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DEPARTEMENT OF PHARMACY

DISSERTATION FOR THE OBTENTION OF THE DOCTOR OF PHARMACY DEGREE

THEME :

THE VALIDATION OF PACKAGING BY THE METHOD WATER VAPOUR TRANSMISSION RATE

Presented by:
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Defended on 10 /07/2019

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MAWADZE Euphrasia

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List of abbreviations

API: Active Pharmaceutical Ingredient

ASTM: American Society of Testing and Materials

CLP: Continental Pharm Laboratories

FDA: Food and Drug Administration

GMP: Good manufacturing practices

HDPE: High Density Polyethylene

GRAS: Generally Regarded As Safe

ICH: International Conference on Harmonization

ISO: International Organization of Standardization

LDPE: Low Density Polyethylene

LOD/LOQ: Limit of Detection/ Limit of Quantitation

PET: Polyethylene terephthalate

PVC: Polyvinyl Chloride

PVDC: Polyvinylidene dichloride

QC: Quality Control

TAPPI: Technical Association of the Paper and Pulp Industry

USP: United States Pharmacopeia

WVTR: Water Vapour Transmission Rate

Glossary

Accuracy
The accuracy of an analytical method is the closeness of the test results obtained by that method to the true value.

Active pharmaceutical ingredient
It is the ingredient in a pharmaceutical drug that is biologically active.

American Society for Testing and Materials
It is an international standards organization that develops and publishes voluntary consensus technical standards for a wide range of materials, products, systems, and services

Food and Drug Administration
It is a federal agency of the United States Department of Health and Human Services. It is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over the counter pharmaceutical drugs.

Good Manufacturing Practices
The good manufacturing practices indicate a token of applied quality in the manufacture of drugs for human or animal use. They guarantee a coherent manufacture and control of products and according to the quality standards adapted to their use.

Hydrolytic resistance of glass
The hydrolytic resistance of glass refers to its chemical durability, or in other words how likely a glass object is to cause contamination to the samples inside.

International Conference on Harmonization ICH
The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration.

International organization for standardization ISO
The International Organization for Standardization is an international standard-setting body composed of representatives from various national standards organizations.

Limit of detection LOD

It is defined as the lowest concentration of an analyte in a sample that can be detected, not quantified.

Limit of quantitation LOQ

The Quantitation Limit is the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operational conditions of the analytical procedures.

Procedure

It is a specified way of accomplishing an activity or a process

Quality assurance

It is a system of all actions taken with the objective of assuring that all the active materials have the required quality for their specified use and that all quality systems are maintained.

Robustness/ruggedness

It is a measure of capacity to remain unaffected by small but deliberate variations

Shelf life

It is the period of time, from the date of manufacture, that a drug product is expected to remain within its approved product specification while stored under defined conditions.

Technical association of the pulp and paper industry TAPPI

It is a registered non profit, international Non-Governmental Organization of about 14,000 member engineers, scientists, managers, academics and others involved in the areas of pulp, and paper, it also includes members of some allied areas of packaging (such as corrugated fiber board, flexible packaging, lamination, adhesives, coatings and extrusion).

Weathering/ Blooming

It is when moisture condenses on the surface of a glass container and extracts some weakly bound alkali leaving behind a white deposit of alkali carbonate; further condensation of moisture will lead to the formation of an alkaline solution which will dissolve some silica resulting in loss of brilliance from the surface of the glass.

Introduction

A decade ago packaging often was an afterthought for many pharmaceutical companies, viewed as merely the final step in manufacturing. But now firms must consider packaging earlier during the development process, it has become an integral part of any pharmaceutical industry.

Packaging is the process by which the pharmaceuticals are suitably packed so that they should retain their therapeutic effectiveness from the time of packaging till they are consumed. It is a broad process and a multifaceted task. It has the responsibility to deliver life saving drugs in every dosage form, therefore the composition and quality of the packaging materials that are used can have a critical impact on the performance, function, and production cost of pharmaceutical medications or drugs. Improper packaging can cause the active pharmaceutical ingredients (API) in medications to degrade faster, and have shorter shelf lives.

The packaging processes and equipment need validation and qualification in the same way as any other part of processing within a pharmaceutical facility. The notions of qualification and validation are regulatory requirements and represent the pillars of quality assurance. The qualification of equipment and installations confirms that the GMP requirements have been achieved, while validation allows the control of different processes.

There are various tests for the determination of quality, integrity and compatibility of packaging materials to assure production of drugs of good quality. Tests applied to packing material can be chemical, mechanical or environmental. The chemical tests include alkalinity of glass, pH value of materials and compatibility test with the medicament, while those for environment test for absorption of water, permeability to water, vapour or gases and characteristics such as light transmission.

Many drugs are moisture sensitive so controlling water vapour into or out of a package is crucial to maintain quality of drug. Scrupulous quality control during the manufacturing, preparation and handling stages becomes squandered effort if the packed drug is not protected against moisture vapour that contributes to its deterioration, shortened shelf life or renders it unfit for sale or consumption. The ability of packaging to protect against moisture can be ascertained by performing various tests during production, as part of the in process controls and after production.

Manufacturers do their best to provide and assure protective packaging for moisture sensitive drugs, however due to constraints sometimes beyond their control; the drug can fail to meet its expected shelf life. This was seen in the packaging of Clavodex tablets and powder at CONTINENTAL PHARM LABORATORIES (CLP). The manufacturer at first ascertained the integrity of Clavodex package using the dye penetration test method. This test method was not adequate enough to validate the packaging as there were product reclamations despite the test

results conforming to the required outcomes. This propelled the manufacturer to propose a study with a more rigorous test method and to collaborate with a testing company abroad.

Our main concern is that can the manufacturer get to the point of validating the packaging used for Clavodex using the Water Vapour Transmission rate (WVTR) method and what are the steps to follow in order to prepare samples to carry out this test?

The aim of this research is to establish and validate a protocol of sample preparation and approbation of WVTR tests for Clavodex tablets and powder for oral solution produced at CLP.

The research will be presented in two parts:

The first part is a theoretical approach to pharmaceutical packaging; it is gives a review of the different aspects of packaging: the types of packaging and packaging materials, the regulations of packaging, the validation of packaging as well as the test methods used to test and validate the integrity of the package.

The second part it is a practical industrial approach to package validation at the pharmaceutical industry Continental Pharm Laboratoires (CLP) in the packaging of Clavodex. It has a brief description of the research and the pharmaceutical industry CLP, an outline of the primary packaging lines at CLP, the equipment and their description and operation. It also describes the adjustments to be done on the machines before and during the preparation of samples and the preparation of the samples for testing. Finally we established the procedures for the adjustments of the packaging machines and the procedure for preparation of samples according to the WVTR method. A discussion of the results and a conclusion will finalise the study.

Theoretical research

Chapter I: Packaging

I. Generalities

Packaging is designed to contain a product so that it is unable to interact with the environment; it is both art and science of protecting or enclosing a product. The quality of packaging plays an important role in maintaining the quality of a drug during storage, transportation, delivery, sale and use.(1)(2)

I.1. Definitions

Packaging has been defined in different ways, because of its perceived numerous functions. It has been defined as the art, science and technology of preparing products for sale in a cost effective manner. In the context of a pharmaceutical product "preparing products for sale" means having a role in preserving and protecting the drug from contamination or degradation, ensuring that the drug retains its therapeutic effectiveness from the time of packaging till they are used, as well as in the presentation and identification of the drug.(3)(4)

The term packaging also covers a set of operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product.(5)

II. Functions and properties of effective packaging

There are various functions of packaging which can be divided into primary and secondary functions. The primary functions concern the technical nature of the packaging and the secondary functions relate to communication of information to the patient about the use of the drug and the storage conditions.

- **Containment**

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging not to leak, nor allows diffusion and permeation of the product; to be strong enough to hold the contents when subjected to normal handling; not to be altered by the ingredients of the formulation in its final dosage form. (6)

- **Protection**

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as: light, moisture, oxygen, biological contamination, mechanical damage. Besides protecting the drug form external factors, the packaging should not interact with it so as to introduce unacceptable changes. The compatibility of the packaging with the active pharmaceutical ingredients is very important in maintaining integrity of the product. In addition it must preserve the physical properties of all dosage forms, not alter the identity of the drug, and preserve the characteristic properties of the drug so that the latter complies with its specifications. (6)(2)

❖ **Presentation and Transmission of information**

Packaging is also an essential source of information on medicinal products. Information is provided by labels and package inserts, which communicate how to use, transport, dispose, store and recycle the product. Labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid. (2)

❖ **Preservation**

Preservation in this context means inhibiting chemical and biological changes. A common example would be the active pharmaceutical ingredients remaining within their specified limits over the shelf life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies.(6)(7)

❖ **Convenience**

This means all aspects of the movement and use of the product from the packaging line to final use and disposal. Packages can have features that add convenience in handling, distribution, opening, closing, use and reuse.(2)

III. Selection of packaging materials

The quality of the packaging material plays a very important role in the quality of the pharmaceutical products. The choice of primary or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, filling method and cost. (4)(6)

The packaging materials used should possess the ideal characteristics such as: (2)

1) Protection from environmental conditions such as humidity, temperature.
2) The product packed in the container must be non-reactive to the container enclosing it.
3) The odour and the taste of the product must not be altered.
4) The packaging material must be non-toxic.
5) FDA approved packaging materials must be used.
6) They must meet applicable tamper-resistance requirements
7) They must have reasonable cost in relation to cost of the product

IV. Types of packaging

Pharmaceutical packaging is classified into 3 different types in terms of its role towards the semi-open product:

IV.1. Primary packaging

The primary package is the material in direct contact with the dosage form. Its main role is to protect the formulation from environmental, chemical, mechanical and other hazards from the last step of production until it is used, while also being compatible with the product.(1)

The material in direct contact must not interact chemically or physically with the drug in such a way that will affect the quality above the tolerated limits set by regulatory authorities. This phase of primary packaging, where the semi-open product is going to be placed in its envelope of protection is delicate and still in contact with the outside environment.(8)

IV.1.1. Primary packaging materials and closures

In accordance with the methods of use and administration of pharmaceutical products, packaging materials vary a great deal and have to meet a great variety of requirements. The most commonly used materials are glass, plastic, rubber, paper and metal.(6)

Table I: Types of raw materials used in primary packaging (6)

Types of materials used	**Uses**
Glass	Ampoules Bottles Vials Syringes Cartridges
Plastic	Closures Bottles Bags Tubes Laminates with paper or foil
Metal	Collapsible tubes Rigid cans Foils Gas cylinders Needles Pressurized containers
Rubber	Closures including plungers

The following is a review of the principal materials which are commonly used in primary packaging, which is enough to give an idea of the problems caused by the choice of packaging materials in pharmacy:

IV.1.1.1. Glass:

It is used for a large number of pharmaceuticals including medicinal products for oral and local use as the first choice. Different types of glass may be necessary, depending on the characteristics and the intended use of product concerned.(6)

In the European and United States Pharmacopeias various grades of glass are classified according to their chemical characteristics and efficacy within the packaging of pharmaceuticals. Its distinction when compared to other packaging materials lies in the unique combination of durability, inertness and transparency. Glass is the only packaging material rated generally regarded as safe (GRAS) by the Food and Drug Administration. (9)

It is mostly used because of its particular properties which are: hardness; transparency; stability; chemical inertness and easy to clean.(10)

IV.1.1.1.1. Types of glass

According to the hydrolytic resistance glass is classified as follows:

a. Type-1: Borosilicate glass.

This is a neutral glass with a high hydrolytic resistance due to the chemical composition of the glass itself. Type 1 glass containers are suitable for most preparations whether or not for parenteral preparations.(8)

b. Type -2: Treated soda lime glass.

It has a high hydrolytic resistance resulting from suitable treatment of the surface. The surface of the glass is treated to remove surface alkali, this process is known as sulphur treatment and it prevents weathering of empty bottles. Weathering /blooming is the dissolving of the salts out of the glass when it is exposed to moisture. The treatment renders the glass more chemically resistant by neutralizing the alkaline oxides on the surface.(4)

The containers made from this type of glass are suitable for most acidic and neutral aqueous preparations whether or not for parenteral use.(8)

c. Type-3: Regular soda lime glass.

This is untreated glass with a moderate hydrolytic resistance. Containers made from this glass are suitable for non-aqueous preparations for parenteral administration, for powders for parenteral administration and for preparations not for parenteral administration.(8)

d. Type- 4: Non Parenteral general purpose soda lime glass.

As the name indicates this type of glass is used to store non parenteral formulations, those intended for oral or topical use.(4)

Table II: types of glass, their composition, properties and uses (4)

Type of glass	Main constituents	Properties	Uses
Type -1 Borosilicate glass Example Pyrex, borosil	SiO_2 80% B_2O_3 12% Al_2O_3 2% Na_2O +CaO 6%	-has high melting point so can withstand high temperature. -Resistant to chemical substances. -reduced leaching action	-laboratory glass apparatus -for injections and for water for injection
Type-2 Treated soda-lime glass	Made of soda lime glass. The surface of which is treated with acidic gas lie SO_2 (dealkalised) at elevated temperature (5000 C) and moisture	The surface of the glass is fairly resistant to attack by water for a period of time. Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant	Used for alkali sensitive products, infusion fluids, blood and plasma. Large volume container
Type-3 Regular soda-lime glass	SiO_2 Na_2O CaO	It contains high concentration of alkaline oxides and imparts alkalinity o aqueous substances. Flakes easily. May crack due to sudden change of temperature.	For all solid dosage forms(for example: tablets, powders) For oily injections. Not to be used for aqueous injection. Not to be used for alkali-sensitive drugs.
Type -NP Non-parenteral glass or general purpose soda lime glass			For oral and topical purpose. Not for ampoules.

IV.1.1.2. Plastic

Plastics are synthetic polymers of high molecular weight. The general advantages of using plastic materials in pharmaceutical packaging include consumer acceptance, preference, excellent safety characteristics (non fragility), less weight than other materials, moisture barrier properties, gas barrier properties, good puncture resistance, low heat conductivity, good sealant properties, and recyclability. (9)

They may contain some additives for example: antioxidants; stabilizers; plasticizers; lubricants; colouring matter and impact modifiers. The nature and amount of the additives are determined by the type of the polymer, the process used to convert the polymer into the container and the intended purpose of the container. (8)

IV.1.1.2.1. Types of plastics:

a. Polyethylene :

It is the most used polymer in packaging. Its properties differ according to degree of crystallinity, molecular mass, the ramification, and also the process of fabrication. There are two forms of polyethylene: (10)

- ***i. Low density polyethylene or high pressure polyethylene:*** these require temperatures of 150 to 250 ° C and a pressure of 1 200 to 1 500 bars for their fabrication. Their molecular mass varies from 10 000 to 30 000 and their density 0.91 to 0.92.
- ***ii. High density polyethylene or low pressure polyethylene:*** it has a higher molecular mass (10 000 to 50 000), therefore making it more dense than the low density polyethylene. It has the advantage of being less permeable to water vapour and gases because of its high density and is mostly used in drug packaging because it offers a good barrier against moisture.

It is mostly used in preparation of plastic bags, plastic films and bottles.

b. Polypropylene

It is also popularly used in pharmaceutical containers, and has properties close to those of polyethylene but it resists oils and fats better. It is most commonly used for making syringes. It is also suitable for sterilization at high temperature because of its high melting point. (11)

c. Polyvinylchloride (PVC)

It is the third mostly used plastic after polyethylene and polypropylene. It has a poor heat stability, and lower melting point than the other two. It can be made softer and flexible by the addition of plasticizers. It is mostly used for making containers used for blood and blood components.(11)

d. Polyamide (nylon)

It is made artificially by the interaction of a diamine and a dicarboxylic acid. It has a good chemical resistance, high strength, high heat resistance and good water resistance. It is impermeable to odours and gases and is not toxic.(11)(10)
Its main application in the packaging area is in laminates.(12)

e. Polystyrene

It is a plastic obtained by the polymerization of styrene. It is resistant to acids, base, alcohol s and to oils. It is used in packaging for bottles or rigid tubes.(10)

IV.1.1.2.2. Permeability of plastic to water vapour

The permeation of plastic materials by oxygen and water vapour are always a concern in choosing and specifying a plastic material to protect a drug. All plastic materials even those coated with a high barrier material exhibit some degree of permeability compared with glass or metal. The permeability of PVC water vapour is low; it is around $3g/m^2/24h$ whilst that of PVDC is reduced 5 -10 times.(13)

IV.1.1.3. Metal

Metal containers are used solely for medicinal products for non parenteral administration. Since metal is strong, impermeable to gases and shatter proof, it is the ideal packaging material for pressurized containers.(9)

The metals that are mostly used in packaging are:

IV.1.1.3.1. Aluminium:

Aluminium foil is the most commonly used packaging material due to its protective characteristics with respect to the effects of moisture, heat and light.(9) It is used in aluminium ointment tubes; screw caps; aluminium strips for strip packaging of tablet, capsules .(4)

IV.1.1.3.2. Tin:

It is the most expensive amongst all the other metals used for pharmaceutical packaging. It has the advantages of being chemically inert and has a good appearance.(11)
It is mainly used for eye ointment still packaged in pure tin ointment tubes.(4)

IV.1.1.4. Rubber

Rubber is mainly used for the manufacture of closures. It is in 2 forms; natural rubber and synthetic rubber. Synthetic rubber is the type mostly used in the pharmaceutical field. It is generally more resistant to ageing and more impermeable to gases and water vapour(10).
Examples of synthetic rubber are: butyl rubber which has a low permeability to water and low water absorption; nitrile rubber ; Chloroprene rubber(1)

IV.1.1.5. Closures

Closures are the most critical component of a pharmaceutical container. An effective closure system prevents the loss of material from the container, prevents contamination of product and prevents loss or entry of moisture. It must also be easily removed and replaced. (14)(11)

Depending on the type of the container, closures may have different shapes and sizes. For a closure system to be effective it is essential to consider the nature of material of container, properties of the product and the stability requirements(9).

IV.1.1.5.1. Types of closures:

The basic types of caps and closures include:

a) Thread screw

They are made of metal or of plastic. As the name indicates they contain threads which get engaged with threads on the neck of the container. These types of closures provide the effective seal which protect the product from physical and chemical reaction. Plastic caps are more popular than metal because plastic are resistant to corrosion. (11)

Figure 1: plastic thread screw cap (11)

b) Rubber closures

These closures do not pose any problem and can be used in contact with a large number of drug preparations.(9)

Figure 2: rubber stoppers (11)

c) Pilfer proof closure

This differs from standard roll on closure in that it has a longer skirt length. When this closure breaks at the bridge, the bank remains at the neck of the container. The closure can be resealed but the broken bank indicates the seal has been broken (9)

Figure 3: plastic pilfer proof closure on a container (11)

d) Roll on closures

Roll on closure contains the aluminium roll on cap which can be easily sealed, opened and closed. These are available in re sealable, non- sealable & pilfer proof type forms.

Figure 4: roll on closures (11)

IV.1.2. Types of containers used as primary packaging:

A container for pharmaceutical use as defined by the European pharmacopeia is an article that contains or is intended to contain a product and is, or may be in direct contact with it. (8)

IV.1.2.1. Primary package for liquid orals

IV.1.2.1.1. Well closed containers

These types of containers provide the protection from shocks, contamination by foreign particles and loss of article under normal conditions of handling, storage and distribution.(2)

Examples: ampoules; vials

The type of material mostly used for this type of container is glass.

Figure 5: well closed containers (11)

IV.1.2.1.2. Air tight containers:

They are impermeable to solids, liquids and gases under ordinary conditions of handling, storage and distribution. If these containers are intended to be opened on more than one occasions then they remain airtight after reclosing.(2)

Examples: bottles used for storing pills

The type of material which is mostly used is plastic.

Figure 6: air tight container (4)

IV.1.2.1.3. Hermetically sealed containers:

A sealed container is a container closed by fusion of the material of the container. These cannot be opened on more than one occasion like the air tight containers. (8)

This type of container is not affected by air and other gases under normal conditions of handling, storage and transport.(14)

Hermetically sealed containers can be divided into 2 types:

a) single dosed container

These are intended for articles for parenteral administration and they are designed to hold single dose. They are mostly made of glass and plastic.(11)

Example: ampoules

Figure 7: single dose containers (4)

b) multiple dose container

This type of container holds multiple doses and their contents are withdrawn at various intervals. It allows withdrawal of successive portions of the contents without changing the quality, strength or purity of remaining portion.

Example: vials

Figure 8: multiple dose containers. (4)

IV.1.2.2. Primary package for solid dosage forms:

IV.1.2.2.1. Strip package

The package is made up of two layers of film. A strip package contains many pockets and each pocket contains single dose of drug.(2) It is a form of unit dose packaging that is commonly used for the packaging of tablets and capsules in length. Different packaging materials are used for strip packaging such as paper, polyethylene, foil and polyethylene lamination.(4)

Figure 9: strip packages (4)

IV.1.2.2.2. Blister package

It is made up of base layer (polyvinylchloride layer) with cavities which contain pharmaceutical product. It provides greater protection then strip package. It contains a lid which is made up of aluminium and paper foil.(15)

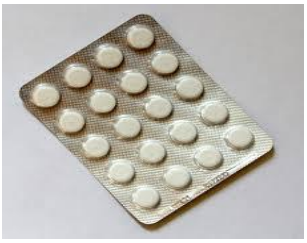


Figure 10: blister package (11)

IV.1.2.2.3. Sachet

Sachets can be fabricated from a single web with a centre fold, using a three or four sided seal or two webs using a four sided seal.(16)

The material of construction can consist of several layers that are individually selected based on their performance characteristics. A typical construction consists of an inner most heat seal layer, which is also the product contact layer. The heat seal layer is designed to bond to itself when heat is applied during the forming process. In addition to the heat seal layer, a barrier layer is commonly included to provide protection from the external environment. Aluminium foil is considered to be the most protective against gas and moisture ingress as well as protection from light transmission. They are mostly used in packaging of powders for oral solution. (17)

Figure 11: sachet of paracetamol powder for oral solution

IV.1.2.3. Primary package for semi solid dosage forms

Semi solid dosage forms include ointments, creams and pastes. The containers used for semi solid dosage forms include tubes and plastic containers.(2)

Figure 12: collapsible tube(11)

IV.2. Secondary Packaging

The package external to primary package is known as secondary package. It is the package in which the primary package is placed and is not in direct conduct with the medicament. This package provides additional protection during warehousing and also provide information about drug product.(1)

Functions (1)

- Protect the flexible containers.
- Protection from tough handling during transportation.
- Provide information of the dosage form and the volume or number of times to take the medicament on a label.
- It holds the notice and can contain accessories for example a plastic measuring cup for liquid oral forms.

Examples: cartons, boxes

IV.3. Tertiary packaging

It provides bulk handling and shipping of pharmaceuticals from one place to another.(14) It is the outer package of secondary packaging and prevents damage to the products. It is used for bulk handling and shipping.(1)

Examples: Barrel, crate, container, pallets, slip sheet.

V. Regulation of pharmaceutical packaging

As the pharmaceutical industries throughout the world are moving ahead towards producing drugs of better quality and becoming more and more competitive, regulatory agencies are being established in various countries across the globe. Regulatory authority and organizations are responsible in effective drug regulation required to ensure the safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public. (18)

Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products. Regulations on packaging are intended to help the manufacturer produce products of good quality. (19)

Some of the regulatory agencies and organizations that regulate pharmaceutical packaging include:

- Food and Drug Administration (FDA)
- The pharmacopoeias
- International Organization for Standardization (ISO)
- International conference on harmonization (ICH)
- ASTM
- Technical association of the pulp and paper industry (TAPPI)

V.1. The pharmacopoeias:

The European and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. (6)

In terms of packaging material, the European Pharmacopoeia provides a list of plastics that are permitted for use in pharmaceutical containers. For each type of plastic, appropriate specifications are given, along with the test methods. Although the main packaging material covered is plastic, it must not be forgotten that glass is still often used. Type I, Type II, Type III and Type IV grades of glass are described in the pharmacopoeia.(19)

USP recognizes that “the use of well-characterized materials to construct a packaging system is a primary means of ensuring that the packaging system is suited for its intended use.(6)

The main guidance on package requirements can be found in the pharmacopoeias, however additional testing over and above that mentioned in the monographs maybe required. Not all tests

in the pharmacopoeia have to be carried out; alternative methods can be used provided that comparative data is provided to show equivalence.(19)

V.2. FDA Packaging Guidelines

FDA plays a major role in the approval of manufacturing materials used in packaging materials and also publishes the list of materials which are generally considered as safe (GRAS). It defines the type of containers to be used, dividing them into parenteral or non parenteral containers, pressurized containers and bulk containers for active ingredients and drug products. The packaging components are discussed for physical, chemical and biological specifications, characteristics and tests to be applied, stability and compatibility. FDA does not approve the containers as such but, the materials used in the container. (20)

FDA's guidance document requires the evaluation of four attributes to establish suitability: protection, compatibility, safety, and performance/ drug delivery. The document also provides a structured approach to ranking packaging concerns according to the route of drug administration and likelihood of packaging component-dosage form interaction.(7)

V.3. International Organization for Standardization (ISO)

Descriptions and tests to be done on metal are found in the norms and standards of the ISO. These have been established in collaboration with manufacturers. ISO also gives requirements for rubber closures for pharmaceutical use.(6)

V.4. International conference on harmonization (ICH)

The ICH provides a guideline on the choice of primary packaging materials. The choice of materials should protect from light and moisture, compatibility of the materials used with the dosage form. It also guides on the choice of a container closure system; the intended use of the drug product and the suitability of the container closure system for storage and transportation.(21)

V.5. American society for testing and materials (ASTM)

The ASTM provides standards for the testing of pharmaceutical packaging. There are a number of testing standards that can be used as a preliminary verification method in packaging development. The packaging standards are useful in the evaluation and testing of the physical, mechanical and chemical properties of packaging and labelling materials. These standards help to identify characteristics such as chemical content, acidity or alkalinity, tensile breaking strength, permeation, tear and water resistance among others. (22)

VI. Quality control of primary packaging material

Pharmacopoeia specifications and standards for quality control established by national drug quality control laboratories, as already mentioned, can only be regarded as general in character and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, that is the finished dosage form in its primary and secondary packaging.(6)

Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The manufacturer must do a quality control at all levels of production, including packaging. (5)

Principle considerations for the Quality Control measures are physical characteristics and the chemical composition. By choosing two or three of the tests done in the initial suitability study, a Quality Control program can be established that will ensure the consistency of the container closure system. (7)

VI.1. Sampling

Sampling comprises the operations designed to select a portion of a pharmaceutical production for a defined purpose, in this case testing the conformity of the finished product or the primary packaging material to the specified requirements. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the material to be sampled. All operations related to sampling should be performed with care, using proper equipment and tools.(23)

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc. The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch. (6)

The tests to be applied to the sample may include:

- Verifying the identity
- Performing complete pharmacopoeial or analogue testing
- Performing special or specific tests

Primary packaging materials should be adequately protected during the sampling operation to avoid environmental contamination. The final use of the packaging should be taken into

consideration and appropriate sampling protection afforded (e.g. in the sampling of parenteral ampoules).(23)

VI.2. Test controls for primary packaging materials

Tests for packaging materials for quality control purposes may vary from one manufacturer to another. They are intended to check the identity of the material concerned. The specifications for packaging materials and containers must always be documented and include the nature, extent and frequency of routine tests. (6)

The tests usually include the following: (10)

VI.2.1. Identification test:

In the case plastic materials and rubber, identification of constituents, dosage of some of them and tests for impurities can give extremely complex problems.

VI.2.2. Mechanical tests:

They are applied either to the materials or the finished product; for example test for resistance to tearing, shock and crushing. A test that is more specific to pharmaceutics is the injection test for closures used on containers for preparations injectables.

VI.2.3. Transparency tests:

A transparency is researched in order to control the limpidity and to preserve the product in the container. In some cases the packaging must protect the medicament from harmful rays.

VI.2.4. Permeability tests:

They test the permeability of material to gas or vapour. The factors which influence permeability are: nature of the gas; characteristics of material; temperature.
The permeability tests are distinguished into:

VI.2.4.1. Water vapour permeability tests:

The ability of a container closure system to protect against moisture can be ascertained by performing the USP <661> Water Vapour Permeation test. The USP sets limits to the amount of moisture that can penetrate based upon size and composition of the plastic components (HDPE, LDPE, or PET)(7).

VI.2.4.2. Gas permeability tests (O_2; air; CO_2):

The test is done with the aid of manometers.

VI.2.4.3. Liquid permeability tests:

The loss in weight of a container and its contents is measured after putting them under various pressures.

VI.2.5. Preservation tests:

For this test, the packaging materials are put under different temperatures; pressure; lighting and humidity for a certain period of time. After this we verify whether the original qualities of materials are the same or have been altered by physical, chemical and physiological tests. It is very important to remember that these preservation tests allowing us to fix the best before date of a drug are to be done on the package which is going to be finally used.(10)

VI.2.6. Chemical resistance tests:

The containers and closures must be chemically inert; there should be no exchange between the container and its contents. The container should not add anything to its contents and neither should it absorb anything from its contents.

Chapter II: Validation of packaging

I. Generalities

The traditional way of operating a pharmaceutical packaging system has been to sample and test everything and to inspect out the defects. This usually left out important influencing features, such as the interface between the packaging materials and the equipment or environment in which the packaging takes place. Nowadays the target is invariably the achievement of a quality packed drug, one that meets the quality requirements in the widest possible sense, and validation is a major tool in accomplishing this.(24)

I.1. Definition of validation

Validation is defined as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.(25)

Validation is a key requirement of all GMP guidelines, as a validated process allows enables a consistent manufacturing and packaging of products in accordance with the product quality and market requirements in a cost effective and secure manner. It is observed that packaging validation per se is generally not specified as a separate validation activity but considered as a part of product process validation activity and some aspects of it are covered during process validation.(26)

I.2. Types of validation

According to the moment when it is done in relation to production, validation can be retrospective, prospective or concurrent. It would normally be expected that process validation be completed prior to the distribution of a finished product that is intended for sale (*prospective validation*). Where this is not possible, it may be necessary to validate processes during routine production (*concurrent validation*). Processes which have been in use for some time without any significant changes may also be validated according to an approved protocol (*retrospective validation*). (27)

I.2.1. Retrospective validation

It is defined as the established documented evidence that a system does what it is purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation process is for a product already in distribution. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment. (28)

The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results. (5)

The retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. (29)

I.2.2. Prospective validation

It is the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-sizes (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorised protocol. All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.(28)

I.2.3. Concurrent validation

Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation. (29)

It is a combination of retrospective and prospective validation**.**This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate documented evidence to show that the production process is in a state of control. It is usually used on an existing product not previously validated or insufficiently validated.(28)

I.2.4. Revalidation

According to the validation life cycle, test methods may require additional validation or revalidation when regulatory agencies issue new requirements or when changes are made to the methodology.(30)

This means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems.(29)

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality.

I.3. The various validation parameters

Typical validation characteristics which should be considered are listed below:(31)

a) Accuracy
b) Precision (repeatability and reproducibility)
c) Linearity and range
d) Limit of detection LOD or limit of quantitation LOQ
e) Selectivity or specificity
f) Robustness or ruggedness
g) Stability and system suitability studies

I.4. Interest of packaging validation

The aim of validation is not to correct or detect deviations in the packed product but to prevent deviations in the final packed product as far as is practicable and economic.(25)

Packaging validation ensures that the packaging process delivers adequate seals which will ensure that the required product environment is maintained over the claimed shelf life of the product. The similar principles apply also if the goal is to maintain sterility, a moisture barrier or some other specific atmosphere.(32)

The basic need for package validation is that it enables the packaging process to meet the product and market requirements in a cost effective and consistently efficient process with minimum down time, rejects and errors. It should not be considered only as a regulatory requirement but also as a business requirement.(26)

II. Key elements of packaging validation activity

II.1. Qualification of new packaging equipment

This includes the Design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) of the equipment and the respective facility and critical utilities. The focus during equipment qualification is the evaluation of variance of various equipment parameters due to the operation of the equipment and the assessment of its impact on critical product quality attributes.(26)

II.1.1. Installation qualification IQ

IQ is a method of establishing with confidence that all major processing, packaging equipment and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings.(28)

The goal of IQ is to show that the machine has been installed correctly and that all documentation is in place.(32)

II.1.2. Operational qualification OQ

It is establishing by objective evidence process control limits and action levels which result in product that has all the predetermined requirements. It confirms that the equipment works as per manufacturers claim. (33)

II.1.3. Performance qualification

The PQ should follow after the successful completion of the IQ and OQ. It establishes evidence that the process under anticipated conditions consistently produces a product which meets all predetermined requirements.(33)

II.2. Validation of a specific product packaging operation of a new product

In this case packaging operations for a new product are validated in an existing packaging line through evaluation of the impact of equipment variance on the critical product quality attributes.(26)

III. Package process validation

It is the total of all the qualifications, certifications and verifications of the packaging process. Package process validation has the goal to ensure that packages produced on equipment that has been installed properly (IQ), inspected properly (OQ), maintained adequately, and recently calibrated will produce packages meeting specifications and predetermined quality attributes when operated by properly trained operators.(25)

It is an activity performed when a new product is being packaged for the first time on an existing packaging line, using current or new packaging materials and configuration. As with any validation process the first step involves preparing a packaging process validation protocol.(26)

III.1. Packaging process validation protocol

The protocol is the experimental design by which the validation is executed. It is an important document that the validation team should come up with. (24)

The protocol must be have a simple and clear format and contain the following: (26)(24)

- A short description of the packaging process for the product, with a summary of the critical process parameters to be monitored during validation.
- Additional testing intended to be carried out, with proposed acceptance criteria and analytical validation as appropriate.
- Sampling plan- where, when, how and how many samples are taken for various tests to be performed during validation.
- Details for recording and evaluation of results.

III.2. Validation master plan (VMP)

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management.(27)

It should provide an overview of the entire validation operation, it organizational structure, its content and its planning. The main elements should be the list of items to be validated and the planning schedule. It should include:(33)

- All activities relating to critical technical operations, relevant to product and process controls within the firm.
- All prospective, concurrent, retrospective validations as well as revalidation.

The VMP should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOPs and validation protocols and reports.(27)

III.3. Validation report

The final validation report should include all the test results together with details of any changes made to the system. If there are test failures, these must be all reported and the resulting actions detailed. Any learning points from the activity must be logged and recommendations for future improvements documented. The validation report must be reviewed and approved by the quality assurance.

Chapter III: Verifying the integrity of pharmaceutical packaging

I. Generalities

A key factor in maintaining the quality of a pharmaceutical product throughout its shelf life is the integrity of its packaging. The package for a specific drug must undergo various tests to prove that it is capable to preserve the drug's efficacy as well as its purity, identity, strength and quality for its entire shelf life. There are multiple methods available to test integrity of the package; selection of an appropriate method is based on the type of package being tested .(34)(35)(36)

I.1. Definition of package integrity

As defined in ASTM F-1327-05, Standard Terminology Relating to Barrier Materials for Medical Packaging;

"*it is the physical capability of a given package to protect its contents with the desired level of protection over a defined period of service; for example, as a barrier to physical, microbiological, or chemical challenges*."(37)

I.2. Importance of testing for package integrity

The following are some of the reasons to test the integrity of a package: (38)(39)

- It proves that the packaging system shall provide physical protection and maintain integrity of the sterile barrier system.
- It is an FDA regulatory requirement
- It allows the validation of materials chosen for packaging a product
- It refines the sealing processes and improve quality of the seal

II. Methods for testing package integrity

Different products and different container types require different testing methods: this section aims at giving an overview of the different integrity test methods which are applied during production, as part of the quality control system and those are applied after production.(40)

A decision as to which method is required will be based on tradition, product cost, and quality assurance, perceived ease of use and cost of implementation. (38)

Before choosing a test method, it is important to start with basic product knowledge. Specifically, what performance criteria the drug will require in order to meet functional and shelf life requirements? The following are some of the general performance criteria required by drugs: (41)

- Sterility maintenance
- Barrier protection- gases, moisture, vacuum maintenance
- Shelf-life verification for package sterility, physical integrity, product stability for efficacy and safety, and barrier protection

The different test methods include:

II.1. Destructive test methods- container closure integrity tests

II.1.1. Blue dye penetration test

Also known as the blue dye test, it is the most used and accepted method for integrity testing of different forms of packaging. It is perceived as simple to use and has low costs, therefore used by almost all pharmaceutical companies.

The test involves immersing the product in a bath of coloured liquid – commonly methylene blue dye – and subjecting it to a vacuum for a set period of time. The chamber is then vented, returning it to atmospheric conditions, and the product is left to soak for an agreed length of time. This method draws the air out of the test product through a hole during the vacuum period; then, on returning to atmospheric conditions, it forces liquid into the product. On completion of the test, the product is dried and inspected for the presence of coloured liquid. (34)(38)

Figure 13: Bell shaped chamber connected to a vacuum pump (42)

II.1.2. Tracer gas test

The most common gas used in this test is helium; this is due to the small size of the helium molecules which enables it to find small holes on a package. There are two types of tests commonly used the bomb test and the sniffer test: (38)

II.1.2.1. Bomb test

The product is exposed to the test gas that is different from the gas already present in the pack. The test gas residue is removed by flushing with air, and the package is opened and the gas within is analysed qualitatively or quantitatively for the test gas.

II.1.2.2. Sniffer test

Each blister pocket is charged with helium using a needle. A sniffer probe is then used to detect the presence of helium around the pocket, which will leak from any hole in the blister.

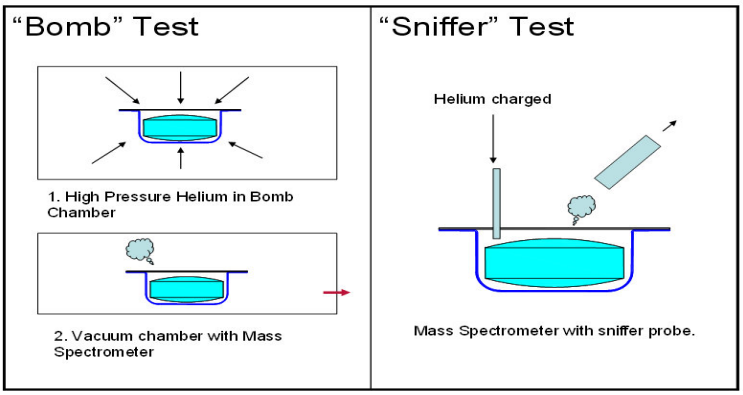


Figure 14: the two types of the tracer gas test(38)

The helium gas testing is the most sensitive method because it can detect holes as small as five microns. However, many blister leak testing applications do not need to find holes of this size, and its inability to identify large holes, time-consuming nature, operating difficulties; complexity and associated costs make it impractical in most instances.(38)

II.2. Non destructive test methods- container closure integrity tests.

The non destructive methods are gaining in popularity as an alternative to destructive testing, they save time, provide objective results, are more sensitive than the dye ingress method, are easier to validate and enable the product to be reused.(38)

II.2.1. Vacuum decay

This method works by measuring the change in pressure within a vacuum chamber containing the pack to be tested. The test product is subjected to a vacuum which is then held and monitored for change. A pack with no hole will cause little change in pressure within the chamber, while a pack containing a small hole will cause the pressure level in the chamber to change as the air within the pack escapes into the chamber. Packs containing large holes require a different measurement technique, because when the vacuum is generated within the test chamber, the head space within the pack equalises with the outside environment and therefore no pressure change is detected during the test phase.(38)(43)

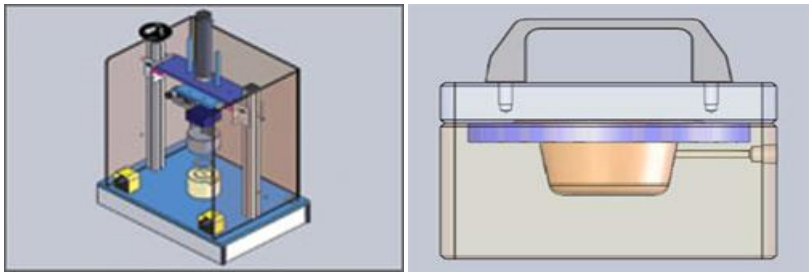


Figure 15: vacuum decay test chamber(43)

II.2.2. Force decay

This method measures the force generated by the test product under a vacuum due to the difference in pressure inside and outside the packaging. Often this type of methodology consists of three distinct phases: evacuation, stabilization and test. The force decay method of leak testing is very effective at finding leaks in packaging. It is simple in principle and can be set up to find small holes down to 10 microns, depending on the type of packaging. It provides a quick non-destructive test and is ideal for finding leaks in flexible packaging.(38)(44)

II.3. Water vapour transmission rate test

Many packaged drugs are moisture sensitive therefore the control of water vapours into and out of the package is critical to the drug's quality. The permeation of moisture through a package is a critical quality attribute for solid oral dosage forms, with moisture uptake being a common cause of product package failures. This permeation by moisture is measured by WVTR (water vapour transmission rate).(45)

II.3.1. Definition WVTR

Water vapour transmission rate (WVTR) referred to alternatively as moisture vapour transmission rate (MVTR), stands for the standard measure of the passing (permeation) of gaseous H_2O through a substrate. It is the steady state rate at which gaseous water vapour passes through a substrate at specific temperature and relative humidity (RH) conditions over a period of time. The unit of measurement is $g/m^2/24$ hr. (45).

I.3.3.2.1. Importance of measuring WVTR

Uptake of moisture by oral solid-dosage forms, such as tablets or capsules, is well known to increase the mobility of chemical species, which causes an increase in the rate of degradation of the drug substance and an increase in the rate of production of undesired by products. Moisture can also have an effect on the physical attributes of the product, such as its drug release rate or appearance. (46)

Considering all these problems caused by moisture uptake, the determination of water vapour transmission rate is of great importance. It intervenes for example in: (47)

- the package selection for moisture sensitive products
- the selection of proper materials for primary packaging
- the evaluation of container performance against moisture
- the consideration of the shelf life of the packaged drug

To develop a supply chain that is cost effective and guaranteed to deliver a high-quality product to the patient, it is therefore of interest to consider moisture uptake during the entire lifetime of the product. (48)

II.3.3. Methods of measuring WVTR

The testing of water vapour permeability is widespread throughout the packaging and other industries. There are a number of WVTR test methods that conform to recognized U.S and international ASTM, ISO, and TAPPI standards(45).

The following are some of the methods used to test WVTR:

II.3.3.1. Gravimetric test method

This is the traditional method that has been used to measure WVTR, it also referred to as the cup method. The Principe of this method involves placing a small sample of the test materials over the top of a pre-made metal cup. The cup may contain water, in which case, the water vapour would pass through the test material and the cup would lose weight over time. (49)

Depending on the application, gravimetric measurement is generally performed either using the Absorption method ("dry cup") or Desorption method ("wet cup"). In the Absorption method, the cup is filled with a water-absorbing material (for example calcium chloride or molecular sieve), and the relative humidity outside the cup is maintained at some high level. All water vapour that permeates through the film is absorbed into the material in the cup, resulting in a net weight gain of the cup system. The cup is weighed at regular intervals on a precision balance. The Desorption method employs the same concept, except that the high humidity atmosphere is located inside the receptacle (either as liquid water or as a salt solution, depending on the relative humidity level desired). In this test, water vapour permeates through the film from the interior of the cup, leading to a net weight loss over time.(50)

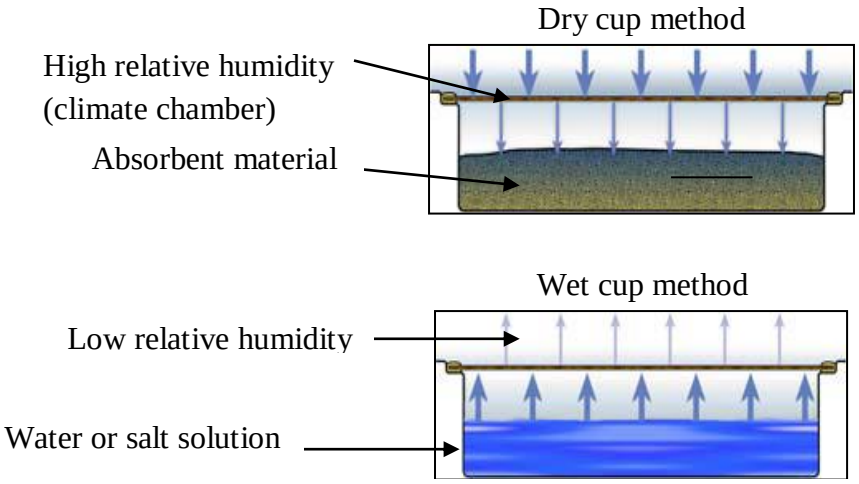


Figure 16: the two types of gravimetric WVTR testing(50)

II.3.3.2. Automated WVTR testing methods

Many of the disadvantages of the gravimetric WVTR test method can be overcome using the new automated test methods. (50)

There are several types of automatic testers available:

II.3.3.2.1. Dynamic relative humidity measurement

A film sample is inserted into test chamber; the lower test chamber has a saturated atmosphere maintained by a small water reservoir, while the upper chamber contains a sensitive, fast-responding relative humidity sensor. The upper chamber is first dried to a defined humidity level using dry air. When the drying is complete, the air-flow is stopped and the valves closed. From that point, the chamber is a closed system, in which transmission of water vapour through the sample causes an increase in relative humidity in the upper chamber. The instrument measures the time required for the upper chamber humidity to increase from a pre-defined lower limit to a pre-defined upper limit. The measured time interval is compared to the time obtained during calibration with a standard film of known permeability, and the result is expressed as the water vapour transmission rate in g/m2/24 hr. (50)

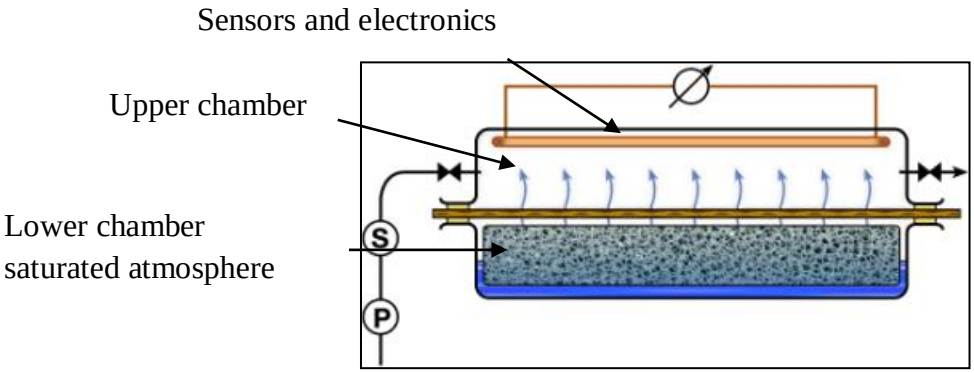
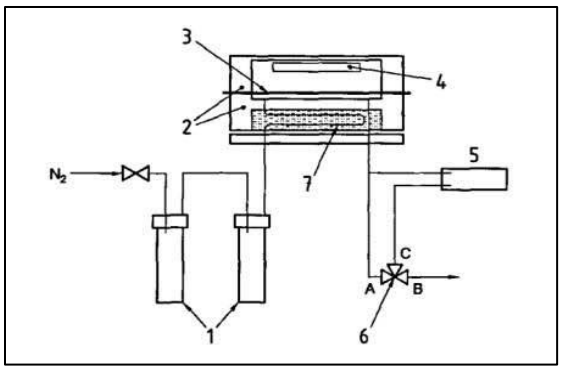


Figure 17:dynamic relative humidity tester(50)

II.3.3.2.2. Electrolytic analysis

The testing principle of this method involves the separation of the gas transmission cell integrated with the test specimen, into a controlled humidity chamber and a dry chamber. A stream of dry carrier gas is then passed over the dry portion of the sample, and this carrier gas transmits the water vapour pervading via the sample from the controlled humidity chamber into an electrolytic cell.(51)



1. Drying tube
2. chamber transmission chamber
3. Specimen
4. Glass fibre board dipped in vitriol solution,
5. Electrolytic cell,
6. Conversion valve
7. Copper tube.

Figure 18: testing principle of electrolytic method(51)

II.3.3.2.3. Calcium test

This method is based on the corrosion of thin calcium films. It involves observation of the optical changes as calcium converts to a transparent calcium salt as water vapour permeates through the barrier material. Because a visual change is observed, the Ca test can distinguish between bulk permeation and defect based permeation, however it does not discriminate between oxygen and water permeation.(52)

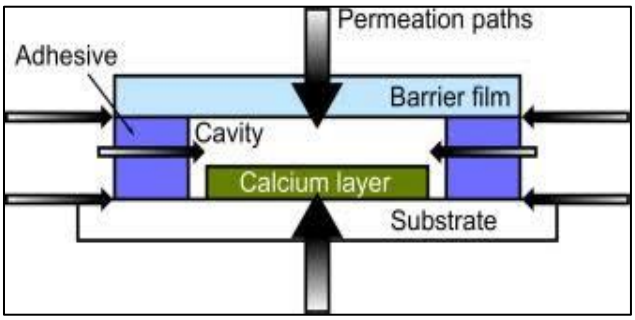


Figure 19: calcium test principle(53)

II.3.4. Comparison of the gravimetric method and the automated testing methods

While gravimetric measurement of WVTR is generally recognised as the "true" method in theory, providing absolute measurements of water vapour transmission rates through films, there are a number of disadvantages of using this method in practice: (50)

- The reproducibility of gravimetric testing can be poor.
- Preparation of the samples can be time-consuming and labour-intensive.
- Gravimetric testing can take many days or even weeks to obtain a result, particularly when high-barrier materials are tested. The time delay in obtaining results makes this type of testing impractical for production quality control, where prompt feedback to allow process adjustments is the key to minimising product variation and off-specification production.

To over the shortcomings of the cup method, several companies tried to automate the water vapour transmission rate testing. These test methods have the following advantages:(54)

- Provide quick and accurate results
- There is less human interaction
- Greater sensitivity, repeatability and precision.
- Reduction of labour costs
- Increase productivity

Practical research

I. Introduction

In the pharmaceutical industry, considerable efforts are made to develop products that are stable and have a long shelf life. Among the most important factors in the stability of the product is the package design. Package designs starts with determination of the physical and chemical properties of the product it will contain and its relevant protection.

In this study we are going to look at the packaging of Clavodex tablets and powder at Continental pharm laboratories, in particular the problems caused by moisture permeation on the packaged drug and determine if the packaging used is adequate to protect the product from moisture vapour. With the aim of carrying out an efficient and effective study we established procedures for the adjustments of the packaging machines used in the packaging of Clavodex powder and tablets, and we went on to prepare the samples of blister packs and bottles so as to send them to the testing company. We also took the time to verify the conditions in which the samples were produced to make sure they conform to the good manufacturing practices.

I.1. Objectives of study

The principal objective is the package validation of Clavodex powder and tablets using the WVTR method.

Secondary objectives:

- Preparation of procedures for the adjustments of machines
- Adjustments of the parameters of machine used in sealing
- Sample preparation according to WVTR

I.2. Type of study:

It's an observational and experimental study.

I.3. Place where the study was conducted

The practical study was conducted at CONTINENTAL PHARM LABORATORIES in Oran during a three months internship (8 January 2019 to 7 April 2019).

I.3.1. Presentation of Continental Pharm Laboratories (CLP)

Continental Pharm laboratory is an industry of fabrication and importation of pharmaceutical products located in the zone industrial En Nedjma Oran.

Created in 1998, CLP was dedicated to importing and distributing pharmaceutical products nationwide. After 5 years of its existence, it transformed into a manufacturing industry. Now it is a company that manufactures and imports pharmaceutical products.

It is the first in the western region to specialise in the production of antibiotics (family of the beta-lactamines) and particularly amoxicillin in three dosage forms:

- Tablet
- Capsule
- Powder for oral suspension

CLP is endowed with different premises, each one consecrated to a particular use; for example offices, storages zones, laboratory for control quality, production zone etc. The activity of each department is surveyed that all drugs produced and packaged conform to the BPF requirements and meet the quality requirements by the management of the assurance quality, which takes all necessary measures to ensure the use they are intended for.

I.3.2. Organisation of CLP

The structural organisation at CLP is implemented to assure the smooth operation of the production unit. It assures the purchase of materials, quality control; storage of raw materials; packing materials and finished product. This organisation is represented by an approved administrative chart. The responsibilities are clearly defined according to each working post and each worker.

Administrative chart

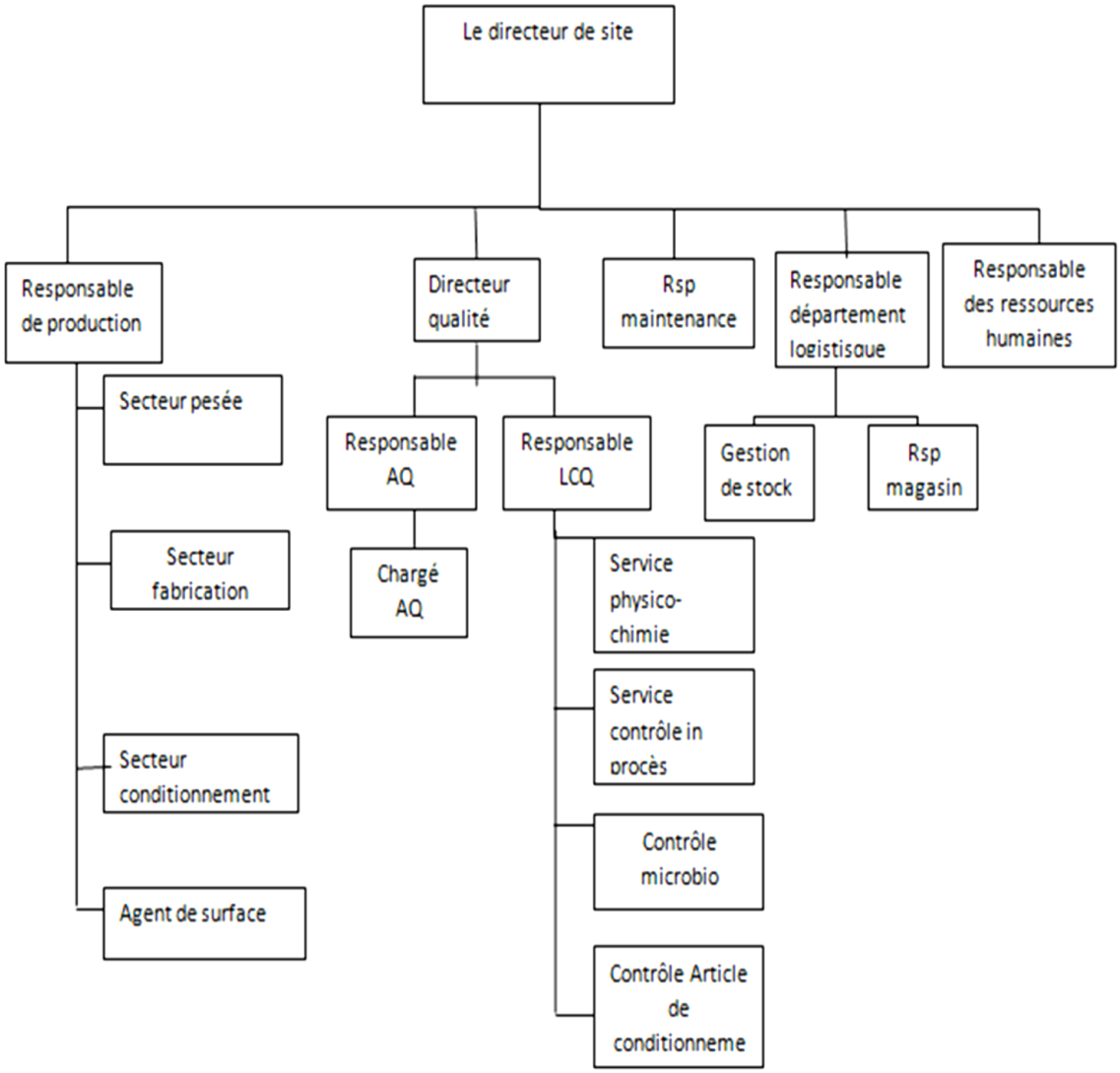


Figure 20: Administrative chart of CLP

I.4. Motivation of theme

The manufacturer's main objective was to come up with guidelines in the manufacture of Clavodex to help reduce the risk of degradation, during and after the manufacturing process. The product Clavodex is composed of 2 active principal ingredients: clavulanic acid and amoxicillin. Clavulanic acid being the most sensitive of the two; it is volatile and unstable when exposed to high temperatures and it is hygroscopic. The degradation in quality of Clavodex is a visible change in colour from white to yellow. Though this change in quality is visible, it is not harmful to the user and neither does it alter the efficacy of the product.

There are many factors that contribute to the degradation in quality of the product and this propelled CLP to investigate if it is moisture permeation into the package that causes this degradation, as well as verifying if it is the type of packaging material used that allows permeation or it is the quality of seals on the packages that allows permeation of moisture. It is the purpose of this study to validate the packaging used in Clavodex and prove it is adequate to protect the product using the WVTR method.

The manufacturer chose the WVTR method for the study because it is the most effective method.

II. Materials and equipment used

This is a brief outline of the primary packaging materials and the primary packaging equipments we used in the preparation of packaging samples of Clavodex powder and Clavodex tablets at CLP.

II.1. Materials used

The materials used in packaging are chosen in such a way to guarantee the quality, efficacy and security of the product. Apart from the quality of sealing on the package, the permeability of the material also plays a huge role in protecting the product from water vapour. In the packaging of Clavodex it is very important to consider the impermeability of the material to water vapour.

In this study we used the following materials to prepare samples:

- Glass containers

Figure 21: glass container

- Plastic caps

Figure 22: plastic cap

- Foil-foil blister packs

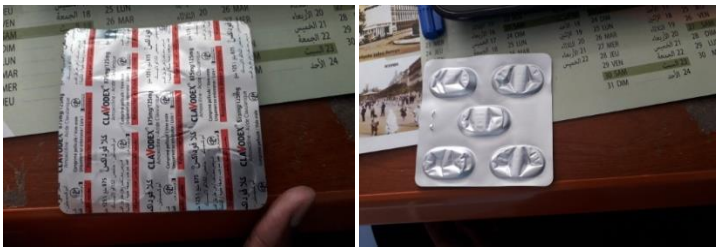


Figure 23: front and back view of blister packs

- Syringe
- Distilled water
- Cotton

II.1.1. Types of materials used in primary packaging at CLP

Primary packaging materials used in the packaging of Clavodex powder and tablets at CLP include:

II.1.1.1. Glass containers

The glass containers are used in packaging Clavodex powder for oral suspension. The glass used for container is USP type III. It is untreated soda lime glass suitable for powders. The container is closed by a screw cap with a polyethylene gasket fitted with a temper evident ring.

II.1.1.2. Blister pack

At CLP there are 2 types of blister packs used in packaging. One type consists of a cavity constructed from clear, thermoformed plastic and the lid is foil; this type is used in the packaging of Amodex tablets. The second type has both the cavities and the lid made of foil; it is used in packaging Clavodex tablets.

The blister pack used in the packaging of Clavodex tablets is a foil/foil lamination used for products that are susceptible to moisture or light. Clavodex is a product that requires the highest form of protection from moisture and therefore it is packed in an alu/alu package.

Characteristics of the forming film

The forming film of the blister pack comprises a lamination of plastic film, adhesive, foil, adhesive and an outer plastic film. The outer film which can be PET or PVC supports the thin aluminium layer and acts as the heat-seal layer.

The foil-foil blisters cannot be made as form fitting like the plastic ones because of the brittleness of the cold formed aluminium. The foil is shaped and moulded around a plug to form a cavity. The cavities made in the cold forming process are larger and allow the product to move inside the blister.(56)

At CLP the forming film used for Clavodex tablets is a cold form foil (alu/alu), it has the advantage of having a near absolute barrier for moisture.

Characteristics of the lidding material

It is an aluminium foil printed on one side and heat sticking on the other side. The lidding material is selected according to size, shape and weight of the product and the style of the package. The surface of the lidding material is compatible with the heat seal coating processes. The lidding material must also guarantee a WVTR that is as low as that of the forming films.(56)
The lidding material used at CLP is an aluminium foil printed on one side and heat sticking on the other side. It is a push through foil.

I.1.2. Quality control of raw materials

The quality of materials used is controlled by the laboratory of control quality at CLP. Each packing material that is bought has a control report which describes the article and the results of the control. The supplier of the materials also provides a certificate of analysis for each article which gives the physical and chemical tests done on the materials and the description and specifications as well as the observations for every test performed. These documents are then compiled and archived at the quality assurance office.

After the analysis of the raw materials, the conforming results obtained by the control quality allow their usage.

II.2. Equipment used

The design and layout of equipment has a great impact on the efficiency of the packaging line. The layout of the equipment should guarantee an easy access for the operators and the engineers to access this equipment when adjustments and or maintenance are required. The layout of equipment at CLP meets these requirements.

The equipment we used in this study is the primary packaging equipment used in the packaging of Clavodex tablets and powder at CLP.

We used in this practical:

- Automatic blister machine (thermo former) - **NMX**

- Bottler filling and capping machine- **RAV 05**
- Bell shaped vacuum with pump

II.2.1. Automatic blister machine (thermo former) - NMX

The blister machine used in this line is an nMX with an alternative movement**.** It is used in the packaging of Clavodex tablets.

Figure 24: NMX blister packing machine

II.2.1.1. Composition of the machine

1. Feeder of the forming film
2. PC vision system
3. Thermo forming post
4. PLC (programme logic computer)
5. Feeder of products
6. Zone of insertion of products
7. Commanding screen and keyboard
8. Feeder of covering film
9. Sealing post
10. Blister cutter
11. Eliminator of empty blisters
12. Eliminator of incomplete blisters

II.2.1.2. Integrated controls of the machine in production:

- **Control of presence of product by the vision system: SEA VISION**

During packaging the PC vision system controls automatically and constantly the presence and physical integrity of the product to locate the blisters that are to be eliminated and provoke the corresponding reject signals.

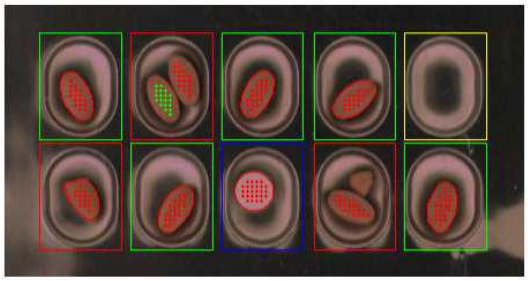


Figure 25: Image of the control SEA vision on blister machine

- **Control of product outside of the blister cavity S43**

It has the function of detecting products, fragments of the product, or other foreign particles present on the formed band or incorrectly placed in the cavity. This type of control is carried out by passing a mobile blade on the forming material.

- **Control of presence of forming material B40**

It stops the machine in phase when the bobbin of forming material is finished and displays a message of alarm.

- **Control of minimum level of forming material B1**

It warns the operator on the imminent change of the bobbin of forming material by a sound and light signal, as well as an alarm message displayed on the screen.

- **Control of junctions on the forming material B6**

It detects the presence of a heat sticking adhesive band that is used for the joining of the two ends of the bobbins. The photoelectric cell transmits the information to the automatic, which then commands the rejection of blisters and stops the loader. The adjustment of the sensibility of the cell is carried out by a button.

- **Control of presence of lidding material S30**

It stops the machine in phase when the bobbin is finished and an alarm message is displayed on the screen.

- **Control of the minimum level of lidding material B3**

It warns the operator on the need to change the bobbin by sound and light signal as well as a visual displayed message.

- **Control of the junction on the lidding material B7**

It detects the presence of a heat sticking adhesive band used for the joining of the two ends of the bobbins. The photoelectric cell transmits the information to the automatic, which then commands the rejection of blisters and stops the loader. Roughly speaking the adjustment of the sensibility of the cell is carried out at once by the button.

- **Control of the pace of the holder at the post sealing exit**

This feature detects the correct position of the formed material (this material must advance a step at each cycle of the machine), as well as the presence of possible objects between the inferior and superior sealing plates using the intermediate of four sensors (S33, S33A, S33B, S33C). Each

time that one of the sensors turns off, the machine stops in phase, the sealing post immediately opens and an alarm message is displayed on the screen.

- **Control of the number of steps between the presence control of the product and the ejection of blisters S68**

It verifies that the number of steps between the axis of the feature which controls the presence of the product and the axis of the cutting post corresponds to the one defined by the format during production. It is composed of a wheel mounted on a sliding trolley detecting the maximum and minimum limit created by the heat sticking band at the entrance of the cutting post. The thermo former stops in phase and displays a warning message each time that the excursion of the wheel goes beyond the defined limits.

- **System of ejection of empty and incomplete blisters**

It has the function of diverting blisters that do not conform, detected by the feature which controls the presence of the product in the conveyor. It is made up of:

- ❖ A photoelectric cell which detects the passage and authorises the rejection, it is positioned on an adjustable support. Roughly the adjustment of the sensibility of the cell determines the separating space between two blisters
- ❖ A feature which ejects a gush of air and a deviation feature, which activates by rejecting empty or incomplete blisters.

II.2.1.3. Operation of the blister machine

The machine is divided into 4 units according to operations done:

A. <u>Forming station</u>: there are two operations done at this level :

- **Unwinding of the forming film:**

A series of rollers unroll and regularly supply the thermoforming station with the forming film. At each cycle a moving clamp moves the forming film forward.

- **Forming of cavities:** it involves 3 steps:

<u>*Heating*</u> - at the preheating station the forming film is heated by 2 plates, one above and the other below to make the film malleable and make the thermoforming easy. This heating process is only used when the forming film is PVC. When the forming film is aluminium the blister cavities are cold pressed into shape at the forming unit.

<u>*Forming*</u> – this part has 2 matrices, one above and one below, the matrice above is brought close to the film and exerts a pressure which allows the formation of the cavities.

<u>*Cooling*</u> – at the forming station the plate which is below is cooled down by a cycle of cold water which makes the cavities rigid but avoids dilatation.

B. Feeding station

The loading area fills the blister cavities with the product.

C. Sealing unit:

- *Supply of the lidding material* - a series of rollers drives the bobbin of aluminium film up to the sealing station.
- *Blister sealing and printing* – when the two films are superposed, they pass on to the sealing plates; the upper plate is grooved and heated to an optimum temperature by electrical resistances. The upper and lower plates come together and exert a certain pressure on the two films to assure the sealing, the sealing occurs only on specified zones. At the same time the pistons inside the plates with the help of the heat from the plates will print the necessary information correctly. After sealing the blisters then move on to the cooling station.

D. Cutting unit:

Once at the cutting zone the last row of the band of blisters is placed under the guillotine. Using 2 blades, one inferior and the other superior the blisters are cut out and brought out towards the secondary packaging station.

The blisters which are empty and faulty are eliminated at different points.

II.2.1.4. Flowchart diagram of packaging on blister machine

We established a flowchart diagram for the primary packaging of Clavodex tablets in blister packs. The general sequence involves cold formation of the blister cavities on the ALU foil, loading the blisters with the tablets, placing the lidding material over the blister and heat sealing the package. The expiry date and batch number are then printed on the blisters before they are cut. The blisters are then ejected; the blisters that conform proceed to secondary packaging via the conveyor belt, while the blisters that have defects drop into the waste system.

Blister packaging line:

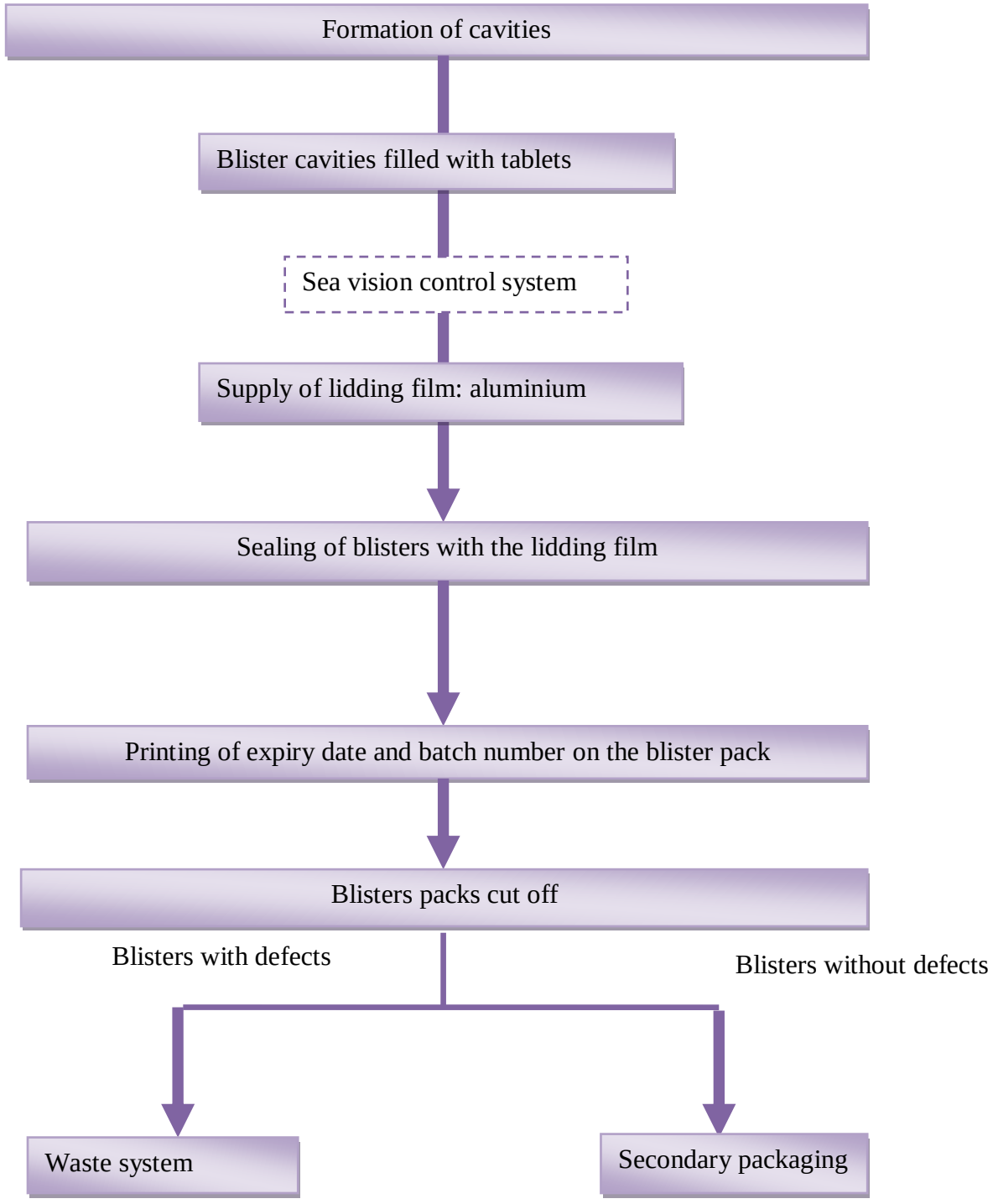


Figure 26: Flowchart diagram of primary packaging on the blister machine

II.2.2. Powder filling and capping machine- RAV 05

The machine used in this line is an automatic RAV 05 which is an entirely autonomous machine unit for the automatic filling of powders or fine granules in bottles. The filling operation as well as the closure of the bottle operation is performed during the machine automatic cycle.

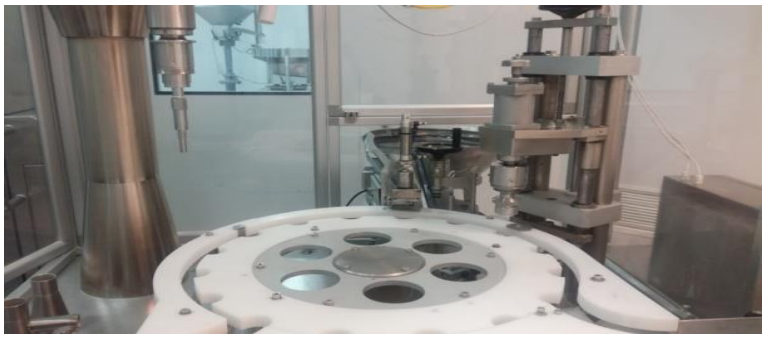


Figure 27: RAV 05 bottle filling and capping machine

II.2.2.1. Composition of the machine:

1. Conveyor belt
2. The carters
3. The carousel
4. Bottle lifter
5. Dosing /filling head
6. Capping head
7. Closing / tightening head
8. Vibrating bowl
9. CFM pump

II.2.2.2. Integrated controls of the machine during production

- **Sensor for the presence of bottle:**

The first sensor is placed below the carousel and just before the bottle lifter sets to command the filling of the bottle; it also commands the insertion and screwing of the cap by means of 2 other sensors.

- **Sensors on the conveyor belt**:

There are 2 sensors on the conveyor belt, one before the carousel and another which is after. The first one is for the commanding the minimum level of bottles and the second one is for commanding the maximum level of bottles.

- **Sensor of presence of cap**:

It is placed before the cap inserter; it detects the presence of the cap and provokes an immediate stop of the machine if the cap is absent.

II.2.2.3. Operation of the machine

- **Filling of the bottles**: The bottles are received by the conveyor belt from the blower, and transported towards the carousel. The carousel is a round with 16 spaces which fixes and transports the bottles towards the filling head, capping head and lastly the tightening head. The bottle lifter lifts up the bottle to the spout of the filling head for filling, and brings it down again after filling is complete. The filler has a predetermined dose it is programmed to put in the bottle.
- **Capping and closing:** The capping head is attached to a vibrating bowl which feeds the machine with caps. The capping head allows the capping of the bottle by means of a piston. After the bottle is capped the tightening head tightens the cap by a strong rotating movement, allowing an air tight sealing of the bottle. The distance between the tightening head and the cap is adjusted by a manual steering wheel placed above the tightening head.

A. Related equipments of the RAV 05

These include the vibrating bowl and the CFM pump.

The vibrating bowl is a dispositive for the distribution of caps; it feeds the machine by the intermediate of a conveyor canal under vibration.

The CFM pump is composed of a control cabinet, security filter,

B. Frame of the RAV 05

It includes the technical parts of the machine:

- Electric motor
- Electrical cabinet
- Peripheral connections: electrical, aspiration, manometer of compressed air

II.2.2.4. Flowchart diagram of powder filling and capping machine

The general sequence of the packaging of powder in bottles involves; the introduction of the bottles on round table and then passage of each bottle to the blower one by one before passing on to the conveyor belt. The conveyor belt then drives the bottles to the dosing head, the bottle is lifted up to the dosing head and brought down after filling. The dosing head fills each bottle with a predetermined dose of the powder. The bottle is capped and the cap is tightened by the tightening head before passing on to the conveyor belt which leads the bottles to the labelling machine and secondary packaging. Unlike the blister machine that automatically detects the blisters with defect, the bottles that do not conform have to be picked out manually by the operators.

Bottle packaging line:

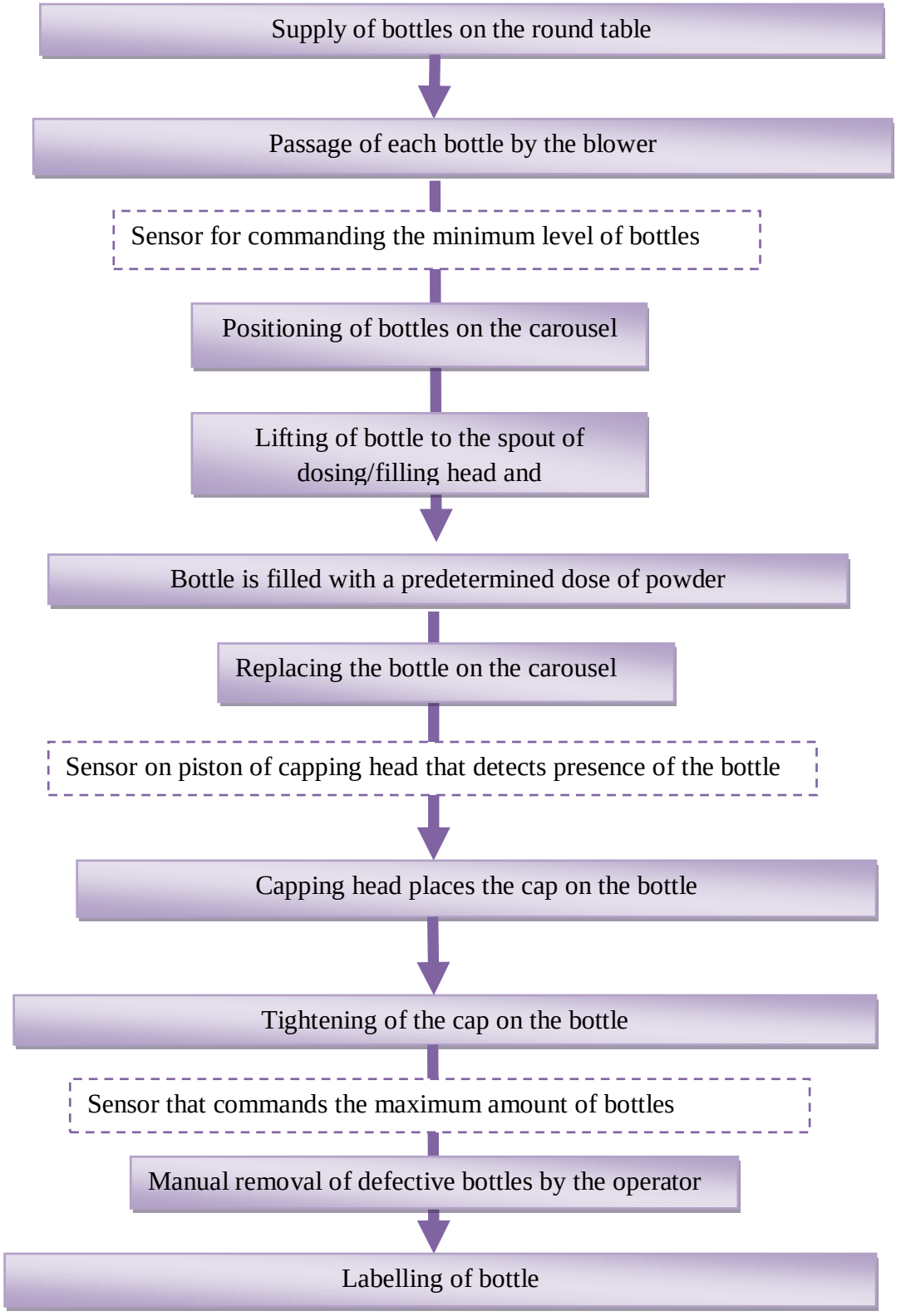


Figure 28: flowchart diagram of packaging on the powder filling and capping machine

II.2.3. Bell shaped vacuum with pump

This piece of equipment is used for the in process control of packaged containers and blisters. As the name suggests, it is a bell shaped chamber with a lid and it is connected to a pump. It is used to detecting any leaks on the packaged product during the methylene blue dye penetration test.

Figure 29: bell shaped vacuum with pump

III. Method

Before preparing the samples required for the WVTR test, the assurance quality service of Continental pharm prepared procedures to assure the best operation of the packaging machines and to help in the necessary adjustments. They also went ahead and prepared a procedure for the preparation of samples.

III.1. Establishing procedures

The assurance quality service had to establish procedure to assure the samples were prepared correctly and according to the good manufacturing practices. The procedure prepared included:

- Procedure for the adjustment of RAV 05, the powder filling and capping machine
- Procedure for the adjustment of NMX, the blister machine
- Sampling procedure
- Procedure of preparation of samples according to the WVTR method

III.2. Execution of the adjustments of the packaging machines

The execution included doing the following:

- Verifying that the operating procedures of the two packaging machines are respected
- Verification of the operating conditions
- Verification of the control systems
- Verifying the preliminaries and assembling; before the start of each operation the operator must carry out some preliminary operations.
- Carrying out empty tests; the empty test allows verifying that the machine is working well, verifying the cutting of blisters, printing, formation, sealing as well as the correct positioning of the bobbins.
- When operating on the batch it is necessary to do an integrity test and a visual control of the manufactured product.

- Carrying out adjustments if necessary; during the packaging operation, the operator is entitled to do certain adjustments; for example the speed of the machine.

III.3. Preparation of samples

In this study we prepared samples of 10 blister packs used in the packaging of Clavodex tablets and 10 glass bottles with plastic caps used in the packaging of Clavodex powder. Instead of the product, we placed cotton soaked with a bit of water inside each blister pack and each bottle.

This testing method involves the evaluation of the loss in weight of package (bottle, blister pack or sachet) containing water and placed in a chamber with a circulating gas which detects water vapour escaping the package. The aim is to conclude on the quality of sealing and the air tightness of the package.

III.3.1. Preparing samples of sealed bottles

Before the samples could be prepared, we had to define and determine the parameters of tightness of cap on the container as well as the air tightness of container. The machine was adjusted a number of times before reaching the optimal conditions of tightness and air tightness of the container.

III.3.1.1. Preparing samples of bottles according to the WVTR method

The procedure for the preparation of samples was established by the company concerned with testing the samples. (See annexe 1)

- The bottles and closures were prepared as they would be used in production. To label the each bottle a marker pen was used.
- A piece of cotton wool was placed into the bottle, to loosely occupy approximately 1/4 of the volume of the bottle.
- Then 1/10 of the volume of the container was filled with distilled water. The amount of water was not critical, as it was there only to create a humid environment for the test.
- Before proceeding to the capping of the bottles we made sure that the threads of the bottle were dry.
- After the bottles were sealed, they were packed upright and separated to avoid breaking them and then send for testing.

III.3.2. Preparing samples of blister packs

The sealing temperature was set at different temperatures and observed for blister quality. Based on the result optimum sealing temperature range was established. The sealing pressure was fixed at 6 bars.

III.3.2.1. Preparing of samples of blister packs according to the WVTR method

The protocol for the preparation of samples of blister packs was established by the quality assurance service (internal protocol).

- The aluminium forming film used for making the blister packs was loaded on the machine and the cavities formed the same way as in normal production.

- A small piece of cotton was placed inside each cavity before adding a few drops of distilled water with a syringe.
- The blister cavities were covered and sealed using the lidding material on the machine.
- Each blister pack was marked using a marker pen and packed with the appropriate documents, before sending for testing.

IV. Results

IV.1. Procedure of adjustment of RAV 05 - powder filling and capping machine

Summary:

I / Objective:

The objective of this procedure is to define and determine the parameters of control of the tightness of caps on the bottles dedicated for the packaging of Clavodex powder for oral solution, as well as their air tightness. After many adjustments, the main concern is to come up with optimal conditions of tightness and air tightness of the bottles.

II / Area of application

The present procedure is applicable to the machine RAV 05 on the bottles dedicated to the finished product for solution oral.

III /Responsibilities

The following are responsible for the execution of this procedure:

- The production operators on the RAV, production department,
- Maintenance staff ; maintenance department,
- The production operators and analysts in terms of control of integrity,

IV/ Associated references and document

IV-1/ References

- Manuel of the machine RAV,
- Procedure on how to use the RAV,
- Good Manufacturing Practices,

IV-2/ Associated DOCUMENTS

- Register of measurements of torque meter ,
- Register of the tests of integrity,
- Report of registered torque-meter tests and integrity tests ,

V / Abbreviations and definitions

NA

VI /Contents

VI-1/ Technical Characteristics of the RAV:

VI-2/ Procedure of adjustment of the RAV 05

This machine has a number of adjustments that have to be performed on it; some adjustments are done by the maintenance team and some by the operators when the machine is in operation.

The adjustments done by maintenance include varying the height of the tightening head to three levels, as well as the tightening torque to nine positions. The operators have to vary the speed of the tightening head up to ten different speeds, as well as the height of the tightening head, while the height of the tightening head is fixed at one value at a time

The adjustments are illustrated in **Table 3** below: one level of the height of the tightening head is considered.

Table III: Adjustments performed on the powder filling and capping machine

		Speed of tightening head									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Positions of the tightening torque	**1**										
	2										
	3										
	4										
	5										
	6										
	7										
	8										
	9										

These adjustments are then optimised to:

- Three levels for the height of the tightening head
- Three positions for the tightening torque
- Four speeds for the tightening head

Table 3 shows the optimised adjustments by the columns and rows coloured in grey. Table 3 is then modified to form Table IV

Table IV: Optimised adjustments of the powder filling and capping machine

	Speed of tightening head				
	H1	**4**	**5**	**6**	**7**
Positions of the tightening torque	**4**				
	5				
	6				

VI-3/ Sampling procedure

The sampling procedure is done according to the number of optimised adjusted parameters.
The identification of samples is done by crossing the adjustments of the speed of the tightening head and the position of the tightening torque for a fixed height H1

Table V below shows the number of adjustments when the height of the tightening head is fixed at one position.

Table V: The number of adjustments when the tightening head is fixed at one position

	Speed of the tightening head				
	H1	**1**	**2**	**3**	**4**
Positions of the tightening torque	**1**	1.1	1.2	1.3	1.4
	2	2.1	2.2	2.3	2.4
	3	3.1	3.2	3.3	3.4

VI-3-1/ Preparing samples of bottles according to the WVTR method

The bottles and closures were prepared as they would be used in production. To label the each bottle a marker pen was used.

- A piece of cotton wool was placed into the bottle, to loosely occupy approximately 1/4 of the volume of the bottle.
- Then 1/10 of the volume of the container was filled with distilled water. The amount of water was not critical, as it was there only to create a humid environment for the test.
- Before proceeding to the capping of the bottles we made sure that the threads of the bottle were dry.
- After the bottles were sealed, they were packed upright and separated to avoid breaking them and then send for testing.

VI-4/ Controls carried out

After the determination of the number of adjustments to carry out on the RAV 05, the samples are numbered up to 10 by the adjustments.

For each adjustment there is a corresponding measure of torque meter as well as an integrity test. To gather all the measurements which are taken, a register are established which records the identity of samples and the results.

Table VI: Record of torque-metre measurements and integrity tests

Positions of the tightening torque	Speed of the tightening head	Identification of samples	Torque-metre Measurements	Conformity of the integrity test	Observations	CONCLUSION
1	1.1	1.1.1				
		1.1.2				
		1.1.3				
		1.1.4				
		1.1.5				
		1.1.6				
		1.1.7				
		1.1.8				
		1.1.9				
		1.1.10				
	1.2	1.2.1				
		1.2.2				
		1.2.3				
		1.2.4				
		1.2.5				
		1.2.6				
		1.2.7				
		1.2.8				
		1.2.9				
		1.2.10				
	1.3	1.3.1				
		1.3.2				
		1.3.3				
		1.3.4				
		1.3.5				
		1.3.6				
		1.3.7				
		1.3.8				
		1.3.9				
		1.3.10				
	1.4	1.4.1				
		1.4.2				
		1.4.3				
		1.4.4				
		1.4.5				
		1.4.6				
		1.4.7				
		1.4.8				
		1.4.9				
		1.4.10				

Position of the tightening torque	Speed of the tightening head	Identification of samples	Torque-metre Measurements	Conformity of the integrity Test	Observations	CONCLUSION
2	2.1	2.1.1				
		2.1.2				
		2.1.3				
		2.1.4				
		2.1.5				
		2.1.6				
		2.1.7				
		2.1.8				
		2.1.9				
		2.1.10				
	2.2	2.2.1				
		2.2.2				
		2.2.3				
		2.2.4				
		2.2.5				
		2.2.6				
		2.2.7				
		2.2.8				
		2.2.9				
		2.2.10				
	2.3	2.3.1				
		2.3.2				
		2.3.3				
		2.3.4				
		2.3.5				
		2.3.6				
		2.3.7				
		2.3.8				
		2.3.9				
		2.3.10				
	2.4	2.4.1				
		2.4.2				
		2.4.3				
		2.4.4				
		2.4.5				
		2.4.6				
		2.4.7				
		2.4.8				
		2.4.9				
		2.4.10				

Positions of tightening torque	Speed of tightening head	Identification of samples	Torque-meter Measurements	Conformity of the integrity Test	Observations	CONCLUSION
3	3.1	3.1.1				
		3.1.2				
		3.1.3				
		3.1.4				
		3.1.5				
		3.1.6				
		3.1.7				
		3.1.8				
		3.1.9				
		3.1.10				
	3.2	3.2.1				
		3.2.2				
		3.2.3				
		3.2.4				
		3.2.5				
		3.2.6				
		3.2.7				
		3.2.8				
		3.2.9				
		3.2.10				
	3.3	3.3.1				
		3.3.2				
		3.3.3				
		3.3.4				
		3.3.5				
		3.3.6				
		3.3.7				
		3.3.8				
		3.3.9				
		3.3.10				
	3.4	3.4.1				
		3.4.2				
		3.4.3				
		3.4.4				
		3.4.5				
		3.4.6				
		3.4.7				
		3.4.8				
		3.4.9				
		3.4.10				

VII/ Register

A copy of this current procedure is kept at the production site and the original document is kept at the assurance quality office; it is valid for three years.

VIII/ANNEXES

IV.2. Procedure of adjustment of the NMX- blister machine

Summary:

I / Objective:

The objective of this procedure is to define and determine integrity of the seal on the blister packs dedicated for the packaging of Clavodex tablets. After many adjustments, the main concern is to come up with the optimal conditions of sealing temperature and pressure.

II / Area of application

The present procedure is applicable to the machine NMX, for the packaging of Clavodex tablets.

III /Responsibilities

The following are responsible for the execution of this procedure:

- The production operators on the NMX, production department,
- Maintenance staff ; maintenance department,
- The production operators and analysts in terms of control of integrity,

IV/ Associated references and document

IV-1/ References

- Manuel of the machine NMX,
- Procedure on how to use the NMX,
- Good Manufacturing Practices,

IV-2/ Associated DOCUMENTS

- Register of the tests of integrity,
- Report of registered integrity tests ,

V / Abbreviations and definitions

NA

VI /Contents

VI-1/ Technical Characteristics of the NMX:

VI-2/ Procedure of adjustment of the NMX

Some adjustments are done by the maintenance team and some by the operators when the machine is in operation.

The adjustments done by maintenance include changing the format of moulding plug according to the size of cavities required, inserting the bobbins of ALU forming foil and the lidding foil, as well as checking that the machine is working well and making adjustments where necessary.

The operators have to adjust the speed of the machine, the intensity of vibration of the feeding bowl and the speed of the levelling roller. They also have to verify the pressure of air and water, that there are no leaks and that the sealing temperature has been reached.

VI-3/ Preparing of blister pack samples according to the WVTR method

The protocol for the preparation of samples of blister packs was established by the assurance quality service (internal protocol).

- The aluminium forming film used for making the blister packs was loaded on the machine and the cavities formed the same way as in normal production.
- A small piece of cotton was placed inside each cavity before adding a few drops of distilled water with a syringe.
- The blister cavities were covered and sealed using the lidding material on the machine.
- Each blister pack was marked using a marker pen and packed with the appropriate documents, before sending for testing.

VI-4/ Controls carried out

N/A

VI-5/ Annexe

IV.4.3. Procedure of the method WVTR

Summary:

I / Objective:

The present procedure has objective of defining and describing the method WVTR and the parameters which can influence the determination of WVTR sealed bottles and blisters.

II / Area of application

The present procedure is applicable to the packaging of Clavodex tablets in blisters and Clavodex powder for oral solution in a bottle.

III /Responsibilities

The following are responsible for the execution of this procedure:

- The production operators on the nMX and RAV 05, production department,
- Maintenance staff ; maintenance department,
- The production operators and analysts in terms of control of integrity,
- The laboratory of quality control

IV/ Associated references and document

IV.1/ Reference:

- USP

IV.2/ Associated Documents:

- Versapem procedure for WVTR testing for sealed containers
- Procedure of use of the powder filling and capping machine- RAV05
- Procedure of the adjustments of the powder filling and capping machine RAV05
- Procedure of use of the blister machine - NMX
- Procedure of adjustments of the blister machine -NMX

V / Abbreviations and definitions

1. **Definition**
   - **Water vapour transmission rate –** is the measurement of passage of water vapour through a substance.
2. **Abbreviation**
   - **WVTR:** water vapour transmission rate
   - **USP :** united states pharmacopeia
   - **CI^{aire} :** conditionnement primaire

VI /Contents

VI.1/ General description of the method

It involves the determination of passage of water vapour across a package (bottle, blister....) introduced in an enclosure that has a gas circulation that detects the leakage of water vapour, the aim is to conclude on the quality of the seal and the integrity of the package.

VI.2/ Application of the method on glass bottle

Variation of Moisture permeability of glass bottles when the speed of the tightening head and the position of the tightening torque is increased.

VI.2.1/ The Adjustments of the powder filling and capping machine.

See –procedure of the adjustments of the powder filling and capping machine.

VI.2.2/ Determination of WVTR

- Place the bottles in an enclosure with gas circulation which detects the moisture vapour that comes from the bottles.

VI.3/ Application of the method on blisters

VI.3.1/ The adjustments of the blister machine NMX

See the procedure for adjustments of the blister machine NMX.

VI.3.2/ Determination of WVTR

Place blisters in an enclosure with gas circulation, it is this gas that detects the quantity of water vapour that escapes and quantifies it by various method according to the type of tester used.

VII/ Registration

VIII/Annexes

IV.4. Verification of conditions during the sample preparation process

IV.4.1. Normal values of temperature and humidity in the room

The values of temperature and humidity of the packaging room must be verified constantly. If there are any slight changes in these two parameters, production has to be stopped and measures taken to have the normal temperature and pressure of the room. The temperature and pressure are monitored by a Hygro-thermometer on the wall of the room and the values are noted down at intervals on a paper kept next to it.

Table below presents the normal values of temperature and pressure of the room:

Table VII: Normal room temperature and pressure

Parameter	Normal value
Temperature	20°C ≤ T≤ 24°C
Humidity	≤20%

IV.4.2. Results of adjustment of the blister machine NMX

To make sure that the samples were prepared in the right way, the parameters of the blister machine had to be controlled and the packaged samples produced also had to be controlled.

IV.4.2.1. Control of parameters of blister machine

The operators had to verify that the temperature of the sealing plate, sealing pressure and the moulding plate of the machine conform to those specified in the documents.

Table VIII: Results of the control of blister machine

Verification	Specification	Result
Temperature of sealing plate	170 -180 °C	170°C
Sealing pressure	6 bar	6 bar
N° of matrix used	3045-2	Verified

IV.4.2.2. Control of blister samples produced

The first blisters produced are verified to make sure they are properly sealed, the cavities are well formed and that they are no folds on the aluminium, the operators then had to test the integrity of the blister pack seals using the dye penetration test with the bell shaped chamber.

- **Integrity test**

- A sample of six blisters was taken by the operators to in process control laboratory.
- The blisters were immersed in the bell shaped chamber filled with a solution of 2% methylene blue and cold water. The pressure was reduced to -0.50 bar for two minutes.
- After two minutes the blisters were taken out and washed with running water.
- They were then dried using an absorbent paper and visually examined by the naked eye to verify the absence of penetration of the methylene blue solution into the blister.
- The operator then opens each blister to verifying the absence of penetration of the dye solution inside.

Table IX: Results from control of blister samples

Test applied	**Specification**	**Result**
Integrity and absence of folds on aluminium	Conform	Conform
Well formed cavities	Conform	Conform
Integrity of seal	Conform	Conform
Dye penetration test	Conform	Conform

IV.4.3. Results of the adjustment of the powder filling and capping machine

To make sure that the samples were prepared in the right way, the parameters of the powder filling and capping machine had to be controlled and the packaged samples produced also had to be controlled.

IV.4.3.1. Control of parameters of machine

On this machine the operators had to control the speed of the tightening head to assure that the bottles were not closed too tight or too loose. The speed of the tightening head used depended on the type of plastic cap used.

Table X: Results of the control of powder filling and capping machine

Verification	**Specification**		**Result**
	Cap type 2	**Cap type 3**	
Speed of rotating head	5	6-7	Conform

IV.4.3.2. Control of bottle samples produced

The first bottles produced are verified to make sure they are closed properly and that there is no water on the threads or the sealing surface of the bottle. It was necessary to also verify that the bottle had no cracks and the cap was not deformed in any way.

The operators proceeded to test the integrity of the seal using the bell shaped chamber. In this case the chamber was not filled with the methylene blue dye, instead it was left empty. Once the bottles where placed inside and the chamber closed, a vacuum of 0.2 bars was created for one minute. The bottles when then inspected for any water droplets on the outside.

Table XI: Results from control of bottle samples

Verification	**Specification**	**Result**
Integrity of sealed container	Conform	Conform
Integrity of closure	Conform	Conform
Absence of broken bottle or cap	Absent	Conform

V. Discussion

The subject of our study was suggested by CLP after complains on the presence of a yellow on the Clavodex product, signalling to them of a sign of instability and as their first option CLP went on to redo the stability studies of the product. The results of the stability studies were conclusive and as always within the normal values. This colour can only develop if the product comes in contact with humidity, with the knowledge that Clavodex is sensible to humidity, CLP thought that the problem can be linked to the packaging process, due to the alteration of one or more parameters during the operation of the packaging machine (blister machine or the powder filling and capping machine); for example the sealing parameters, which play a very important role in the packaging chain of this product since it determines the air tightness of the package to penetration of humidity.

So, we started our study by first looking at the possible causes of the deterioration. Our main focus turned to the packaging process of the product as this degradation is linked to moisture permeation.

Our first instinct was to study the types of materials used in the packaging of Clavodex tablets and powder for oral solution:

- For the Clavodex tablets packaged in an all foil blister pack, the materials used proved that the package is adequate to protect the tablets from moisture. The forming material used is an ALU, cold formable foil which is used for products that are susceptible to moisture and according to literature reviews it is the only material that provides 100% barrier to moisture. The lidding material is a push through aluminium foil, which has close to 0 moisture permeation.
- For the powder for oral solution packaged in a glass bottle sealed with a plastic screw cap, the materials also proved that the sealed container is enough to protect the package from moisture. The glass according to the USP is a type 3 regular soda lime glass, and glass is well known for being a good moisture barrier. The plastic cap used is reinforced by a polyethylene gasket which seals the junction between the two surfaces.

After the assurance that the type of materials used is enough to give protective packages to our product, we went on to study the integrity of the seals on the packages:

The forming and lidding material of the blister pack are heat sealed together and the quality of the seal is determined by the sealing temperature and pressure of the blister machine. A heat seal is strong and rigid but if the temperature doesn’t reach the stipulated degree it may compromise the seal strength of package.

For the sealed glass bottles the quality of the seal is determined by how tight or loose the cap is on the bottle, which is determined by the screwing force of the machine and how it is adjusted.

Seeing that the integrity of the seal is affected by the parameters of the machine, we went on to study the composition, operations and controls of the machines. This enabled us to come up with flowchart diagrams for both machines. The flowchart diagram represents the different steps of packaging and it helped us in comparing what must be done and what is done in reality. Our knowledge of how the machines function enabled us to establish a procedure for the adjustment of each machine and a procedure for the preparation of samples according to the WVTR method.

To assure that the samples were produced under the right conditions and meet the same quality the requirements as those required in actual production, we had to:

- Establish procedures : Procedure of adjustment of the blister machine- NMX, Procedure of the adjustment the powder filling and capping machine RAV 05,Procedure of the method WVTR
- Verify the conditions during the sample preparation method.

The normal values of temperature and humidity must always be in the given ranges; (between 20- 24 °C for the temperature and less than or equal to 20% for the humidity) in the packaging room. If the values go beyond these given limits an alarm will sound to warn the operators and the packaging operation is put on hold until the conditions are adjusted back to normal by the maintenance team.

From the results of control of parameters of the machines the:

- Temperature of sealing plate, sealing pressure, number of matrix used were all within the specified values for the blister machine
- Speed of rotation of the tightening head were according to the specification for powder filling and capping machine

From the results of control of samples produced the:

- Integrity and absence of folds on aluminium, well formed cavities, Integrity of seal, Dye penetration test of blister samples produced the results obtained were all up to standard
- Integrity of sealed container, Integrity of closure, absence broken bottle or cap of bottle samples the results conformed to the specifications.

These results confirmed to us that the produced samples had the required seal quality and the control of the samples reassured us that the samples had been produced according to good manufacturing practices as well as according to the test method requirements.

After the adjustment of all parameters and verifying controls, we prepared samples of bottles and blisters according to the WVTR method, respecting procedures

The samples were packed and put in storage, until they are send to the testing company. The industry could not send the samples for testing; due to internal problems, therefore we could not have the results from WVTR test.

Conclusion

Pharmaceutical industries are judged according to their capacity to produce products of good quality that guarantee the safety of the user and meet the stipulated shelf life, and the packaging of the pharmaceutical product plays an important role in meeting all these requirements. It is therefore important to perform tests on the packaging materials, the finished packaged product, as well as researching on the different parameters that can affect the quality of the product. In this context of searching for permanent improvement in the quality of the Clavodex products at CLP, we carried out this study on the preparation and validation of procedures for the adjustments of packaging machines and preparation of samples according to the WVTR method.

This study allowed us to illustrate that the search for quality first passes by the creation of an adequate environment, where the choice of materials and the packaging operation itself have a great influence on the quality of the product produced. The packaging equipment and how they are adjusted also must be reflected on, which leads us to the need to perform a study on the quality risk management of the packaging process of Clavodex to determine where the real problem is.

In conclusion the need to perform a WVTR test on the Clavodex products is great as the dye penetration test method used has proved to be insufficient. It is the results from the WVTR that will prove if the problem in degradation of Clavodex is due to moisture permeation in the package.

We recommend CLP to set up a quality risk analysis based on the method Failure Mode and Effects and Criticality analysis, which allows identification and evaluation of the risk and how to reduce or make it acceptable therefore, classifying the risks and putting in place the actions to manage the risks. It is an integral part of an efficient pharmaceutical quality system in the context of continuous improvement of the quality of their products.

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Annexes

Annexe 1: Preparation of samples of bottles according to the WVTR method

Water Vapour Transmission Rate Measurement on Sealed Containers – Sample Preparation.

1. Prepare and if required clean 10 -20 bottles and closures as they would be used in production. Do not use paper labels, but label each with a marker pen.
2. Place a piece of tissue paper or cotton wool into the bottle, to loosely occupy approximately 1/4 of the volume of the bottle. It is important that the material does not contain any water-soluble components, such as lanolin etc.
3. Add roughly 1/10 of the volume of the container in de-ionized or distilled water. So for a 200ml bottle, add 20 ml water. The amount of water is not critical, as it is there only to create a humid environment for the test.
4. Ensure the threads or sealing surface of the bottle are dry and close the bottle in the same way as it is carried out in production. Ideally this should be done on a production line. Alternatively it should be torqued or sealed in the laboratory under similar conditions to those in production.
5. Pack the bottles upright, and if glass, separated so that they are not broken. Desiccant is not necessary, but placing the samples in a plastic bag is helpful, especially if they are travelling by air.
6. Include all serial numbers and descriptions as are required on the report in the covering note, also the temperature required for the test. Although this is most commonly 30°C, please confirm.

Annexe 2: Procedure of use of blister machine NMX

PROCEDURE D'UTILISATION NMX :

I. OBJET :

Présentation de la thermo formeuse nMX, de ses différents composants, ainsi que le champ d'actions et les niveaux d'intervention des différents opérateurs; à fin d'assurer une utilisation correcte et un nettoyage (entretien) efficace de cet appareil.

II. DOMAINE D'APPLICATION :

Cette procédure s'applique sur la thermo formeuse « nMX » au niveau de l'atelier de blisterage (BOX: 309).

III. RESPONSABILITE :

L'operateur de la machine est responsable de l'application de cette procédure. Le superviseur de production, le responsable de production ainsi que les agents de maintenance veillent à l'application de cette procédure.

IV. REFERENCES ET DOCUMENTS ASSOCIES :

A. REFERENCE :

Manuel d'instructions nMX : Révision. DEC 2014.

B. DOCUMENTS ASSOCIES :

Log book de la thermo formeuse nMX.

V. DEFINITIONS ET ABREVIATIONS :

1. DEFINITIONS :

 Thermo formeuse nMX: la thermo formeuse nMX est une machine automatique conçue pour conditionner en « blister » différents médicaments solides oraux. Sa capacité de production est d'environ 500 blister/min, dans la mesure où les dimensions et la forme du produit le permettent. (figure: photo)

Fabricant : Partena
Modèle : nMX
Matricule : MX.211
Année de fabrication : 2014

 Ruban : le matériel de formage, le matériel de couverture et les deux quand ils sont soudés ensemble qui avancent le long de la machine.

 Le format : l'ensemble de un ou plusieurs blisters existant dans un pas de formage pour le conditionnement de un ou plusieurs produits.

 Pas de formage : la zone sur le ruban qui, à chaque cycle machine, est intéressée par le formage et la fermeture des alvéoles (environs 6 blisters/cycle).

2. ABREVIATIONS :

 ALU : Aluminium

 PVC : Polychlorure de vinyle

VI. LE CONTENU :

1. DESCRIPTION GENERALE :

A) COMPOSANTS DE LA MACHINE :

La machine est équipée des unités suivantes :

 Unité de formage : déformation à chaud ou à froid du matériau de formage, et comprend les groupes suivants:

- ✓ Transmission unité de formage ;
- ✓ Porte bobine matériau de formage ;
- ✓ Rouleaux de transfert matériau de formage ;
- ✓ Pince d'entrée poste de préchauffage ;
- ✓ Poste de préchauffage ;
- ✓ Poste de formage.

 Unité de transfert pinces et chargeurs : alimentation des produits dans les alvéoles individuels, et comprend les groupes suivants :

- ✓ Pince de sortie poste de formage ;
- ✓ Transmission unité de transfert pinces et chargeurs ;
- ✓ Système de transfert pinces et chargeurs.

 Unité de scellage : thermoscellage du matériau d'operculage avec le matériau de formage, et comprends les groupes suivants :

- ✓ Transmission unité de scellage ;
- ✓ Porte bobine matériau d'operculage ;
- ✓ Poste de scellage ;
- ✓ Poste de refroidissement ;
- ✓ Pince de sortie poste de scellage.

 Unité de découpe : découpe de la bande thermoscellée en blisters, et comprend les groupes suivants:

- ✓ Transmission unité de découpe ;
- ✓ Rouleaux de contraste ;
- ✓ Poste de perforation rotative ;
- ✓ Pince d'entrée poste de découpe ;
- ✓ Poste de codification ou perforation intermittent ;
- ✓ Poste de découpe ;
- ✓ Système de prise et lâcher blister ;
- ✓ Système de transfert blisters.

B) ZONES DE TRAVAIL :

Toute zone à proximité d'une machine, où les opérateurs sont appelés à accomplir leurs tâches, est appelée zone de travail, et comprend :

Zone A :

- Mise sous/hors tension de la machine ;
- Commande du fonctionnement en mode automatique ou en mode manuel ;
- Remplacement des bobines du matériau de formage et d'operculage ;
- Réarmement de la machine en cas d'arrêts.

Zone B :

- Chargement du produit dans le préalimentateur.

Zone C :

- Réarmement de la machine en cas d'arrêt provoqué par bourrage de blisters sur le tapis de transfert.

(Figure p 12 chap3)

C) INTERFACE OPERATEUR-MACHINE :

Moyen de communication entre l'operateur et la machine, comprend :

- Panneau de mise sous/hors tension de la machine.
- Clavier de commande regroupant les boutons poussoirs, les sélecteurs d'actionnement et de réglage de la machine, dans lequel le panneau opérateur est intégré. (sélections : figure 15/16/17 page 15/16 chapitre 8 ASEM)
- Clavier de commande dans la zone de sortie blisters permettant l'arrêt en phase et l'arrêt d'urgence (position ½ p83 chap8) dans cette zone de travail.

(Figure page 16 chap3)

D) DISPOSITIFS D'AVERTISSEMENT ET DE SIGNALISATION :

La machine est équipée de dispositifs d'alerte et de signalisation suivants :

Signalisation sonore : générée par une sonnerie et s'active :

- En appuyant sur le bouton de marche automatique ;
- Lorsque le niveau minimal produit et matériau de formage et/ou d'operculage est atteint.

Signalisation lumineuse : signal lumineux sur la verrine à couleur :

- Lumière rouge : arrêt à cause d'une alarme ;
- Lumière orange : attente de redémarrage de machine en aval ;
- Lumière verte : machine en marche ;
- Lumière blanche : machine sous tension

Pictogrammes :
Avertissement : rappel sur des arguments significatifs
Danger d'électrocution
Danger de nature mécanique
Danger de nature mécanique
Danger pour transport de charges suspendues
Danger d'écrasement des mains
Danger de coupures aux mains

SYSTEMES DE CONTROLE DE LA THERMOFORMEUSE :
1. Contrôle produit hors alvéole S43 : a pour fonction de détecter les produits, les fragments de produits ou les corps étrangers présents sur la bande formée ou, mal positionnés dans l'alvéole. Cette tâche de contrôle est effectuée par effleurage du matériau de formage par une lame mobile (pos 1 p38 chap8+ figure).

2. Contrôle présence matériau de formage B0 : (pos7 p14 chap8) qui arrête la machine en phase lorsque la bobine est épuisée en affichant un message d'alarme.

3. Contrôle niveau minimal matériau de formage B1 : (pos6) qui alerte l'opérateur du changement bobine imminent par un signal sonore et lumineux ainsi qu'un message d'alarme affiché sur l'écran.

4. Contrôle jonction sur le matériau de formage B6 : (pos9 p14 chap8) qui détecte la présence du ruban adhésif thermosoudable utilisé pour la jonction des deux bouts des bobines. La cellule photoélectrique transmet l'information à l'automate ; celui-ci commande ensuite le rejet des blisters et l'arrêt du chargeur. Le réglage de la sensibilité de cette cellule s'effectue par l'intermédiaire du bouton (pos10).

5. Contrôle présence matériau d'operculage S30 : (pos7 p42 chap8) arrêtant la machine en phase lorsque la bobine est épuisée, un message d'alarme est affiché sur l'écran.

6. Contrôle niveau minimal matériau d'operculage B3 : (pos6) qui alerte l'opérateur du changement de bobine par un signal sonore et lumineux ainsi que la visualisation d'un message d'alarme.

7. Contrôle jonction sur le matériau d'operculage B7 : (pos8) qui détecte la présence du ruban adhésif thermosoudable utilisé pour la jonction des deux bouts des bobines. La cellule photoélectrique transmet l'information à l'automate ; celui-ci commande ensuite le rejet des blisters et l'arrêt du chargeur. Le réglage grosso-modo de la sensibilité de la cellule s'effectue à la fois, par l'intermédiaire du bouton (pos12).

8. Contrôle pas sur la pince de sortie poste de scellage : Ce dispositif détecte la position correcte du matériau formé (ce matériau doit avancer d'un pas « P » à chaque cycle de machine) ainsi que la présence d'éventuels objets entre les plaques de scellage inférieurs et supérieurs, par l'intermédiaire de quatre capteurs **(S33, S33A, S33B, S33C).** A chaque fois que l'un de ces quatre capteurs s'éteigne, la machine s'arrête en phase, le poste de scellage s'ouvre immédiatement et un message d'alarme s'affiche sur l'écran.

9. Contrôle présence de produit avec vidéo caméra « SEA VISION»: compare le pas de formage roulant en dessous des télé-caméras, durant le cycle productif, avec le « pas de formage étalon ». en cas de discordance ou de

valeurs hors plage, le système localise les blisters défectueux et génère les signaux d'éjection.

10. Contrôle nombre de pas entre le contrôle présence de produit et l'éjection blisters S68 : qui vérifie que le nombre de pas entre l'axe de lecture du dispositif de contrôle présence du produit et l'axe du poste de découpe correspond à celui définie par le format en cours de production. Il est composé d'une roue monté sur un chariot coulissant (pos p52 chap8) détectant l'anse maximale et minimale créée par la bande thermosoudée à l'entrée du poste de découpe. La thermoformeuse s'arrête en phase et un message d'alarme s'affiche à chaque fois que l'excursion de la roue dépasse les valeurs seuils.

11. Système d'éjection des blisters vides et incomplets : a pour fonction de détourner les blisters non conformes, détectés par le dispositif de contrôle présence de produit dans le convoyeur (pos1 p74 chap8). Il est pourvu de :

✓ une cellule photoélectrique **B7D** (pos2 p74 chap8) qui détecte le passage et autorise le rejet, positionnée sur un support réglable. Un réglage grosso-modo de la sensibilité de la cellule détermine l'espace séparant entre deux blisters. Une éjection de blisters bons pourrait être justifiée par une double lecture du blister résultante d'un réglage trop soigné de la sensibilité de cette cellule ;

✓ un dispositif d'éjection à jet d'air et un dispositif de détournement (pos4 et 5), qui s'activent en rejetant les blisters vides ou incomplets.

12. Système d'interception des blisters non éjectés : a pour fonction de détecter et dévier, sur le convoyeur (pos4 p76) les blisters vides ou incomplets n'ayant pas été éjectés dans le convoyeur (pos3). Il est composé de :

✓ Trois cellules photoélectriques **B4C, B4D** (pos8) et **B9D** (pos9) qui arrêtent la machine en phase en générant une alarme, lors de l'interception d'un passage de blisters vides ou incomplets, et autorisent le détournement ;

✓ Un dispositif de rejet à jet d'air (pos2) qui détourne les blisters sur le convoyeur de ramassage (pos4).

13. Système de détournement des blisters bons : ce système s'active à l'arrêt de la machine en aval et a pour fonction de dévier les blisters bon sur le convoyeur (pos 5 p78). Il est muni d'une cellule photoélectrique **B1C** (pos7) qui autorise le détournement ainsi qu'un dispositif de rejet à jet d'air qui détourne les blisters sur le convoyeur de ramassage.

14. Dispositifs de contrôle niveau minimal produit :

✓ Au niveau du pré-alimentateur : le détecteur **B2** (pos2 p32 chap8) alerte l'opérateur, par un signal sonore et un message d'alarme

lorsque l'approvisionnement de la trémie de chargement (position), descend en dessous du niveau minimal préétabli.

✓ Au niveau du chargeur à plaque : lorsque le niveau produit dans le chargeur est insuffisant, le dispositif de contrôle **S47** (pos2 p34 chap8) active le vibreur linéaire (pos4 p32 chap8) pour convoyer le produit à l'intérieur du chargeur. Une fois le niveau est rétabli, le vibreur s'arrête.

2. MODE D'UTILISATION :

A) VERIFICATIONS PRELIMINAIRES ET MONTAGE :

Avant chaque mise en marche, l'operateur se doit d'effectuer les opérations préliminaires dans l'ordre suivant :

 Vérifier que tous les carters ainsi que les protecteurs mobiles et fixes de sécurité sont fermés ;

 Vérifier l'alimentation de la machine ;

 Mettre la machine sous tension (tourner le sélecteur à clé vers la droite et appuyer sur la touche lumineuse blanche) (figure p86 chap8);

 Vérifier la pression d'air (6-8 bars) et d'eau (1-2.5 bars) et qu'il n'y a pas de fuite ;

 Vérifier la propreté du préalimentateur (figure p32 chap8) puis vérifier et monter le canal de descente, la trémie de chargement (photo), le rouleau d'arasement et le chargeur à plaque du produit canalisable (figure p34 chap8 ou p16/17/60 chap9);

 Appuyer sur la touche reset en bleu (bouton poussoir de réarmement) sur le clavier de commande (figure p85/86 chap8) ;

 S'identifier dans le panneau operateur en utilisant l'accès utilisateur Admin (**mot de passe** : Ad1023) (figure 6/7/8/9 page 8/10 chapitre 8 ASEM)

 Effectuer un changement de format si nécessaire (voir procédure de changement de format) et/ou un changement de poinçons (nouveau lot).

 Attendre que les températures de formage (cas d'un format ALU/PVC) aient atteint (130˚) et celle du scellage (170˚) ;

 Appuyer sur le bouton poussoir de mise en marche en mode automatique pour commencer le cycle productif.

B) MISE EN MARCHE :

i. Mode de marche :

Deux modalités de marche sont possibles sur la thermoformeuse :

 Marche en mode automatique : la thermoformeuse marche en continu suivant les paramètres saisis. l'actionnement se fait en appuyant sur le bouton de marche en mode automatique (position).

 Marche en mode manuel : la thermoformeuse exécute uniquement quelques phases individuelles du cycle de conditionnement standard. Ce mode de marche est habilité en tournant vers la droite le sélecteur de marche par à-coups (position).

L'actionnement se fait en appuyant sur la touche mobile de marche par à-coups positionné sous le plan de chargement. (image des positions p82/85 chap8)

ii. Essais à vide :

L'essai à vide permet de s'assurer du bon fonctionnement de la machine, vérifier la découpe des blisters, le marquage, le formage, le scellage ainsi que le positionnement correcte des bobines. Il s'effectue comme suite :

 Désactiver la camera ;

 Désactiver l'accouplement en aval ;

 Désactiver le chargeur à plaque ;

 Diminuer la vitesse ;

 Appuyer sur le bouton mise en marche en mode automatique et effectuer les vérifications nécessaires.

 Arrêter la machine en appuyant sur le bouton d'arrêt en phase (position).

iii. Démarrage du lot :

Avant de démarrer proprement le lot, charger le produit dans le préalimentateur et activer le chargeur. Appuyer sur le bouton marche, effectuer un essai en présence du produit et un test d'étanchéité.

Effectuer l'opération de conditionnement primaire (blisterage) sans oublier les contrôles de conformité nécessaires, à savoir :

 Un test d'étanchéité de 6 blisters (selon le format adopté) chaque 30 minutes ;

 Un contrôle visuel de 18 blisters chaque 15 minutes.

iv. Réglage :

Pendant l'opération de conditionnement, l'operateur de la machine est habilité à effectuer certains réglages sur la thermoformeuse ; entre autre :

 La vitesse de la machine ;

 L'intensité de la vibration du préalimentateur lorsque le niveau du produit dans le chargeur n'est pas adéquat ;

 Le capteur de niveau du produit qui contrôle le fonctionnement du préalimentateur ;

 La vitesse du rouleau d'arasement qui oriente et convoie le produit dans les canaux de descente.

(Page 15/16 chapitre 8 ASEM tableau réglages usuels position 12/1/5)

v. Fin du lot et mise hors tension de la machine :

 Quand le produit d'un lot s'épuise, appuyer sur le bouton d'arrêt en phase pour arrêter la machine et effectuer un vide de ligne (voir procédure de vide de ligne).

 En fin de journée, après épuisement du produit présent dans le préalimentateur, mettre la machine hors tension, après l'avoir arrêté, en tournant à gauche le sélecteur de tension. Attendre 15 minutes avant de couper/isoler le circuit de refroidissement.

Remarque : Après avoir éteint le panneau operateur, il est nécessaire d'attendre au moins 5 minutes avant de pouvoir le rallumer.

vi. Cas particuliers :

 Procédure de changement de poinçons :

Avant de commencer un nouveau lot effectuer un changement de poinçons selon les étapes suivantes :

✓ Desserrer puis retirer le moule de codage ;

✓ A l'aide d'une clé Allen, dévisser les vis (figure p64 chap8) sur le porte-poinçons pour libérer les poinçons ;

✓ Retirer les anciens poinçons à l'aide d'une pince ;

- ✓ Placer les nouveaux poinçons selon les instructions du dossier de conditionnement ;
- ✓ Remplir les espaces vides avec les cales ;
- ✓ Serrer les vis du porte-poinçons puis placer le moule de codage et serrer la manette.

Procédure de changement de bobines :

Lorsque la machine est à l'arrêt en phase pour épuisement de bobine ou au vouloir de l'operateur, adopter la procédure suivante pour remplacement de :

Bobine-matériau de formage : (ALU/PVC)

- ✓ Bloquer le matériau de formage en tournant le levier (position) en sens horaire ;
- ✓ Exécuter la découpe du matériau de formage en agissant sur le poigné (position) ;
- ✓ Débloquer manuellement la bobine épuisée sur l'arbre de détente et l'enlever ;
- ✓ Installer la nouvelle bobine et s'assurer qu'elle soit bien centrée ;
- ✓ Dérouler le matériau, en suivant le schéma indiqué sur la machine, jusqu'à le faire passer en dessous du rouleau de blocage (position) ;
- ✓ Bloquer l'extrémité initiale de la bobine en tournant le levier (position) en sens horaire, puis effectuer la découpe en agissant sur le poigné;
- ✓ Joindre les deux extrémités à l'aide d'un ruban adhésif thermoformable et débloquer le matériau en tournant les leviers en sens inverse ;
- ✓ Démarrer à petite vitesse pour éliminer la jonction, puis reprendre le cycle productif. (figure p13/14 chap8)

Bobine-matériau d'operculage : (ALU)

- ✓ Ouvrir le protecteur mobile face au porte bobine ;
- ✓ Effectuer une découpe rectiligne du film d'operculage ;
- ✓ Débloquer la bobine épuisée sur l'arbre expansible et l'enlever ;
- ✓ Insérer la nouvelle bobine et s'assurer qu'elle soit centrée et la bloquer ;
- ✓ Exécuter la découpe rectiligne du film de la nouvelle bobine, puis superposer les deux extrémités et les joindre à l'aide d'un ruban adhésif thermoformable et le dérouler en suivant le schéma indiqué sur la machine

En cas de matériau d'operculage ayant des spots de repère pour le dispositif de centrage d'impression, effectuer la jonction en superposant les extrémités de telle façon à faire coïncider les deux spots de repère ;

- ✓ Soulever manuellement le balancier pour enrouler et tendre le matériau, puis relâcher ;
- ✓ Fermer le protecteur mobile, démarrer à petite vitesse pour éliminer la jonction, puis reprendre le cycle productif. (figure p42 chap8)

Procédure de changement de format :

Avant d'effectuer un changement de format, déterminer, à l'aide d'une fiche de changement de format, les parties à remplacer, s'approvisionner de ces parties ainsi que de matériaux de conditionnement et de produits.

Adopter la procédure suivante pour effectuer un changement de format :

- ✓ Exclure les dispositifs de contrôle présence de produit, le fonctionnement du chargeur, le poste de scellage ainsi que l'accouplement en aval ;
- ✓ Démonter la grille, le chargeur à plaques et les dispositifs de contrôle pour remplacer les pièces du format à adopter;

✓ Enlever les matériaux de conditionnement en les coupant en amant du poste de formage et de scellage ;
✓ Démonter l'unité de formage et de scellage, effectuer un changement de poinçons, de matrices, de plaques de formage et de scellage, ainsi que les autres pièces du format. Les monter dans le sens inverse du démontage ;
✓ Régler le pas machine en se servant du connecteur pour MARCHE PAR A COUPS ;
✓ Introduire les matériaux de conditionnement correspondants au format ainsi que les dispositifs de contrôle et créer la ligne ;
✓ Démonter les rouleaux et la plaque de contraste, le guide de frictionnage, le poste de perforation, le poste de découpe, l'outil de codage et le disque de format ;
✓ Démonter la tige de contrôle nombre de pas ;
✓ Monter l'unité de découpe dans le sens inverse du démontage ;
✓ Insérer la bande thermosoudée dans l'unité de découpe, régler la pince pour centrer la découpe ;
✓ Monter la grille et le chargeur à plaque correspondant au format ;
✓ Régler les guides du groupe de courroies sur la machine en aval ;
✓ Sélectionner le format monté à présent sur le dispositif de contrôle présence de produit puis activer le mode automatique du chargeur ;
✓ Activer le préalimentateur, le chargeur et l'accouplement en aval ;
✓ Introduire le produit dans le préalimentateur et le chargeur. La machine est prête pour la production.

Autres : gestion des principaux problèmes rencontrés pendant les opérations de blisterage : Problèmes :	**Actions correctives :**
□ Coupure de courant	✓ Attendre 5 minutes avant la remise sous tension de la machine.
□ Alarme fin matériau de formage et/ou d'operculage	✓ Remplacer les bobines épuisées selon la procédure de changement de bobines. ✓ Effectuer une jonction du film en cas de déchirure
□ Produit hors alvéole	✓ Dégager le plan machine des corps étrangers/ fragments produits et loger correctement le produit dans les alvéoles. ✓ Vérifier l'emplacement du produit sous la camera de contrôle.

□ Surcharge scellage sur les capteurs S33	✓ Centrer le film et enlever l'objet oublié entre les deux plaques de scellage. ✓ Nettoyer la plaque de scellage, après refroidissement, et contrôler qu'il n'y a plus de produits hors alvéole.
□ Arrêt de la machine en aval	✓ Redémarrer la machine en aval ou désactiver l'accouplement en aval.
□ Alimentation irrégulière du produit dans la trémie	✓ Vérifier s'il y a présence d'un fragment du produit coincé dans la plaque de canalisation et l'enlever. ✓ Vérifier la charge de la trémie puis positionner le capteur S47 (position 2 p34 chap8) pour régler l'alimentation de la plaque ou agir sur la vitesse de vibration du bol.

Distribution irrégulière ou manque du produit dans les alvéoles	✓ Vérifier la position et ou le fonctionnement du chargeur. ✓ Vérifier la présence d'un fragment du produit dans la plaque de distribution du produit (photo) et l'enlever.
□ Bourrage entrée magasin blisters B16 (position photo arrière et p80 chap8)	✓ Arrêter la machine, vérifier le magasin de blisters et le dégager du bourrage.
□ Anomalie de flux des blisters sur les convoyeurs de sortie B5D □ Ejection de blister incomplet non effectuée. B9D B4D B9D	✓ Vérifier à l'endroit des capteurs indiqués dans le message d'alarme, et les vider de blisters. ✓ Vérifier la position des capteurs. ✓ Eliminer la cause et appuyer sur le bouton de réarmement et mise en marche de la machine.

Alarme contrôle présence de produit	✓ Vérifier si le dispositif de contrôle est positionné correctement.
Blister mal formé et/ou test d'étanchéité du blister non conforme	✓ Vérifier l'état et la position des bobines matériaux de formage et d'operculage. ✓ Vérifier le poste de formage et de scellage. ✓ Vérifier l'unité de découpe et de perforation.
Pince hors pas S34 (position1 p51 chap8)	✓ Positionner correctement la pince à la sortie du poste de scellage.
Nombre de pas erroné entre l'axe du dispositif de contrôle du produit et l'axe de découpe.	✓ Positionner correctement la bande thermoformée par rapport à la pince dans le poste de découpe, de façon à ce que le nombre de pas soit celui préfixé.

Distribution irrégulière ou manque du produit dans les alvéoles	✓ Vérifier la position et ou le fonctionnement du chargeur. ✓ Vérifier la présence d'un fragment du produit dans la plaque de distribution du produit (photo) et l'enlever.
Bourrage entrée magasin blisters B16 (position photo arrière et p80 chap8)	✓ Arrêter la machine, vérifier le magasin de blisters et le dégager du bourrage.
Anomalie de flux des blisters sur les convoyeurs de sortie B5D Ejection de blister incomplet non effectuée. B9D B4D B9D	✓ Vérifier à l'endroit des capteurs indiqués dans le message d'alarme, et les vider de blisters. ✓ Vérifier la position des capteurs. ✓ Eliminer la cause et appuyer sur le bouton de réarmement et mise en marche de la machine.

□ Alarme contrôle présence de produit	✓ Vérifier si le dispositif de contrôle est positionné correctement.
□ Blister mal formé et/ou test d'étanchéité du blister non conforme	✓ Vérifier l'état et la position des bobines matériaux de formage et d'operculage. ✓ Vérifier le poste de formage et de scellage. ✓ Vérifier l'unité de découpe et de perforation.
□ Pince hors pas S34 (position1 p51 chap8)	✓ Positionner correctement la pince à la sortie du poste de scellage.
□ Nombre de pas erroné entre l'axe du dispositif de contrôle du produit et l'axe de découpe.	✓ Positionner correctement la bande thermoformée par rapport à la pince dans le poste de découpe, de façon à ce que le nombre de pas soit celui préfixé.

C) DEMONTAGE :

Le démontage s'effectue dans l'ordre inverse du montage.

D) LE NETTOYAGE :

La thermoformeuse NMX nécessite trois types de nettoyage :

- ✓ Nettoyage quotidien
- ✓ Nettoyage hebdomadaire
- ✓ Nettoyage de fin de compagne

i. Nettoyage quotidien :

✓ Aspirer, à l'aide d'un aspirateur, l'intérieur de la machine à savoir : la trémie de chargement, le bol vibrant, le canal de descente et le plan de chargement, et les nettoyer avec gaz sèche ;

✓ Dépoussiérer la plaque de scellage après refroidissement ;

✓ Nettoyer la camera, la plaque de refroidissement, le site de découpe et le tapis de sortie des blisters ;

✓ Nettoyer les carters et les surfaces en inox avec une gaze humide puis sécher avec une gaze sèche.

ii. Nettoyage hebdomadaire :

En plus du nettoyage quotidien :

- ✓ laver à l'eau la plaque de canalisation, le rouleau d'arasement, la trémie et la cuvette ;
- ✓ souffler les pièces lavées avec l'air comprimé puis sécher avec une gaze sèche.

iii. Nettoyage de fin de compagne :

En plus du nettoyage quotidien :

- ✓ Toutes les pièces démontables sont lavées à l'eau, puis soufflées et séchées ;
- ✓ Désinfecter les parties du format en contact directe avec le produit à l'aide d'une gaze humidifié par une solution détergente compatible avec le matériau à nettoyer.

E) VIDE DE LIGNE :

A chaque fin de lot, l'opérateur doit procéder de la manière suivante :

- ✓ Vider la trémie de chargement, le bol vibrant et le canal de descente ;
- ✓ Vider le plan de chargement et le tapis convoyeur de blisters ;
- ✓ Vider la zone de marquage blisters et changer les poinçons ;
- ✓ Vider les corbeilles de récupération du déchet de découpe et de blisters vides ;
- ✓ Vider les bacs de reblistère et de comprimés non conformes ;
- ✓ Vérifier le vide sur toute la zone de travail de la machine et en dessous de celle-ci.

Abstract

The role of packaging is to preserve and protect a drug from contamination and degradation, so the drug retains its therapeutic efficacy. All manufacturers do their best to provide protective packaging for moisture-sensitive medications, but sometimes the drug may not reach its intended life. This is the case of the product Clavodex CONTINENTAL PHARM laboratory (CLP), for which an alteration of the tablets and powder was found on finished product in its packaging. This thesis presents the approach taken by CLP to verify the quality and integrity of packaging using the WVTR method, to achieve it, we have established procedures for the adjustment of packaging machines and a procedure for the preparation of samples for testing, thus checking the conditions of their preparation. At the end we prepared the samples in accordance with the established procedures and good manufacturing practices, to control them and then send them for the WVRT test.

Keywords: packaging, Clavodex, WVRT, good manufacturing practices.

Résumé

Le conditionnement a pour rôle de préserver et de protéger un médicament de la contamination et de la dégradation, ainsi le médicament conserve son efficacité thérapeutique. Tous les fabricants font de leur mieux pour fournir et assurer un emballage de protection pour les médicaments sensibles à l'humidité, mais parfois le médicament peut ne pas atteindre sa durée de vie prévue. C'est le cas du produit Clavodex du laboratoire CONTINENTAL PHARM (CLP), pour lequel une altération du produit comprimé et poudre a été constaté sur produit fini dans son emballage. Cette thèse présente l'approche adoptée par CLP pour vérifier la qualité et l'intégrité du conditionnement à l'aide de la méthode WVTR, pour la réaliser, nous avons établi des procédures pour l'ajustement des machines d'emballage et une procédure pour la préparation des échantillons pour test, ainsi vérifier les conditions de leur préparation. À la fin nous avons préparé les échantillons conformément aux procédures établies et aux bonnes pratiques de fabrication, les contrôler puis les envoyer pour faire le test de WVRT.

Mots clés : conditionnement, Clavodex, WVRT, bonnes pratiques de fabrication.

نبذة مختصرة

يتمثل دور العبوة في الحفاظ على الدواء وحمايته من التلوث والتدهور ، لذلك يحتفظ الدواء بفعاليته العلاجية. يبذل جميع المصنّعين قصارى جهدهم لتوفير عبوات واقية للأدوية الحساسة للرطوبة ، ولكن في بعض الأحيان قد لا يصل الدواء إلى العمر المقصود منه. هذه هي حالة منتج Clavodex CONTINENTAL PHARM (CLP) ، حيث تم العثور على تغيير للأقراص والمسحوق على المنتج النهائي في عبوته. تعرض هذه الأطروحة النهج الذي تتبعه CLP للتحقق من جودة وسلامة العبوة باستخدام طريقة WVTR ، ولتحقيق ذلك ، وضعنا إجراءات لتعديل ماكينات التعبئة والتغليف وإجراءات لإعداد عينات للاختبار ، وبالتالي التحقق من الظروف من تحضيرها. في النهاية ، قمنا بإعداد العينات وفقًا للإجراءات المعمول بها وممارسات التصنيع الجيدة ، للتحكم فيها ثم إرسالها لاختبار WVRT.

الكلمات الرئيسية: التغليف ، WVRT ، Clavodex ، ممارسات التصنيع الجيدة.