fragments of glass in the pharmaceutical drug, also the requirement for breaking the opening means that ampoules are single use containers. On the other hand, glass vials can be reused for multiple injections and are typically used to carry multiple doses of the pharmaceutical drug, however because rubber stoppers are used to seal the glass vial there is a requirement to analyze the stoppers as they are a possible source of contamination or a possible breach in the seal of the glass vial.[13], [14]

For this analysis, several areas are taken into consideration to ascertain the quality of the glass container batch: [15]

- Visual Inspection
- Dimensions
- Chemical analysis
- Spectral transmission (amber glass)

5.2.1.1. Physical Analysis

- Visual Inspection

When it comes to the analysis of the appearance of any batch of primary packaging including rubber stoppers, flip-offs, twist-offs and glass containers, pharmaceutical companies follow a classification of non-conformance along with what is called an *Acceptable Quality Limit* (AQL) (Table 2 - Classification of non-conformance with each respective AQL (%)):[15]

Table 2 - Classification of non-conformance with each respective AQL (%)

Non-conformity	Brief explanation	AQL (%)
Critical	Nonconformity likely to cause a personal injury or potential hazard to the patient. This classification includes any nonconformity that compromises the integrity of the container and risks of contamination of the sterile product	None allowed
Major A	Nonconformity leading to serious impairments. This classification includes any nonconformity that makes the packaging unusable	0.65
Major B	Nonconformity leading to less serious impairments. This classification includes any nonconformity that causes a reduced efficiency in production	1.5
Minor	Nonconformity that does not impact the product quality or process capability	6.5
N/A	Imperfection that lacks the magnitude or impact to be classified as a nonconformity. As such, an imperfection classified is N/A is acceptable	N/A

For this analysis, a batch sample is selected and analyzed to find all nonconformities. Each nonconformity has an AQL (%) which is the limit of nonconformities that can be present in the sample, for example the most limiting AQL is in the critical non-conformity where there is none allowed or in other words a 0% AQL, meaning that any critical non-conformity can lead to the rejection of the entire batch.

For the glass vials analyzed in this internship there is an extensive list of nonconformance standards, but for the purposes of this thesis an abridged version of this list will be displayed in Table 3

Table 3- List of nonconformance standards

Nonconformance	Location	Classification	AQL(%)
Crack	General	Critical	0
Wavy Top - compromising seal integrity	Seal Surface		
Loose Glass - Not removable	General		
Internal Contamination - Not removable	General		
Chip - seal integrity intact	General	Major A	0,65
Bruise	General		
Ridge - seal integrity intact	Seal Surface		
Line over finish	Seal Surface		
Bent Neck	Finish	Major B	1,5
Internal Contamination – Removable	General		
External Contamination - Not removable	General		
Sunken Neck	Neck		
Belt Marks	General	Minor	6,5

Loose Glass - Removable	General		
Twisted	Neck,Shoulder or Finish		
Tooling Mark	Finish		
Orange Peel Texture	General	Minor or N/A	6,5 or N/A
Pressure Mark	Finish		
Scuff	Body		
Wavy Bottom	Bottom		

- Dimensions

The measuring of the dimensions of containers is relevant as it ensures that the containers are of the correct size and shape. The correct size and shape are set, considering that the containers will need to fit into machinery responsible for filling and sealing each container. Not only that, but this measuring also ensures that the correct amount of medication is dispensed. The glass containers analyzed during this thesis were glass vials and glass ampoules (, previously mentioned. Each dimension measured along with their respective AQL (%) for each sample is displayed on table 3 for glass vials, and Table 4 for glass ampoules.

Table 4 - Analyzed measurements along with their respective type of defect and AQL (%) for each sample of glass vials

Dimensions (mm)	Type of defects	AQL (%)
External diameter	Major	1.0
Wall thickness	Major	1.0
Total height	Major	1.0
External collar diameter	Major	1.0
Thickness of base	Major	1.0
Collar height	Major	1.0
Internal collar diameter	Critical	None allowed

Figure 3 represents how the measurements for glass vials are taken.

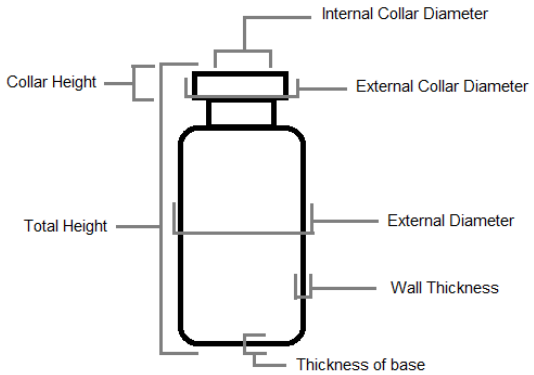

Figure 3- Representation of the measurements taken for the glass vials used in Hikma.

Table 5 show the major defect and respective AQL (%) for each dimension.

Table 5 - Analyzed measurements along with their respective type of defect and AQL (%) for each sample of glass ampoules.

Dimensions (mm)	Type of defects	AQL (%)
Total height	Major	1.0
External diameter of the strangulation	Major	1.0
External diameter of the body	Major	1.0
External diameter of the neck	Major	1.0

Figure 4 represents how the measurements for the glass ampoules are taken:

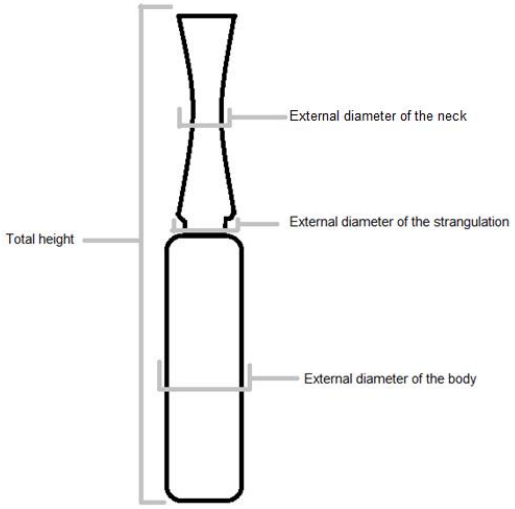

Figure 4 - Representation of the measurements taken for the glass ampoules used in Hikma.

5.2.1.2. Chemical analysis

The chemical analysis of pharmaceutical vials and ampoules has as it aims the determination of the type of glass that makes up the glass containers, the arsenic content in the vials as well as the spectral transmission of amber glass vials. The chemical analysis as well as the specifications for glass ampoules and glass vials are identical and as such apply to both glass containers.

Before any chemical analysis there is a need to ensure the availability of the needed solutions, and if needed prepare them fresh. This especially applies to the hydrolytic resistance analysis since there is a requirement to use volumetric solutions.

- Volumetric solution preparation

A volumetric solution is a standard solution used in analysis based on the measurement of volumes of reaction in solutions. Essentially it is a solution that contains a specific quantity of solvent per stated unit of volume.

A significant portion of chemical analysis in a quality control lab requires the use of volumetric solutions which is one of, if not the first steps of each analysis. Accurate and reliable titration results are only achievable when the exact concentration of the volumetric solution is determined, this concentration is called the normality factor of the volumetric solution.

The determination of the normality factor is essential because it allows for the determination of the exact amount of reactant needed to neutralize or react with the solution being titrated, this acquired information is important for accurate and transparent titration results. [16]

- Hydrolytic resistance

There are three types of glasses used in the pharmaceutical industry according to European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP) as shown in Table 6.[15]

Table 6 - Glass types according to EP and USP

Glass Types	Composition	Characteristics
Type I	Neutral or borosilicate glass. Holds significant amounts of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides in the glass network	High hydrolytic resistance and high thermal shock resistance due to the chemical composition of the glass itself
Type II	Usually it is made of soda-lime-silica glass	High hydrolytic resistance resulting from suitable treatment of the surface
Type III	Usually it is made of soda-lime-silica glass. Silica glass holding alkaline metal oxides, mainly calcium oxide, in the glass network	Moderate hydrolytic resistance due to the chemical composition of the glass itself

Essentially each glass type is selected depending on the pharmaceutical drug that the containers are meant to hold. As type I glass is chemically inert it is suitable for all products, type II glass is suitable for most acidic and neutral aqueous products and type III glass is suitable for non-parental products.

Table 7 shows tests performed to ascertain the glass type as well as the reason for each for the realization of each analysis:

Table 7 - Hydrolytic analysis of glass containers according to EP and USP

Tests to be performed	Reason	Glass type		
		Type I	Type II	Type III
Hydrolytic Resistance of Inner Surfaces (Surface glass test)	Distinguishes between Type I and II containers with high hydrolytic resistance and Type III containers with moderate hydrolytic resistance	x	X	X
Hydrolytic Resistance of Glass Grains	Distinguishes Type I borosilicate	x	X	X

(Glass grains test)	glass from Type II and Type III soda-lime-silica glass			
Hydrolytic Resistance of Etched Surface (Surface etching test)	Where it is necessary to find whether high hydrolytic resistance is due to inner surface treatment or to the chemical composition of the glass containers	x	X	-

Besides the determination of glass type, hydrolytic resistance analysis has another main goal. The determination of the glass container resistance to the action of water at high temperatures and pressures

For the hydrolytic resistance of the inner glass surface the limit values considered for the titration are shown in Table 8:[15], [17]

Table 8 - Limit values for the surface glass test according to USP

Filling volume (mL)	**Maximum Volume of 0.01 M Hydrochloric Acid per 100 mL of Test Solution (mL)**	
	Type I/Type II	**Type III**
NMT 1	2.0	20.0
1-2	1.8	17.6
2-3	1.6	16.1
3-5	1.3	13.2
5-10	1.0	10.2
10-20	0.80	8.1
20-50	0.60	6.1
50-100	0.50	4.8
100-200	0.40	3.8
200-500	0.30	2.9
NLT 500	0.20	2.2

The hydrolytic resistance of the glass grains indicates the alkali content of the glass container. The limit values considered for this titration are shown in Table 9:[15], [17]

Table 9 - Test limits for hydrolytic resistance of the glass grains

Filling volume (mL)	Maximum Volume of 0.02 M Hydrochloride per Gram of Test Glass (mL)	
	Type I	**Types II and III**
All	0.1	0.85

The hydrolytic resistance of the etched surface is an analysis that is only applied to glass vials and provides information on the inner surface durability of the base glass. The limit values for the analysis of the etched surface are identical to the inner glass surface analysis, and as such the limit values considered are the same (Table 8).

- Arsenic analysis

The presence of arsenic in glass containers poses a serious health concern since this component can be harmful to the eyes, skin, liver, kidneys and lungs, this exposure also causes cancer. [18]

Taking this information into consideration the analysis of the presence of arsenic becomes essential to ensure the safety of patients that require the vaccines or injectables contained in these glass vials.

This analysis consists of the use of a commercially available arsenic test kit by Merck. This test consists of the adding of zinc and a solid acid to the solution obtained in the hydrolytic analysis of the inner glass. These components will react with any arsenic (III) and arsenic (IV) to form arsenic hydride in its gaseous state. This gas will react with the mercury (II) bromide contained in the reaction zone of the test strip provided by the test kit to form yellow-brown mixed arsenic mercury halogenides.

The concentration of arsenic in the sample is measured by visual comparison of the final color of the test strip with the fields of a color scale provided by the test kit.

- Spectral Transmission (amber glass)

The spectral transmission analysis consists of the UV (ultraviolet) analysis of the glass using a specialized spectrophotometer, this type of analysis is designated as spectrophotometry.

Spectrophotometry is a highly effective method when it comes to the analysis of inorganic compounds. One of its key advantages is its wide analytical range, which eliminates the need for sample dilution. This technique is versatile, low-cost, easy to implement, and often uses plug-and-play equipment. It is due to these characteristics that spectrophotometry is among the most flexible analytical methods available[19]

The absorption, transmission, or reflection of light (electromagnetic radiation) over a certain range of wavelength is exhibited by every compound. Spectrophotometry is the measurement of the amount of light that a chemical substance absorbs or transmits. This technique is useful in any field that deals with chemical substances or materials. [19]

The measurements required for spectrophotometry are done using a spectrophotometer, which is an instrument used to measure the number of photons (intensity of light) absorbed by a sample solution after a light beam passes through it. By measuring the intensity of light detected, the amount of a known chemical substance can be determined.[20] There two types of spectrophotometers based on the range of wavelengths of the light source they use:

- Ultraviolet (UV) -visible spectrophotometer – This spectrophotometer uses light over the ultraviolet range (185-400 nm) and visible range (400-700nm) of the electromagnetic radiation spectrum. [21]
- Infrared (IR) spectrophotometer: Uses light over the infrared range (700-15000 nm) of the electromagnetic radiation spectrum. [22]

As previously stated, the spectrophotometry of interest in this analysis is the UV spectrophotometry. This analysis measures the amount of wavelengths that are absorbed or transmitted from a sample in comparison to a blank sample. The comparison to a blank sample is done to, in a way, exclude the influence of the blank (typically water) on the final spectrum, in other words to solely obtain a spectrum of the components excluding the blank. The interaction between the sample and the wavelengths emitted by the UV spectrometer is influenced by the sample composition, meaning that through this analysis its possible ascertain what components are present in the sample and at what concentrations. [23]

Some pharmaceutical drugs and components are extremely sensitive to UV radiation, as such amber glass containers that absorb a comprehensive range of light waves of the light spectrum are used to store them. The analysis of the spectral transmission serves to test whether the amber glass in the batch is capable of absorbing the specified amount of UV radiation. The observed spectral transmission in colored glass containers must not exceed the limits given in Table 10:[15]

Table 10 - Limits of spectral transmission for colored glass containers

Nominal Volume (mL)	**Maximum Percentage of Spectral Transmission at Any Wavelength between 290 nm and 450 nm**	
	Flame-Sealed Containers	**Containers with Closures**
NMT 1	50	25
1 – 2	45	20

2 – 5	40	15
5 – 10	35	13
10 – 20	30	12
NLT 20	25	10

5.2.2. ANALYSIS OF RUBBER STOPPERS

In the pharmaceutical industry, rubber stoppers are used as container closures. There are two types of rubber stoppers that are more frequently used in the pharmaceutical industry, elastomeric stoppers and chlorobutyl stoppers. There are some differences between both, elastomeric stoppers are made of natural or synthetic rubber and are highly resistant to physical stress while chlorobutyl stoppers are made of butyl rubbers like copolymers of isobutylene with isoprene or butadiene and are resistant to chemical attacks and decay. The procedure for both stoppers is the same and as such they will henceforth be referred to as rubber stoppers unless specifically mentioned otherwise. [24]

There are considerable advantages to the use of rubber stoppers, including low leaching potential, minimum chemical interaction with the enclosed pharmacological formulation, and their use allows to ensure airtight and waterproof conditions.

The characteristics of rubber stoppers play an important role in the preservation as well as the delivery of the pharmacological formulation from the manufacturer to the consumer, as such the following analysis are employed:

- Visual Inspection
- Dimensions
- Infrared Spectrum
- Total Ash
- Reducing Substances
- Absorbance
- Appearance of Solution S
- Acidity or Alkalinity
- Extractable Heavy Metals
- Extractable Zinc
- Ammonium
- Residue on Evaporation
- Volatile Sulphides
- Fragmentation

- Penetrability
- Self-Sealing Capacity

5.2.2.1. Physical Analysis

- Visual Inspection

For the visual inspection of rubber stoppers, pharmaceutical companies follow a checklist of defects along with their respective type of defect and AQL(%), as shown in Table 11:

Table 11 - Classification of each defect of rubber stoppers with their respective AQL (%)

Type of Defects	Defects	AQL (%)
Minor	Surface not smooth	4.0
Major	Unsymmetrical	1.0
	Strips	1.0
	Cracks	1.0
Critical	Dirty rubber	0.10
	Unusual color	0.10

For this analysis, a batch sample is selected and analyzed to find all defects. Each defect has an AQL (%) that is the limit of defects that can be present in the sample.

- Dimensions

In Hikma there are three different types of rubber stoppers differentiated by their internal diameter, 20 mm rubber stoppers, 13 mm rubber stoppers and 32 mm. The measuring of the dimensions of rubber stoppers is relevant as it ensures that they are of the correct size and shape. The correct measurements are set taking into account that the stoppers are required to make a vacuum seal on the glass container, ensuring that no air or moisture infiltrates the vial and consequently degrades the pharmaceutical product.

Figure 5 shows how the measurements are determined for rubber stoppers:

Figure 5 - Representation of the measurements taken for the rubber stoppers used in Hikma.

- Infrared Spectrum

IR spectrophotometry is the analysis of the interactions between matter and infrared light. This analysis measures the absorption or transmission of IR radiation by a given sample and provides detailed information about functional groups and chemical bonds present in the sample. Each compound has a unique IR spectrum and as such can function as a “fingerprint” that allows for the identification of a given compound in a sample and to additionally determine its purity and concentration. [25]

This infrared analysis of rubber stoppers is analyzed through attenuated total reflection (ATR) analysis of the stopper. The ATR is a technique that allows for the direct analysis of a solid or liquid sample without additional preparation. In Hikma, there are two methods employed for this type of analysis, direct ATR of the rubber stopper and ATR of the pyrolysate of the rubber stopper.

The direct ATR analysis of the stopper involves the direct analysis of the stopper through the IR spectrometer and comparing the resulting spectrum with the standard spectrum. [26]

The ATR of the pyrolysate of the stopper involves the controlled burn of the stopper until there is a release of pyrolysate fumes and the appearance of pyrolysate. In essence, the pyrolysis of the stopper is its thermal decomposition into its constituent parts. The pyrolysate is then analysis through the IR spectrometer and compared to a standard spectrum.

Generally, both methods can be employed for every rubber stoppers (except rubber stoppers filled with carbon black), however they both result in different infrared spectrums and, as such, the choice between both relies on the availability of the respective standard spectrum.

- Total Ash

This analysis consists of the burning of a sample of the product to ashes under very high temperatures, normally using a muffle furnace or a microwave oven. The ashes are then weighed to determine the percentage of inorganic components present in the rubber stopper. This determination is relevant because inorganic components are highly reactive and since the

rubber stopper is in direct contact with the pharmaceutical drug, a high percentage of inorganic components would result in a less pure and unstable product.

5.2.2.2. Chemical analysis

The chemical analysis of rubber stoppers has as its aims the determination of any possible contaminants in the stoppers as well as the determination of the chemical composition of the stoppers. Before starting any of the chemical analysis, there is a need to prepare the solution S.

The analysis of the fragmentation, self-sealing and penetrability are physical analysis, but because the stoppers used in these analysis need to be prepared alongside the solution S, they are represented in this section.

- Preparation of solution S

Solution S is prepared by adding a set number of rubber stoppers (depending on the number of stoppers needed in the analysis of fragmentation, self-sealing and penetrability) to a proportionate amount of water. This water with stoppers is then autoclaved at high temperatures. This process allows for the liberation of possible contaminants in the stoppers, that are then dissolved in the water, allowing for their posterior analysis.

- Appearance of Solution S

This analysis consists of the visual comparison of the color and opalescence of the solution S.

Color analysis of solution S

For the color analysis, solution S is compared to a premade reference colored solution supplied by Merck. There are seven colored reference solutions which are differentiated by their components, as shown in Table 12:

Table 12 - Composition if reference solutions GY_1-GY_7

Reference solution	**GY_1**	**GY_2**	**GY_3**	**GY_4**	**GY_5**	**GY_6**	**GY_7**
Standard solution GY (mL)	100.0	75.0	50.0	25.0	12.5	5.0	2.5
10 g/L HCL (mL)	0.0	25.0	50.0	75.0	87.5	95.0	97.5

This particular analysis tests the color intensity related to pH, as such the reference solution chosen equates to the upper limit of color intensity in solution S as established by the regulatory agencies, reference solution GY_5.

Opalescence analysis of solution S

The opalescence of a solution can have varied undesirable causes like particle formation, fluctuations in density or concentration and a possible liquid-liquid phase separation. As such this is an attribute that must be tested, and if encountered must be remedied. The reference suspension for this analysis can have various degrees of opalescence that are prepared by diluting a standard of opalescence with water according to Table 13:[27], [28]

Table 13 - Reference suspensions of opalescence I - IV

	I	**II**	**III**	**IV**
Standard of opalescence	5.0 mL	10.0 mL	30.0 mL	50.0 mL
Water R	95.0 mL	90.0 mL	70.0 mL	50.0 mL

The chosen reference suspension varies according to the solution to be analyzed. For this particular analysis, the reference suspension to be compared to equates to the upper limit of opalescence permitted by the regulatory agencies, reference suspension II.

- Reducing Substances

Reducing substances can cause the degradation of chemical compounds by reducing them, i.e., the transfer of electrons. The presence of high levels of reducing substances in solution S is unacceptable since it puts at risk the quality and integrity of the pharmaceutical drug contained by the vial and sealed by the stopper.

- Absorbance

This analysis consists of the UV spectroscopy of the solution S. As previously stated in chapter 1.2.1.3. UV spectroscopy allows for the determination of the presence of components within a test sample. In the context of the absorbance analysis of rubber stoppers the solution S will be analyzed through the UV spectrometer and compared with a blank sample of water. The maximum limit of absorbance for this analysis is 0.2 which established an upper limit on the amount of absorbing components in solution S obtained from the rubber stoppers.

- Acidity or Alkalinity

This analysis is responsible for the determination of the pH of the solution S. After the process of autoclavation and dissolution of the contaminants of the stoppers in solution S, the water will change pH. This means that the closer the solution S is to neutral pH the better quality and the less contaminants there are in the stoppers. As the pH can be alkaline or acidic depending on the contaminants present in the stoppers, the analysis changes slightly depending on this factor, if its acidic the solution S will be titrated with an alkaline solution, if its alkaline the solution S will be titrated with an acidic solution.

- Extractable Heavy Metals

Heavy metals are some of the possible contaminants present in the rubber stoppers. These heavy metals represent a risk to the chemical integrity of the pharmaceutical drug and, more importantly, a critical risk to the health of the consumer. As such testing for their presence in solution S is crucial. This analysis consists of the preparation of a standard with the maximum concentration of heavy metals allowed in specification, and then with the addition of thioacetamide reagent R and Buffer 3.5 pH to the standard, sample and blank. The buffer 3.5 pH serves as stabilizer to the pH changes in the solutions, while the thioacetamide reagent R will react the heavy metals present in the solutions to precipitate colored sulfides. So, in essence, this analysis consists of comparing the final coloring of the sample with the coloring of the standard. [29]

- Presence of Zinc, Ammonium and Volatile Sulphides

The presence of zinc, ammonium and volatile sulphides in the rubber stoppers can cause issues with the stability and, therefore, the quality of the pharmaceutical drug. Not only that, but their presence also poses a health hazard to the consumer. So, their presence needs to be determined and quantified to ensure the quality of the pharmaceutical drug contained by the vial and sealed by the stopper. Like with the analysis of heavy metals, the analysis of the presence of zinc, ammonium and volatile sulphides also consist of the precipitation of the component relevant for each analysis in the given solution S and comparing the final coloring with the respective standard.

- Residue on Evaporation

This analysis consists of boiling a set amount of solution S in appropriate vessels, to allow the water to evaporate, and then proceeding to weigh what remaining residue. Before evaporating the solution there is a need to tare the vessels to later subtract the weight of the vessels that have the residue with the weight of the tared vessels to obtain the accurate weight of the residue. This analysis is effective since the boiling point of water is relatively low when compared to contaminants like lead or zinc.

- Fragmentation

This analysis determines the number of fragments released by the rubber stopper upon needle penetration. This analysis is important because the fragmentation of the stopper puts in jeopardy the seal it has on the vial, the purity of the pharmaceutical drug and therefore the quality and stability of the pharmaceutical product.

- Penetrability

This analysis determines the force required to penetrate the stopper with a needle. This analysis is important as it ensures that the pharmaceutical product can be safely and effectively extracted from the vial.

- Self-Sealing Capacity

This analysis determines the capacity of the stopper to reseal after multiple penetrations by a needle. This analysis is relevant because it ensures that even after the stopper has been penetrated by a hypodermic needle, the pharmaceutical product is still in a vacuum seal protected from air or moisture.

5.2.3. ANALYSIS OF FLIP-OFFs

A flip-off is a plastic cap that covers the rubber stopper of a vial containing injectable drugs or vaccines and its use allows for the sealing of the vial. The vial sealing process is a critical step for the manufacturing of pharmaceutical drugs, since it is this sealing that allows for the adequate protection of the pharmaceutical drug against humidity and contaminations and serve as an indicator to partial use or sabotage.

As the flip-off is never in direct contact with the pharmaceutical drug contained in the vial, there is no need to chemically test the flip-off, so the only analysis done for each batch of flip-offs is the visual inspection and the measuring of their dimensions. [30]

5.2.3.1. Visual Inspection

Like with other primary packaging, the visual inspection of flip-offs requires the selection of a sample of the received batch for a posterior inspection according to Table 14:

Table 14 - Classification of each defect of flip-offs with their respective AQL (%)

Defects	Type of defects	AQL (%)
Dirty unit	Minor	4.0
Very dirty unit	Major	1.0
Damaged		1.0
Oxidized		1.0
Different flip-off color	Critical	0.1

Different shape	0.1

5.2.3.2. Dimensions

The measurement of the dimensions of flip-offs is crucial since any nonconformance means that the seal responsible for the protection of the pharmaceutical drug would be compromised, resulting in a possible breach by humidity or contamination into the vial holding the pharmaceutical drug.

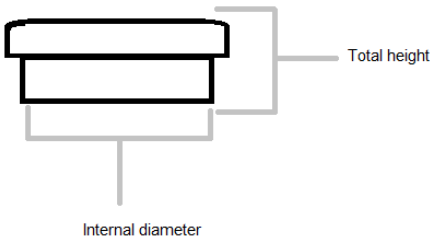

Figure 6 - Representation of the measurements taken for the flip-offs used in Hikma.

5.2.4. ANALYSIS OF TWIST-OFFs

Functionally a twist-off doesn't deviate from a flip-off. The difference between the two is that a twist-off seals IV(Intravenous) bags, twist-offs seal the pharmaceutical solution in the IV bag allowing for its preservation against humidity and air infiltrations, not only that twist-offs also allow for a simple a quick unsealing of the bag. The analysis done for this primary packaging is the visual inspection and the technological proof.

5.2.4.1. Visual Inspection

For the visual inspection of twist-offs, a sample is selected from the received batch to be inspected according to Table 15:

Table 15 - Classification of each defect of twist-offs with their respective AQL (%)

Defects	Type of defects	AQL (%)
Dirty Unit	Minor	4.0
Very dirty unit	Major	1.0
Damaged		1.0

Presence of foreign particles		1.0
Different shape	Critical	0.10

5.2.4.2. Technological proof

The most important characteristic of a twist-off is their ability to seal a typical IV bag, as such this analysis consists of using 13 twist-offs, from the sample taken for visual inspection, and using them to seal 13 different IV bags and verifying whether the seal is complete.

6. PROCEDURES

6.1. GLASS CONTAINERS

6.1.1. MATERIALS AND EQUIPMENT

The materials and equipment required for the analysis of glass containers are the following:

- Caliper
- Autoclave
- Burette
- Pippete
- Laboratory heating plate
- Erlermeyers
- Siever-Shaker
- Electric mortar & pestle grinder
- Analytic balance
- Ultrasonic bath
- Drying oven
- Spectrophotometer

6.1.2. REAGENTS

The reagents required for the analysis of glass containers are the following:

- Water R (Purified Water) - Prepared by distillation, reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authorities.
- Water R1(Carbon-dioxide free purified water): Prepared from distilled water R by multiple distillation.

- Methyl Red Solution
- Hydrochloric acid 0.01 M (volumetric solution)
- Hydrochloric acid 0.02 N (volumetric solution)
- Tromethamine
- Bromocresol green

Physical analysis

6.1.3. VISUAL INSPECTION

The visual inspection of glass containers is performed by following these steps:

- Take a sample of the batch of glass vials to be analyzed
- Inspect visually for any nonconformities according to the classification on Table 3

6.1.4. DIMENSIONS

The measurement of the dimensions of glass containers is performed by following these steps:

- From the sample taken for the visual inspection, randomly select 10 vials and check the measurements displayed in Table 2

Chemical analysis

6.1.5. PREPARATION OF VOLUMETRIC 0.01 N HYDROCHLORIC ACID

The preparation of volumetric 0.01N Hydrochloric acid required for the chemical analysis of glass containers is performed by following these steps:

- Accurately weigh about 25 mg of tromethamine
- Dry the weighed tromethamine at 150 °C for 3 hours
- Dissolve the tromethamine in 50 mL of water
- Add 2 drops of bromocresol green
- Titrate with the 0.01 hydrochloric acid to a pale-yellow endpoint
- Calculate the normality factor according to the following formula:

$$N = \frac{mg\ tromethamine \times ({}^{Assay}/_{100})}{121.14\ \times mL\ HCl} \quad (1)$$

Where:

N = normality factor

Assay = potency of tromethamine used in the preparation

6.1.6. PREPARATION OF VOLUMETRIC 0.02 N HYDROCHLORIC ACID

The preparation of volumetric 0.02N Hydrochloric acid required for the chemical analysis of glass containers is performed by following these steps:

- Accurately weigh about 0.1 mg of tromethamine
- Dry the weighed tromethamine at 150 °C for 3 hours
- Dissolve the tromethamine in 50 mL of water
- Add 2 drops of bromocresol green
- Titrate with the 0.02 hydrochloric acid to a pale-yellow endpoint
- Calculate the normality factor according to the same formula in 2.1.4.6.

6.1.7. SURFACE GLASS TEST – HYDROLYTIC RESISTANCE OF THE INNER SURFACE OF GLASS CONTAINERS

The glass surface test is performed by following these steps:

- Select six dry containers from the sample batch and remove any dirt or debris
- Weigh the empty containers with an accuracy of 0.1 g
- Place containers on a horizontal surface and fill them with water R to about the rim edge. Avoiding overflow and the introduction of air bubbles. Adjust the liquid levels to the brimful line
- Weight the filled containers to obtain the mass of the water
- Calculate the mean value of the brimful capacity in mL and multiply it by 0.9
- This final volume is the filling volume for this vial batch

- After determining the final volume, divide the volume of test solution to autoclave with the final volume to determine the number of vials to autoclave, according to Table 16:

Table 16 - Number of vials and minimum volume of test solution

Filling volume of each vial (mL)	Volume of test solution to titrate (mL)	Volume of test solution to autoclave (mL)	Number of titrations for each vial batch
v ≤ 3	25	100	2
3 < v < 30	50	200	
30 < v ≤ 100	100	300	

- After determining the number of containers to autoclave, remove any debris or dust from each container
- Fill each container to the brim with water R and allow to stand for 20 ± 5 min
- Empty the container
- Carefully rinse twice with water R and once with water R1
- Allow to drain
- Fill each container with water R1 to their filling volume
- Cap each container with an inert material such as a dish of neutral glass or aluminum foil previously rinsed with water R
- Place the containers on the tray of the autoclave
- Place the tray in the autoclave such that it remains clear of water
- Close the autoclave and start the cycle
- Combine the liquids from each of the autoclaved glass containers and mix
- Carry out the titration within 1 hour after taking the containers from the autoclave
- Proceed to the titration of the volume shown in table 6, and using the titrant solution and indicators shown in Table 17:

Table 17 - Titrant solution and indicator according to EP/USP

EP/USP Solutions	
Titrant solution	Hydrochloric acid 0.01 M (volumetric solution)
Indicator	0.05 ml of Methyl red solution R as indicator for each 25 mL of solution

- Perform a blank titration using an equal volume of water R1 used as the volume to titrate (table 6) and use the same amount of indicator solution
- Titrate the test solution with the same acid until the color of the resulting solution is the same as that obtained in the blank
- Calculate the volume (mL) with the following equation:

$$V = (V_1 - V_0) \cdot f \cdot \frac{100}{V_s} \quad (2)$$

Where:

V_1 – Volume of the titrant solution used for the sample titration (mL)

V_0 - Volume of the titrant solution used for the blank titration (mL)

f – Factor used for the correction of the volume of the titrant solution (mL)

V_s – Volume of test solution to titrate as per table 14 (mL)

6.1.8. SURFACE ETCHING TEST – HYDROLYTIC RESISTANCE OF THE ETCHED SURFACE OF THE GLASS CONTAINERS

The surface etching test of the glass containers is performed by following these steps:

- The volume of test solution is described in table 6 and is the same as the autoclaved volume for the surface glass test
- Rinse the containers twice with water R

- Fill each container to the brimful point with a mixture of 1 volume hydrofluoric acid R and 9 volumes of hydrochloric acid R and allow to stand for 10 minutes
- Empty the container and rinse carefully at least 5 times with water R
- Immediately before the analysis, rinse once again with water R
- Fill each container with water R1 up to the filling volume
- Cap each container with an inert material such as a dish of neutral glass or aluminum foil previously rinsed with water R
- Submit the containers thus prepared to the same autoclaving procedure described in 2.1.6.15. to 2.1.6.17.
- Perform the titration as described in 2.1.6.19 to 2.1.6.23.

6.1.9. GLASS GRAINS TEST – HYDROLYTIC RESISTANCE OF GLASS GRAINS

The glass grains test is performed by following these steps:

- Rinse the container to be tested with water R and dry in the oven
- Wrap at least 3 of the glass containers in clean paper
- Crush to produce 2 samples of about 100 g each in pieces not more than (NMT) 30 mm across
- Place 30-40 g of the pieces taken from one of the samples in the electric mortar & pestle grinder
- Turn on the electric mortar & pestle grinder and let it work for about 10 seconds
- Transfer the contents of the mortar to the sieve-shaker
- Turn on the sieve shaker for about 1 minute
- Remove the glass fragments that remain on the sieve's mesh size 710 µm and mesh size 425 µm
- Submit these portions to further fracture
- Transfer to a weighing bottle those glass grans that passed through sieve mesh size 425 µm and are retained on sieve mesh size 300 µm

- Repeat the crushing and sieving procedure with both glass samples until two samples of grains are obtained, each of which weighs more than 10 g
- Spread each sample on a piece of glazed paper and remove any iron particles by passing a magnet over them
- Transfer each sample into their respective beaker for cleaning
- Add to the grains in each beaker 30 mL of acetone R and scour the grains by suitable means, such as a plastic-coated glass rod
- After scouring the grains, allow to settle and decant as much acetone as possible
- Add another 30 mL of acetone R, swirl, decant again and add new portion of acetone R
- Fill the bath of the ultrasonic vessel with water at room temperature
- Place beaker in the rack and immerse it until the level of acetone R is at the level of the water
- Apply the ultrasound for 1 min
- Swirl the beaker, allow to settle, and decant the acetone as completely as possible
- Repeat the ultrasonic cleaning procedure
- If any turbidity persists, repeat the ultrasonic cleaning and acetone washing until the solution remains clear
- Swirl and decant the acetone
- Dry the grains, first by putting the beaker of a warm plate to remove excess acetone and then heating at 140 °C for 20 min in the drying oven
- Transfer the dried grains from each beaker into separate weighing bottles, insert the stoppers and cool in the desiccator
- Weigh two portions of 10 g of the cleaned and dried grains into 2 separate conical flasks
- Add 50 mL of water R1 into each conical flask by means of a pipette
- Distribute the grains evenly over the flat bases of the flasks by gentle shaking

- Pipette 50 mL of water R1 into a third conical flask, which will serve as a blank
- Close the flasks with neutral glass dishes or aluminum foil rinsed with water R
- Place all three flasks in the autoclave containing the water at ambient temperature and ensure that they are held above the level of the water in the vessel
- Close the autoclave and start the cycle
- Proceed with titration for each of the 3 flasks according to Table 18:

Table 18 - Titrant solutions and indicator according to EP/USP

EP/USP Solutions	
Titrant solution	Hydrochloric acid 0.02 N (volumetric solution)
Indicator	0.05 ml of Methyl red solution R as indicator

6.1.9.1. Titrate the blank solution immediately then titrate the test solutions until the color matches that obtained in the blank solution

6.1.9.2. Calculate the Volume (mL) of hydrochloric acid 0.02 N per g of glass, using the following formula:

$$V = (V_1 - V_0) \cdot \frac{f}{p_{used}} \quad (3)$$

Where:

V_0 – Volume of titrant solution used on the blank titration (mL)

V_1 – Volume of titrant solution usued on the sample (mL)

P_{used} – Weight of the sample (g)

6.1.9.3. Repeat the test if the highest and lowest observed values differ by more than the permissive range on Table 19:

Table 19 - Permissible range for the values obtained

Mean of the values obtained (mL HCL 0.02M / g of Glass Grains)	Permissible range of the values obtained
NMT 0.10	25% of the mean
0.10 - 0.20	20% of the mean
NTL 0.20	10% of the mean

6.1.10. ARSENIC

- Analyze the solution obtained in the hydrolytic resistance of inner surface using a Kit Merck quant #17917 (or equivalent)
- Using the syringe provided by the test kit, add 10 mL of the solution obtained in the hydrolytic resistance of the inner glass to a Nessler flask
- Add 1 micro-spoon (provided by the test kit) of solid acid (provided by the test kit)
- Swirl until the reagent is completely dissolved
- Add 2 red dosing spoons (provided by the test kit) of zinc (provided by the test kit)
- Immediately close the reaction tube with the screw cap (provided by the test kit)
- Insert the test strip (provided by the test kit) through the screw cap
- Leave to stand for 20 min
- Compare the color of the test strip with the colors of the color field to determine the approximate concentration of arsenic

6.1.11. SPECTRAL TRANSMISSION FOR AMBER GLASS CONTAINERS

The spectral transmission test for amber glass containers is performed by following these steps:

- Break the glass container or cut it with a circular saw fitted with a wet abrasive wheel
- Select a fragment of the container to be mounted on the spectrophotometer
- If the fragment is too small to cover the opening in the specimen holder. Mask the uncovered portion with an opaque paper or tape
- Before placing in the support, wash, dry and wipe the fragment with lens tissue

- Mount the fragment with the aid of wax or other convenient means like tape, taking care to avoid leaving fingerprints or other marks

- Place the fragment in the spectrophotometer with its cylindrical axis parallel to the slit and in such a way that the light beam is perpendicular to the surface of the section and the losses due to reflection are minimal

- Measure the transmission of the fragment with reference to air in the spectral range of 290 to 450 nm, continuously or at intervals of 20 nm

- The observed spectral transmission for amber glass containers does not exceed 10 % at any wavelength in the range of 290 to 459 nm, disregarding the type and capacity of the container being analyzed

6.2. RUBBER STOPPERS

6.2.1. MATERIALS AND EQUIPMENT

The materials and equipment required for the analysis of rubber stoppers are the following:

- Caliper
- Spectrophotometer IR
- Muffle Furnace
- Desiccator
- Analytical Balance
- Crucibles
- Erlenmeyers
- Aluminum Foil
- Autoclave
- Laboratory Heating Plate
- Membrane Filter Paper 0.5 µm
- Buchner Flask
- Vacuum Pump
- Buchner Funnel
- Hypodermic Needle
- Capper
- Decapper
- Texture analyzer
- Vacuum Oven
- Litmus Paper

6.2.2. REAGENTS

The reagents required for the analysis of rubber stoppers are the following:

- Dilute sulphuric acid R
- 0.002 M potassium permanganate
- Potassium iodate R

- 0.01 M sodium thiosulphate
- Starch solution R
- Opalescence solution
- GY5 solution
- Bromothymol blue R1
- 0.01 M NaOH
- 0.01 M HCl
- Lead nitrate
- Deionized water
- Water R
- Buffer solution pH 3.5 R
- Thioacetamide reagent R
- Dilute sodium hydroxide solution R
- Alkaline potassium tetraiodomercurate solution R
- Citric acid R
- Sodium sulfide R
- 0.1 % methylene blue

Physical analysis

6.2.3. VISUAL INSPECTION

The visual inspection of rubber stoppers is performed by following these steps

- Take a sample from the batch received by the manufacturer
- Check for defects according to Table 9

6.2.4. DIMENSIONS

The measurement of the dimensions of rubber stoppers is performed by following these steps:

- From the sample taken in 2.2.2.1., randomly select 10 rubber stoppers
- Measure flange thickness and internal diameter of each rubber stopper

6.2.5. INFRARED SPECTRUM

The infrared spectrum test for rubber stoppers is performed by following these steps:

- Examine the stopper by attenuation total reflectance
- The resulting IR spectrum obtained must equal the IR spectrum of the standard

- If direct ATR surface analysis is not feasible, heat 1-2 g of the stopper to be analyzed in a heat resistant tube over an open flame
- Keep heating the tube until the condensation of pyrolysis vapors
- Examine the pyrolysate of the sample by attenuation total reflectance
- The resulting IR spectrum obtained must equal the IR spectrum of the standard

6.2.6. TOTAL ASH

The total ash test for rubber stoppers is performed by following these steps:

- Heat a crucible to 600 ºC for 30 minutes
- Allow to cool in a desiccator for 1 hour and weigh the tare
- Evenly distribute 1 g of the stoppers to be analyzed in the crucible
- Heat the crucible with the stoppers to 600 ºC for 1 hour
- Allow to cool in a desiccator for 1 hour and weigh
- Heat the crucible with the stoppers to 600 ºC for 15 minutes
- Allow to cool in a desiccator for 1 hour and weigh
- If mass is not constant, repeat the steps 2.2.6.6 to 2.2.6.7.
- Calculate the total ash percentage through the following formula

$$Total\ Ash\ (\%) = \frac{wa - wt}{wr} \times 100$$

Where:

wa = weight of the constant mass

wt = weight of the tare

wr = weight of the rubber stoppers

Chemical analysis

6.2.7. PREPARATION OF SOLUTION S

The preparation of solution S required for the chemical analysis of rubber stoppers is performed the following way:

- Wash a number of uncut rubber stoppers, corresponding to a surface area of 100 ± 10 cm^2 (28 rubber stoppers of 13 mm diameter, 20 rubber stoppers of 20 mm diameter and 7 rubber stoppers of 32 mm diameter)
- Add 200 mL of water R and weigh
- Prepare a blank in the same manner using 200 mL of water without the stoppers
- Cover the flask with aluminum foil or borosilicate-glass beaker
- A bigger amount of rubber stoppers may be required for all the physical tests, therefore the amount of rubber stoppers can be increased, increasing the volume of water R, to comply with the proportion between surface area and volume of 100 cm^2/200 mL
- If the solution S preparation is only required for the physical testes described in x. to x., then the step of weighing before and after autoclaving is not mandatory
- Place the flask in the autoclave
- Close the autoclave and start the cycle
- After the cycle ends, make up the original water mass lost after the autoclave cycle
- Shake and immediately separate the solution from the rubber stoppers by decantation

6.2.8. REDUCING SUBSTANCES

The reducing substances test for rubber stoppers is performed by following these steps:

- To 20 mL of solution S add 1 mL of dilute sulphuric acid R and 20 mL of 0.002 M potassium permanganate
- Boil for 3 minutes
- Cool
- Add 1 g of potassium iodate R and 0.25 mL of starch solution R (indicator) and titrate immediately with 0.01 M sodium thiosulphate, to a colorless end point

- Carry out titration using 20 mL of the blank
- Difference between titration volumes must not be greater than 3 mL

6.2.9. ABSORBANCE

The absorbance test for rubber stoppers is performed by following these steps:

- Filter solution on a membrane filter 0.45 µm, rejecting the first few mL of filtrate
- Measure the filtrate at wavelengths from 220 nm to 360 nm using the blank prepared in 5.
- Absorbance must not exceed 0.2

6.2.10. APPEARANCE OF SOLUTION S

The appearance of solution S test for rubber stoppers is performed by following these steps:

- **Color analysis of solution S**
- Compare solution S with the pre-prepared solution GY_5
- Solution S must not be more intensely colored than reference solution GY_5
- **Opalescence analysis of solution S**

Standard of opalescence

- Dilute 15 mL of primary opalescent suspension to 1000 mL of water R (After prepared, this solution lasts 24 h)

Reference suspension II

- Mix 10 mL of standard of opalescence with 90 mL of water R
- Shake before use
- Solution S must not be more opalescent than reference suspension II

6.2.11. ACIDITY OR ALKALINITY

The acidity or alkalinity test for rubber stoppers is performed by following these steps:

- Check with litmus paper if solution S is acidic or alkaline

- Pipette accurately 20 mL of solution S and add 0.1 mL of bromothymol R1 and titrate according to Table 20:

Table 20 - Titration for the acidity or alkalinity analysis for rubber stoppers with its respective volume limits for each titration

pH	Titrant	Volume limits for titration
Acidity	0.01 M NaOH	≤ 0.3 mL
Alkalinity	0.01 HCL	≤ 0.8 mL

6.2.12. EXTRACTABLE HEAVY METALS

The extractable heavy metals test for rubber stoppers is performed by following these steps:

Test Solution (Sample)

- 12 mL of the test solution to be examined
- Prepare a blank by mixing 2 mL of the test solution to be examined with 10 mL of water R

Reference Solution (Standard)

- Weight accurately 160 mg lead nitrate
- Dissolve and dilute in 500 mL of deionized water (200 ppm)
- On the day of use dilute 1 mL to 100 mL with water to prepare 2 ppm lead standard solution
- Mix 10 mL of lead standard solution R and 2 mL of the test solution to be examined
- For each solution add 2 mL of buffer solution pH 3.5 R
- Mix and add to 1.2 mL of thioacetamide reagent R
- Mix immediately
- Examine solutions after 2 minutes
- Any brown color in the test solution must not be more intense than in the reference solution

6.2.13. EXTRACTALE ZINC

The extractable zinc test for rubber stoppers is performed by following these steps:

- Preform test using the Zinc test kit from Merck
- Inject 5 mL of test solution to a test tube with a 5 mL syringe (provided by the test kit)
- Add and mix 4 drops of reagent Zn-1
- pH must be within range of 0.9 – 1.0, adjust, if necessary, with reagent Zn-1
- Add and mix 1 level gray dosing spoon of reagent Zn-2 (provided by the test kit)
- Add and mix 1 level grey micro spoon (provided by the test kit) of Zn-3 (provided by the test kit)
- Leave to stand for exactly 5 minutes
- Add and mix 4 drops of reagent Zn-4(provided by the test kit)
- Immediately compare the color obtained in the test solution with the color card (provided by the test kit)
- Amount of zinc must be less than or equal to 0.1 ppm

6.2.14. AMMONIUM

The ammonium test for rubber stoppers is performed by following these steps:

Test Solution (Sample)

- Dilute 5 mL of solution S to 15 mL with water R. Make alkaline, if necessary, by adding dilute sodium hydroxide solution R
- Add 0.3 mL of Potassium tetraiodomercurate – Potassium hydroxide solution (Nessler reagente) solution R

Reference Solution (Standard)

- Mix 10 mL of ammonium standard solution (1 ppm NH_4), 5 mL of water and 0.3 mL of alkaline potassium tetraiodomercurate solution R
- Close each test tube and mix

- After 5 minutes, any color in the test solution must not be more intense than in the standard (2ppm in solution S)

6.2.15. RESIDUE ON EVAPORATION

The residue on evaporation test for rubber stoppers is performed by following these steps:

- Evaporate 50 mL of solution S to dryness on water-bath
- Dry at 100 to 105 ºC
- The final residue must not weight more than 2 mg

6.2.16. VOLATILE SULPHIDES

The volatile sulphides test for rubber stoppers is performed by following these steps:

- Place rubber stoppers with a total surface area of 20 ± 2 cm2 (6 closures with a diameter of 13 mm, 4 closures with a diameter of 20 mm and 1.5 closures with a diameter of 32 mm) in a 100 mL conical flask
- Add 50 mL of a 20 g/L solution of citric acid R
- Place a piece of lead acetate paper over the mouth of the conical flask
- Maintain the position of the paper with the aid of the aluminum foil used to close the flask
- The standard is prepared by mixing 50 mL of a 20 g/L solution of citric acid R and 5 mL of a freshly prepared 0.0308 g/L solution of sodium sulfide R in water
- Heat in an autoclave at 121 ± 2 ºC for 30min
- The color of the lead acetate paper on the sample must not be more intense than the paper of the standard

6.2.17. FRAGMENTATION

The fragmentation test for rubber stoppers is performed by following these steps:

- Add, in 12 clean vials a volume of water R corresponding to the nominal volume minus 4 mL
- Close the vials with the closures to be examined and secure with a cap

- Allow standing for 16 h
- Using a hypodermic needle with a diameter of 0.8 mm, inject 1 ml of water R into the vial and remove 1 mL of air
- Carry out this operation 4 times for each closure, piercing each time at a different site
- Use a new needle for each closure and verify that at no point the needle is not blunted during the test
- Pass the liquid in the vials through a filter of approximately 0.5 µm pores
- Count the number of rubber fragments visible to the naked eye
- The total number of rubber fragments must not exceed 5 fragments

6.2.18. PENETRABILITY

The penetrability test for rubber stoppers is performed by following these steps:

- Fill 10 suitable vials to the nominal volume with water
- Close the vials with the closures to be examined and secure with a cap
- Determine penetrability using a texture analyzer and a new hypodermic needle for each closure
- The force required for piercing each closure must not exceed 10 N

6.2.19. SELF-SEALING CAPACITY

The self-sealing capacity test for rubber stoppers is performed by following these steps:

- Fill 10 suitable vials with water to the nominal volume with water
- Close the vials with the closures to be examined and secure with a cap
- Using a new hypodermic needle for each closure, pierce each closure 10 times at different sites
- Immerse the 10 vials in a solution of 0.1% (1 g per liter) methylene blue and reduce external pressure to 20 cmHg for 10 min
- Restore to atmospheric pressure and leave the vials immersed for 30 minutes

- Rinse the outside of each vial
- None of the vials contain any trace of the blue solution

6.3. FLIP-OFFS

6.3.1. MATERIALS AND EQUIPMENT

The materials and equipment required for the analysis of flip-offs are the following:

- Calliper

6.3.2. VISUAL INSPECTION

The visual inspection of flip-offs is performed by following these steps:

- From the batch received, select a sample to be visually analyzed
- Inspect visually for any nonconformities according to table …

6.3.3. DIMENSIONS

The measurement of the dimensions of flip-offs is performed by following these steps:

- From the sample select 10 different flip-offs to be measured
- Measure the total height and internal diameter of each flip off

6.4. TWIST-OFFS

6.4.1. VISUAL INSPECTION

The visual inspection of twist-offs is performed by following these steps:

- Take a sample of the received batch and verify for any non-conformances according to Table 15

6.4.2. TECNHOLOGICAL PROOF

The technological proof of twist-offs is performed by following these steps:
Using the sample selected in 2.4.1. seal 13 different IV bags and verify the viability of the seal

7. RESULTS

For the quality control analysis of Hikma there are two methods of analysis for any batch to be analyzed, reduced analysis and full analysis. The main difference between the two methods is the number of analysis to be realized. As the name implies, full analysis requires doing all of the analysis associated with the batch, while the reduced analysis involves doing only the crucial and critical analysis associated with batch and considering the other non-critical analysis from the data provided by the supplier. Full analysis is only done every 6 batch received of the given product or after a year has passed since the last full analysis. This system expedites the quality control analysis without compromising on the strictness required in the pharmaceutical industry.

Throughout the internship more than 200 batches of glass containers, rubber stoppers, twist-offs and flip-offs were analyzed, none were out of specification. Due to the extensive amount of analyzed batches, and since all of them were conformant, a reduced sample of the total batches will be displayed to maintain the coherence of the thesis and to analyze the acquired data.

7.1. RUBBER STOPPERS

As stated in chapter 1.2.2. Hikma uses and analysis three different types of rubber stoppers differentiated by their internal diameter, however during this internship only two of these types were analyzed, 20 mm rubber stoppers and 13 mm rubber stoppers. Additionally, since while this internship only 20 mm rubber stoppers had full analysis, only 20 mm rubber stoppers will be displayed and analyzed in this thesis.

The Table 21 shows a sample of the batches of analyzed rubber stoppers in Hikma.

Table 21 - Acquired data on full analysis of batches of rubber stoppers along with their respective specifications.

Analysis	Specification	1202062023	1203062023	1204062023	1205062023
Visual Inspection (Conforms to check list provided in 1.2.1)	AQL = (0.1 / 1.0 / 4.0) %	Conforms	Conforms	Conforms	Conforms
Infrared Spectrum	Match the standard	Conforms	Conforms	Conforms	Conforms
Total Ash	44.6% - 48.6%	45.54 %	45.55 %	45.57 %	45.39 %

Dimensions					
Flange thickness (mm)	3.18 - 3.68	3.30 – 3.45	3.39 – 3.50	3.34 – 3.48	3.36 – 3.49
Internal Diameters (mm)	13.33 - 13.35	13.33 – 13.35	13.33 – 13.35	13.33 – 13.35	13.33 – 13.35
Chemical Analysis					
Alkalinity or Acidity	NMT 0.3 mL 0.01M NaOH NMT 0.8 mL 0.01M HCl	0.06 mL 0.01M NaOH	0.06 mL 0.01M NaOH	0.07 mL 0.01M NaOH	0.07 mL 0.01M NaOH
Absorbance	NMT 0.2 nm	<0.02 nm	<0.02 nm	<0.02 nm	<0.02 nm
Reducing Substances	NMT 3.0 mL	0.40 mL	0.55 mL	0.35 mL	0.50 Ml
Extractable Heavy Metals	NMT 2 ppm	<2 ppm	<2 ppm	<2 ppm	<2 ppm
Extractable Zinc	NMT 5 ppm	<5 ppm	<5 ppm	<5 ppm	<5 ppm
Ammonium	NMT 2 ppm	<2 ppm	<2 ppm	<2 ppm	<2 ppm
Residue on Evaporation	NMT 2.0 mg	0.0 mg	0.3 mg	0.3 mg	0.6 mg
Volatile Sulphides	Meets the Requirements	Conforms	Conforms	Conforms	Conforms
Fragmentation	NMT 5 fragments	0 fragments	0 fragments	0 fragments	0 fragments
Penetrability	NGT 10 N	5.70 N	5.75 N	5.65 N	5.66 N
Appearance of solution					
Opalescence	NMT Reference Susp. II	Conforms	Conforms	Conforms	Conforms
Color	NMT Reference Sol. GY5	Conforms	Conforms	Conforms	Conforms

Table 21 displays 4 batches of rubbers stoppers along with their respective specifications. For the analysis of the dimensions, a medium of the 10 measurements taken for the flange thickness and internal diameter was presented, when it comes to the analysis of the appearance of solution, visual analysis, extractable heavy metals, extractable zinc, ammonium

and volatile sulfides, due to their qualitative nature are presented as either conforming to the specification or presented as less than the upper limit given by the specification.

The fact that all of the quantitative analysis showed values well below the limits established by the specification's sheds light on the quality of the rubber stoppers acquired and analyzed in Hikma.

Another observation worth mentioning is that, though the analysis of alkalinity and acidity consider an acidic or alkaline solution S, every batch of rubber stoppers analyzed had a slightly acidic pH. This fact is probably related either to the material of the stopper or the contaminants dissolved in the solution S from the rubber stoppers.

7.2. FLIP-OFFS

For dimensions there are two types of flip-offs relevant for this thesis, 20 mm flip-offs and 13 mm flip-offs. Each corresponding to the dimensions of the glass vials and, rubber stoppers. When it comes to the flip-offs, there was a considerable number of batches that belonged to both types and so both will be equally represented in Table 22and Table 23.

Table 22 - Acquired data on analysis of batches of 20 mm flip-offs along with their respective specifications

Analysis	Specification	0904052023	0900052023	0901052023	2114102022
Visual Inspection (according to chapter 1.2.3.)	AQL = (0.1 / 1.0 / 4.0) %	Conforms	Conforms	Conforms	Conforms
Dimensions					
Total Height (mm)	9.0 - 9.8	9.41 - 9.60	9.46 - 9.55	9.45 - 9.59	9.47 - 9.54
Inner Diameter (mm)	20.25 - 20.35	20.27 - 20.31	20.28 - 20.31	20.28 - 20.31	20.27 - 20.31

Table 23 - Acquired data on analysis of batches of 13 mm flip-offs along with their respective specifications

Analysis	Specification	1104062023	1105062023	110602023	1054052023
Visual Inspection (according to chapter 1.2.3.)	AQL = (0.1 / 1.0 / 4.0) %	Conforms	Conforms	Conforms	Conforms
Dimensions					
Total Height (mm)	7.55- 7.95	7.57 - 7.63	7.56 - 7.65	7.56 - 7.64	7.50 - 7.60
Inner Diameter (mm)	13.35 - 13.45	13.36 - 13.40	13.36 - 13.40	13.37 - 13.41	13.36 - 13.39

For the dimensions, both the maximum and minimum value of each measurement, that way it can be clearly seen that for the represented batches there are no measurements out of the specifications.

7.3. GLASS CONTAINERS

In Hikma there are different types of glass vials differentiated by their internal and external mouth diameter, and their volume capacity. Since only vials of 20 mm of external mouth diameter and 8 ml of volume capacity had a considerable amount of full analysis samples, only they will be displayed and analyzed in this thesis.

The following table shows a sample of the batches of analyzed glass vials in Hikma.

Table 24 - Acquired data on analysis of batches of 20 mm external diameter and 8 ml volume capacity glass vials along with their respective specifications

Analysis	Specification	1268072023	0884052023	1117062023	1253072023
Visual Inspection (according to chapter 1.2.1.)	AQL = (0.65/1.5/6.5) %	Conforms	Conforms	Conforms	Conforms
Dimensions (mm)					

External diameter	25.25 - 25.75	25.42 - 25.51	25.33 - 25.60	25.35 - 25.61	25.33 - 25.32
Wall Thickness	1.15 - 1.25	1.18 - 1.20	1.18 - 1.21	1.17 - 1.22	1.18 - 1.22
Total Height	37.0 - 38.0	37.2 - 37.8	37.31 - 37.65	37.35 - 37.79	37.38 - 37.71
External collar diameter	19.7 - 20.2	19.8 - 20.1	19.95 - 20.06	19.90 - 20.11	19.82 - 19.85
Internal Collar diameter	12.4 - 12.8	12.54 - 12.71	12.48 - 12.72	12.58 - 12.77	12.47 - 12.72
Thickness of base	≥0.70	0.85 - 1.05	0.84 - 1.08	0.86 - 1.03	0.82 - 0.97
Collar height	3.4 -3.8	3.66 - 3.75	3.68-3.74	3.60 - 3.74	3.62 - 3.75
Chemical Analysis					
Hydrolytic resistance of internal surface	NMT 1.0 mL HCL 0.01N	0.39	0.38	0.45	0.37
Hydrolytic resistance of the sprayed glass	NMT 0.1 mL HCL 0.02N/g	0.038	0.057	0.055	0.058
Hydrolytic resistance of the etched surface	NMT 1.0 mL HCL 0.01N	0.39	0.27	0.06	0.07
Arsenic (ppm)	≤0.1	0.1	0	0.1	0.1

As can be surmised from observing Table 24, none of the data is out of specifications. In the chemical analysis it can be observed that for the hydrolytic resistance tests, all results are well below the limits given by the specifications, which, once again, sheds light on the quality of the products procured by Hikma.

For the arsenic analysis, it can be observed that most values are in the limit given by the specification with result being 0 ppm, this is explained by the nature of the testing kit used in Hikma. As previously explained in chapter 1.2.1., this testing kit functions by comparing the final color of the prepared solution with the coloring strip supplied by the testing kit, this coloring strip has colors corresponding to 0 ppm, 0.05 ppm and 0.1 ppm arsenic content, this means that if the solution has a mere 0.07 ppm arsenic content, by comparing the coloring of the solution with the coloring strip the only conclusion an analyst can make is that the arsenic content of the solution is approximately 0.1 ppm arsenic content.

7.4. TWIST-OFFS

For the twist-offs analyzed in Hikma there were only two analyses realized, the visual inspection and the technological test. This is explained by the fact that twist-offs are only used to plug IV bags, meaning that, if they can reliably seal the IV bag then they are fit for use.

The Table 25 shows a sample of the batches of twist-offs analyzed in Hikma.

Table 25 - Acquired data on analysis of batches of Twist-Offs along with their respective specifications.

Analysis	Specifications	787042023	1007052023	788042023	786042023
Visual Inspection (according to chapter 1.2.4.)	AQL = (0.1, 1.0, 4.0) %	Conforms	Conforms	Conforms	Conforms
Technological proof	Conforms	Conforms	Conforms	Conforms	Conforms

As can be seen, all results are conformant with the specifications.

If at any point during the analysis there is the detection of any noncorformant results, then as stated in chapter 1.1.5. a set of well defined procedures will be triggered to ascertain the cause and if there is a need to reject the specific batch or to simply repeat the analysis (in case of a mistake or error in part of the analyst or the equipment/reagents)

8. CONCLUSIONS

This internship had two main goals, the first goal was, of course, the quality control analysis of the primary packaging materials used in Hikma, the second goal was the personal growth of the intern as an individual and as a member of a functional and successful pharmaceutical company.

At this point it can be confidently stated that both objectives were accomplished successfully. Due to the nature of the products manufactured in a pharmaceutical company like Hikma there are strict requirements for each quality control analysis carried out, and because Hikma functions as a continuous manufacturer there was a constant supply of batches to be analyzed which made it so that the intern had to develop autonomous as well as cooperative qualities to ensure a swift but effective workflow.

In conclusion, because all the analyses carried out for each batch were within their specific specifications it can be surmised that all analyses were well performed and that the intern managed to develop the qualities necessary to excel in this type of work environment.

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