POLITECNICO DI TORINO

Master Degree in Biomedical Engineering

Validation of the injection molding process to produce the primary packaging of tissue heart valves

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ABSTRACT

Nowadays medical device companies that need a high degree of fulfillment of the specified requirements, i.e. a high quality, of product/service, must manage properly the company's manufacturing processes. In particular, the focus is to analyze in advance the conditions of the production process in order to establish the features, constraints and parameters (also called the "process window") that guarantee the desired level of quality of the process output. For this reason every company has to validate all its manufacturing processes when the output of these processes cannot be verified by further inspection activities (visual or dimensional measurement) with potential shortcomings to appear during product use. Through validation it is given the objective evidence that a specific process is capable to provide a product compliant to specified requirements in a repeatable way.

This work is focused on the re-validation of the injection molding process used to produce the components of the tissue heart valve sterile barrier. The sterile barrier is the primary packaging of the heart valve and provides its aseptic preservation until the implant in the patient. This re-validation is needed since the injection molding equipment used to obtain these components has been changed.

Firstly, the validation technical protocol was developed. This is a document that establishes how the validation will be conducted and that foresees three operative phases: Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). The aesthetical requirements of the components, used during the validation, are also defined through an improved visual inspection procedure.

The results of the operative phases of validation are collected and analyzed in order to assess if the process is still capable to produce an output within specifications after changing the injection molding equipment.

1 INTRODUCTION

This thesis is the final work of a stage period of about three months performed in HV (Heart Valves) R&D department of LivaNova (Sorin Group Italia S.r.l.) in Saluggia (VC), one of the biggest industries in the world in prosthetic heart valves production.

This work is carried out on the re-validation of injection molding process after an equipment change, particularly the injection molding machine.

This re-validation aims to carry out a series of tests to validate the injection molding process for the production of different high-performance plastic objects, i.e., components that are part of the primary packaging of LivaNova tissue heart valves. They are critical components because they require prolonged contact with implantable cardiac surgery devices and because they have to preserve the sterility of these implantable devices.

These components are manufactured by an external supplier; the data obtained by the external supplier have been crossed with data directly collected on the components in order to perform the validation activities.

Firstly, it is given a short background on the heart valves, their disease and the prosthetic heart valves. Then the Tissue Heart Valve (THV) sterile barrier is described focusing on the raw material and the manufacturing technique of the components object of this study.

After that, the focus is moved on developing the validation technical protocol, that is based on the three validation phases of Installation Qualification, Operational Qualification and Performance Qualification.

Finally, the validation activities are performed, and the results are collected to assess if the process is still capable to produce the components of THV sterile barrier within specifications after changing the injection molding equipment.

2 BIBLIOGRAPHY

2.1 BACKGROUND

2.1.1 CARDIAC HEART VALVES

The heart is the main organ of the circulatory system and it is formed by four chambers. The two at the top, the atria, receive blood that is returning to heart from veins and transfer it to the lower chambers, the ventricles. Ventricles generate the pressure needed to pump blood inside arterial vessels. The left atrium (LA) and left ventricle (LV) form the left heart, while the right atrium (RA) and right ventricle (RV) form the right heart. Left and right atria and ventricles are separated by a wall called atrioventricular septum, which prevents right heart blood to mix with left heart blood.

Between atrium and ventricles and between ventricles and blood vessel there are four heart valves, as shown in Figure 2.1:

- The two atrioventricular (AV) valves, the mitral valve (bicuspid valve), and the tricuspid valve, which are between the upper chambers (atria) and the lower chambers (ventricles).
- The two semilunar (SL) valves, the aortic valve and the pulmonary valve, which are in the arteries leaving the heart.

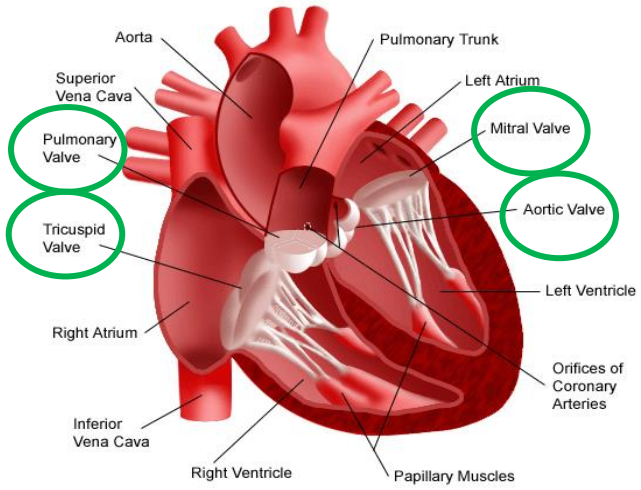

Figure 2.1. Interior view of the heart

The mitral valve and the aortic valve are in the left heart; the tricuspid valve and the pulmonary valve are in the right heart.

The cardiac valves are composed by fibrous tissue coated by endocardium, which is squamous epithelium continuous with the endothelium of blood vessels. They are structured in leaflets or cusps surrounded by fibrous rings of the cardiac skeleton.

Their function is to guarantee the unidirectionality of the blood flow from the atria to the ventricles and from the ventricles to the blood vessels, as shown in Figure 2.2. Their closure and their opening are totally driven by blood pressure, without any nervous or muscular control.

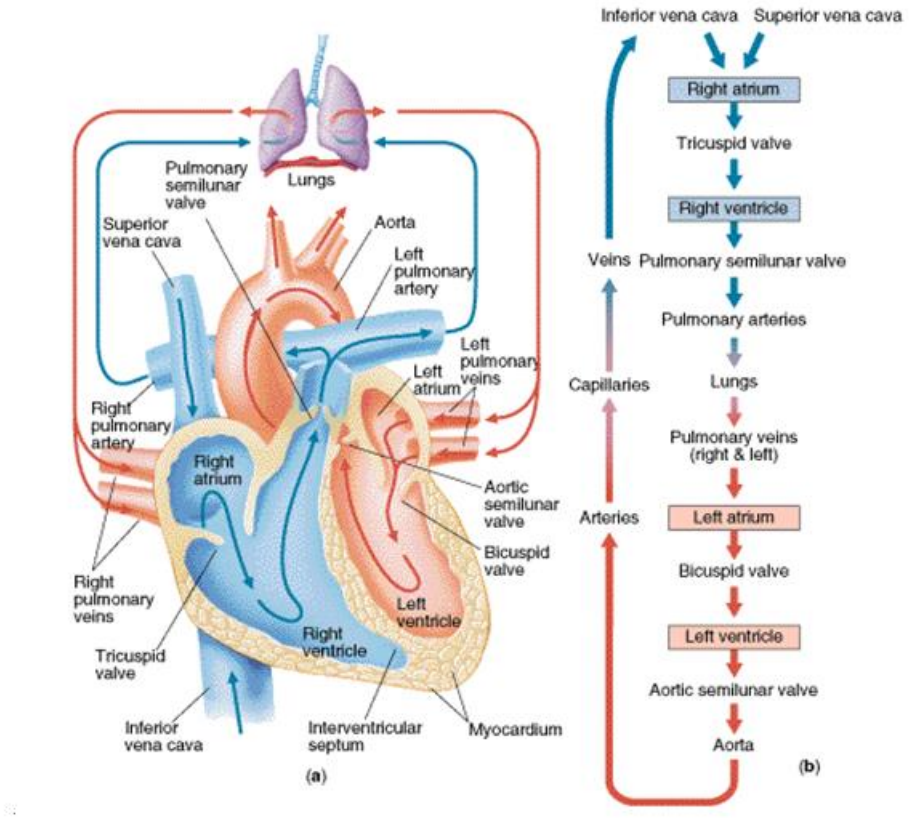

Figure 2.2. Blood flow

Mitral valve, also known as bicuspid valve, (see Figure 2.3) has two flaps and has the subvalvular apparatus composed by chordae tendineae anchored to papillary muscles located in the internal wall of ventricles. This apparatus prevents the prolapse of the valve into the atrium. A normally functioning mitral valve opens in atrial diastole when the arterial blood has fulfilled the left atrium and it causes enough pressure. After that, there is atrial systole in

order to eject the remaining blood from atrium. Then the mitral valve closes to avoid that blood flows in the wrong sense.

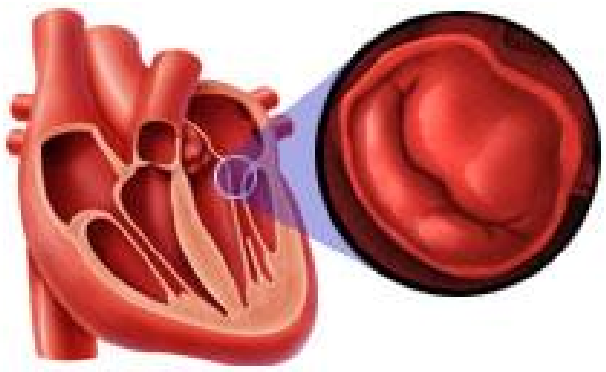

Figure 2.3. Mitral valve

Tricuspid valve has the same characteristic of the mitral one except for to be located between the right atrium and right ventricle and for to have three faps (see Figure 2.4).

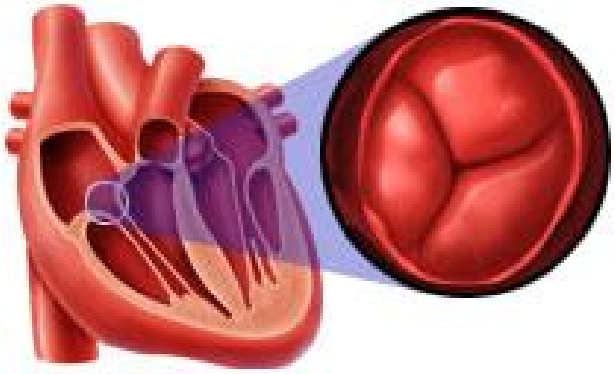

Figure 2.4. Tricuspid valve

Aortic valve is located between the base of the aorta and the left ventricle outflow tract (LVOT) and has three half-moon shaped cusps: the left coronary cusp, the right coronary cusp, and the non-coronary cusp (see Figure 2.5). In a functional aortic valve during ventricular systole there is an increase of pressure in the left ventricle and when the pressure is greater than the pressure in the aorta, the aortic valve opens, and the blood reaches the aorta. After the ventricle systole, the pressure of the aorta and of left ventricle increases and drops, respectively.

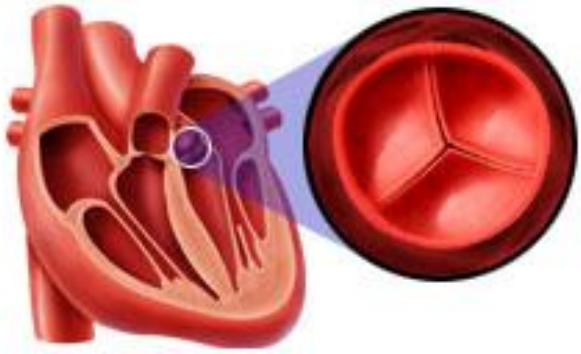

Figure 2.5. Aortic valve

Pulmonary valve work as well as the aortic one with the difference that it divides right ventricle from pulmonary trunk[1] (see Figure 2.6).

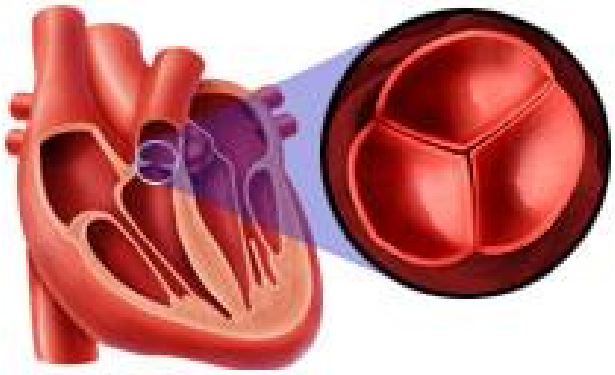

Figure 2.6. Pulmonary valve

2.1.2 AORTIC AND MITRAL VALVES DISEASES

The valvular heart diseases (VHD) are valve stenosis in which valve does not open all the way so not enough blood passes through it, and valve insufficiency in which valve does not close all the way so blood leaks backwards.

It is important to have the appropriate work-up for patients with VHD that includes a through history for evaluation of causes and symptoms, accurate assessment of the severity of the valvular abnormality by proper diagnostic test, and quantification of the severity of valve dysfunction and therapeutic interventions, if necessary. Particularly, diagnosis tests include chest radiography, electrocardiography, echocardiography, cardiac catheterization, exercise testing.

2.1.2.1 AORTIC VALVE STENOSIS

Aortic valve stenosis is the most prevalent form of cardiovascular disease in the Western world after hypertension and coronary artery disease. It is a condition in which the aortic valve has become narrowed or constricted (stenotic) and does not open-and-close properly (see Figure 2.7). The leaflets may be calcified, thickened, have reduced their mobility and thus restricted opening.

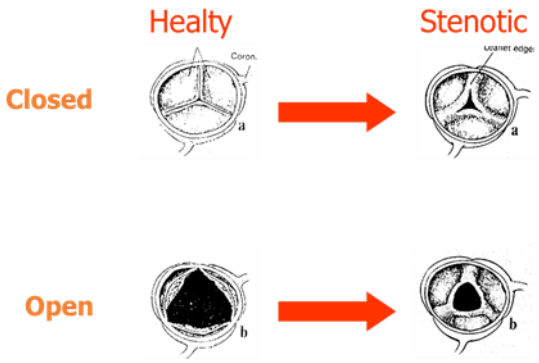

Figure 2.7. Aortic valve stenosis

The cause of aortic valve stenosis can be congenital in which valve are malformed at birth and complications (i.e. calcification, cups prolapse, etc.) appear later in the life, or acquired in which disease develops during the lifetime of the patient. In this last case the disease can be

- infective, thus it is caused by bacteria, fungus or virus;
- inflammatory caused by infective virus;
- degenerative and therefore age related (e.g. Calcific, Fibrotic, Floppy valve, Lipidosis/ Atherosclerosis, acquired bicuspid valve, etc);
- neoplastic.

The risk factor for the development of degenerative calcific aortic stenosis are

- diabetes;
- hypertension;
- smoking;
- elevate levels of low-density lipoprotein cholesterol.

The severity of stenosis increases gradually over many years and the rate of progression varies a lot.

The aortic valve stenosis' consequence is that the heart will have to pump harder to force the blood to pass the progressive obstruction. Thus, there is a progressive systolic pressure overload on the LV, that adapts increasing LV wall thickness while maintaining its normal chamber size, developing a concentric hypertrophy.

No medical treatments are recommended to delay its progression and the aortic valve replacement is the treatment of choice, particularly for older individuals. Percutaneous balloon valvotomy could be suitable option for young patients with noncalcified aortic valves.

2.1.2.2 AORTIC VALVE INSUFFICIENCY

Aortic valve insufficiency (AI), also known as aortic regurgitation, is the leaking of the aortic valve that causes leakage of blood flow in the reverse direction during left ventricular diastole.

The cause of the aortic valve insufficiency can be congenital or acquired, in which disease can be

- rheumatic fever;
- Infective Endocarditis;
- trauma;
- aortic dilatation (i.e. Marfan syndrome, aneurysm, syphyllis):
- tumors;
- inflammatory disease (i.e. aortitis);
- antiphospholipid syndrome;
- the use of anorectic drugs;
- lupus erythematosus,
- giant cell arteritis;
- Takayasu arteritis; ankylosing spondylitis;
- Jaccoud arthropathy;
- Whipple disease;
- Crohn disease.

The consequence of the chronic AI is that the heart has to do extra work to pump the required volume of blood forward. The left ventricle responds to an excess of volume of blood that is directly related to the severity of AI, by developing an eccentric hypertrophy. Through this

adaptation it is tried to regulate to normal levels the LV wall stress, the force acting against the myocardial cells, by maintain the ratio of the LV cavity radius to wall thickness:

$$LV\ wall\ stress = \frac{LV\ pressure * radius}{2 * wall\ thickness}$$

Moreover, it is developed a concentric hypertrophy in order to compensate the increase of wall stress that together with the eccentric hypertrophy attempts to guarantee the normal LV function.

The progressive LV dilatation can deteriorate the systolic function and in a reversible situation the aortic valve replacement can restore the normal loading conditions. The long-term vasodilator therapy can also be used for patients that are poor surgical candidates.

2.1.2.3 MITRAL VALVE STENOSIS

Mitral valve stenosis is a narrowing of valve's lumen that obstructs the flow of blood from LA to LV.

The causes are congenital, in which the valve is narrow at birth, or acquired which comprehend:

- rheumatic fever;
- severe mitral annular calcification;
- left mitral myxoma;
- prior exposure to chest radiation.

The consequence of mitral valve stenosis is LA enlargement to provide for more pression in order to properly fulfil the LV.

Patients with severe mitral stenosis should be considered for percutaneous balloon valvotomy if it is possible; otherwise, it should be considered for surgical valve replacement.

2.1.2.4 MITRAL VALVE INSUFFICIENCY

Mitral valve insufficiency, also known as mitral regurgitation, is a condition in which the valve does not close tightly and as a result, there is blood flow backward.

In case of primary insufficiency of mitral valve, the causes are attributed to an anatomic malformation of the valve and they can be congenital or acquired in which pathology can be:

- degenerative (Barlow's disease and Fibroelastic deficiency) that lead to prolapse and damages at the chordae;
- rheumatic fever;
- fibroelastic deficiency;
- myxomatous disease;
- Endocarditis;
- Cardiomyopathy;
- endomyocardial fibrosis; carcinoid disease with right-to-left shunting;
- ergotamine toxicity;
- radiation therapy; systemic lupus erythematosus;
- diet-drug toxicity.

On the other hand, in the secondary mitral valve insufficiency, the valve is anatomically normal, and the disease is caused by an impairment of heart contractile function of the left ventricle related to ventricle dilatation, which is often secondary to an ischemic cardiopathy.

The consequence is that LV becomes bigger in order to pump the needed volume of blood, developing eccentric hypertrophy. Regarding the LA, the volume overload causes enlargement and therefore the filling pressure in the LA decrease allowing the drainage of the pulmonary vein.

For patients with severe mitral regurgitation and normal LV function should be practiced the surgical repair of the valve only when the likelihood of success is over 90%, otherwise, it should be practiced the replacement of the valve by a prosthetic one.

For patients with functional mitral valve associated with LV dysfunction, pharmacological therapy produces a reverse modeling that leads to decrease of the severity of mitral regurgitation[2].

2.1.3 PROSTHETIC HEART VALVES

The selection of the right approach to treat heart valve diseases is influenced by a number of factors including age, comorbidity, lifestyle and other medical conditions. If the disease is mild, valves can be treated through medication. However, when medical treatment is not enough, it is necessary the use of prosthetic heart valves (PHVs) in order to replace natural ones by surgical procedure. In some case it is preferable maintaining and to repairing the pathological valve to restore its physiological function[3].

The main requirements that prosthetic heart valves should have are:

- open and close passively, according upstream and downstream pressure levels;
- open and close quickly;
- do not produce pressure drop to the blood going through the valve during its opening;
- do not allow backward flows;
- maintain its chemical-physical and mechanical characteristics even for a time that covers the lifespan's patients;
- do not alter the blood and particularly do not cause hemolysis and/or coagulation (antithrombogenicity);
- be radiopaque in order to be investigate through bioimaging techniques;
- do not be immunogenic;
- develop a physiological hemodynamics;
- do not alter the adjacent tissues;
- be available in many sizes;
- be easy to implant;
- do not make noise noticeable by the bearer.

PHVs can be divide in two types: mechanical heart valves (MHVs) and tissue heart valves (THVs).

2.1.3.1 MECHANICAL HEART VALVES

All MHVs are composed by three components:

- occluder that opens and closes passively;
- housing in which the occluder is inserted;
- sewing ring, by means of which the MHV is connected to the heart.

There are several different models available for aortic and mitral replacement surgeries. The materials used to produce the MHVs, include metals, polymers and ceramics. The main advantage is that they have a durability virtually unlimited with an excellent mechanical reliability. However, patients with MHVs need anticoagulant and antiplatelet lifelong treatments because there is the risk to form blood clots due to the change of physiological hemodynamics and in some case due to the material of MHVs. Moreover, there is the risk of cavitation damages and they produce noise. In relation with these characteristics, the use of

MHVs is preferred in young people with a life expectancy greater than 10 or 15 or requiring anticoagulant therapy for other reasons and they are not used in women of child-bearing age and in children.

MHVs have been modified for what concern materials and structure over the year.

First generation of MHVs had “caged-ball” structure composed by a ring and three or four symmetric elements realized in Stellite 21 or titan alloy (once in stainless steel) that form the cage, a movable element made of Silastic added with barium sulfate and a suture ring covering the metal one, made of Teflon, Dacron or Delrin (see Figure 2.8). Even though this kind of structure presents an excellent durability, it is almost outdated because of problems related with valve function: it produces pressure drop, it alters the neighboring tissues, it produces high turbulent shear stress related to an elevate hemolytic potential and vortex regions (thrombogenicity).

Figure 2.8. MHV caged-ball (Starr-Edwards - 1960)

In order to overcome deficiencies of “ball and cage” structure, the “single-tilting-disk” structure was created composed by a central occluder disk, realized once in Delrin and then in graphite added with tungsten powder making the mobile organ radiopaque, which is coated by pyrolithic carbon mirror-like finished that lends high antithrombogenicity (see Figure 2.9). The disk is secured by metal inlet and outlet struts to a metal ring covered by a suture ring in Teflon or Dacron. The cage is made of titanium processed by cutting tools or EDM techniques or Stellite which consents the MHVs’ manufacturing by microfusion and weldings. The latest techniques are not recommended because they impair the fatigue strength of the cage leading to its break. Such MHVs have an excellent durability, better hemodynamic and moderate pressure drop compared to previous ones, but they generate backward flows and noise.

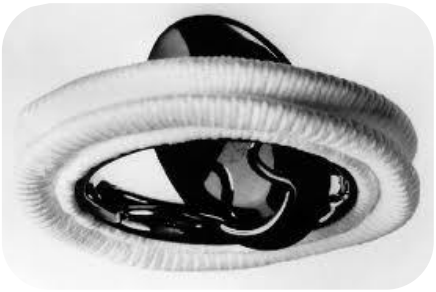

Figure 2.9. MHV single-tilting disk (Biork-Shiley - 1969)

A further improvement is given by the "bileaflet-tilting-disk" structure (see Figure 2.10). MHVs with this structure have an excellent durability and they allow central flow of blood, almost laminar, compared to the previous structures, thanks to the optimal open of the two leaflets; nevertheless, they generate backward flows and noise.

Figure 2.10. MHV bileaflet-tilting-disk (St. Jude - 1977)

Livanova's MHVs have this last structure and there are two production lines both providing for mitral and aortic MHVs: Carbomedics valves and Bicarbon valves.

Concerning Carbomedics valves, they are constituted by two mirrorlike finished pyrolytic leaflets added with 20% of Tungsten for them X-ray visualization hinged to a solid pyrolytic mirror-like finished carbon orifice that can rotate. Adjacent to the orifice there is a titanium stiffening ring which is covered by a soft Dacron sewing cuff.

Thanks to mandrel manufacturing process, pivots are molded to an optimized contour. This leaves the inner surfaces of the Carbomedics pivots completely open to washing flow when the leaflets are closed. Moreover, they present 78° leaflet opening angle established by means of hydrodynamic testing as the optimal balance between forward flow and regurgitant volume. This balance minimizes energy loss while promoting quiet operation. The sewing cuff conforms to the tissue rather than forcing the tissue to conform to the sewing cuff (see Figure 2.11 and Figure 2.12).

Figure 2.11. Carbomedics Mitral Valve Optiform (1999)

Figure 2.12. Carbomedics Aortic Valve Top Hat (1993)

Bicarbon valves have mirror-like finished pyrolytic leaflets related to the housing with an exclusive hinge mechanism in order to minimize friction between the pivot and the housing recess. Moreover, the leaflets are curved in order to improve hemodynamic. The titanium housing is coaptated with Carbofilm^{TM}, providing optimum rigidity and safety with reduced thickness of the radial section and offering a larger geometrical orifice area. The Dacron sewing ring is coated with Carbofilm^{TM} avoiding leaflets blocking, perivalvular leakage, reduction of the opening angle, and minimizing pannus formation (see Figure 2.13). Carbofilm^{TM} is a high-density, ultra-thin film (approximately 1000 times thinner than Pyrolytic Carbon) of turbostratic pure carbon which is obtained by means of a “physical” process at room temperature. Carbofilm^{TM} may be deposited on almost any substrate, including complex shapes. It does not change the morphological and physical characteristics of the coated component (polymers, polyester fabrics and metal alloys). Film continuity is retained even under deformation of the substrate.

Figure 2.13. Bicarbon Aortic Valve Overline (2003)

2.1.3.2 TISSUE HEART VALVES

THVs, also known as biological or bioprosthetic valves, are derived from human valves (homografts and autografts), animal valves (porcine xenograft valves) or animal tissue (bovine pericardial valves). Such valves are primarily used in the aortic and pulmonary positions and are occasionally used to replace the mitral valves. The main advantages of THVs compares to MHVs are that it can be avoided the lifelong anticoagulant therapy to prevent the development of blood clot, they have a better hemodynamics, they have not structural defects and they do not produce hemolysis. However, they have limited functional and mechanical reliability over time because of in vivo degradation, therefore it is requested a re-operation in 10 to 20 years. Primarily, the in vivo degradation is caused by calcification that may lead to stenosis or insufficiency if the closure of leaflet is impaired. Older people have less tendency to tissue's calcification compared with young people. For these reasons the use of THVs are preferred for elderly patients, patients with a life expectancy lower than 10/15 years or those patients who cannot (or do not want) have a lifelong anticoagulant therapy.

Autografts valves are human valves transplanted from one place to another in the same patient. The most common procedure (Ross' procedure) consists in replacement of the aortic valve with the autologous pulmonary valve and the substitution of the last valve with a homologous pulmonary one.

Homograft valves are human valves taken from donors that are cryopreserved thanks to liquid nitrogen and are trimmed to size and shape before implantation in the recipient. Normally, there are not problems of rejection enabling the avoidance of immunosuppressor therapy. The main defect is related to the availability of such THVs.

Porcine xenograft valves consist of intact pig aortic valves that are subsequentially inserted in a rigid supports (stents) and preserved in low-concentration glutaraldehyde solution. Stent allows the valve's shape retention and it is covered by sewing cuff usually made of Dacron, to maximize the facility of implantation (see Figure 2.14). However, this support increases the encumbrance of the THV that may cause the obstruction of the hematic flow, degeneration and calcification and it makes the THV more rigid. In order to overcome the limitations of such rigid support, in the '80s stent-less THVs have been produced that improve the hemodynamic and antithrombogenic performances, but they request more skills to the surgeon. Occasionally, these THVs are assembled from up to 3 separate segments of aorta and

the associated cusp material in an effort to improve the valve's symmetry and hence its perceived performance[4]. Defects related with such THV are that it produces pressure drop, it is not available in many sizes and it degrades in vivo.

Figure 2.14. Porcine xenograft aortic valve

The bovine pericardial valve is fabricated from up to a unique or more separate pieces of glutaraldehyde-treated calf pericardium with a constant thickness of 0.4 mm, affixed to a supporting stent, once in titanium and now in polymeric material, and sewing cuff, in a configuration very similar to that of the porcine xenograft. As well as the porcine valves, there are stent-less solutions[4]. Regarding defects, bovine pericardial valves share with xenograft porcine ones the degradation in vivo.

Bovine pericardial valves are manufactured including mitral, aortic, stent, and stent-less solutions at LivaNova.

Mitroflow aortic tissue heart valve is obtained from one single sheet of pericardium mounted on the outside of the stent coated with sewing cuff and it is ideal for patients with a small annulus (see Figure 2.15).

Figure 2.15. Mitroflow Aortic THV

Solo Smart aortic tissue heart valve is a stent-less solution virtually identical to the native aortic valve (see Figure 2.16).

Figure 2.16. Solo Smart Aortic THV

Solo Smart aortic tissue heart valve has a "temporary stent", i.e. Nitinol holder, that gives support and facilitates the THV implantation (see Figure 2.17).

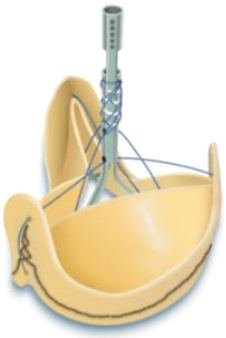

Figure 2.17. Solo Smart Aortic THV

Pericarbon more mitral tissue heart valve is a stented valve that features a two-sheet design. The sewing cuff is coated with Carbofilm^{TM} (see Figure 2.18).

Figure 2.18. Pericarbon More Mitral THV

Perceval sutureless aortic valve is composed by three bovine pericardial cusps mounted on a self-expanding and self-anchoring nitinol stent which is covered a thin Carbofilm^{TM} coating. It has an inflow skirt that allow to fit the THV into the aortic annulus and an outflow ring that stabilizes the THV at the sinotubular junction. The nitinol stent exerts an outward radial force promoting the fixation of the implant. It has two set of struts:

- "sinusoidal", which conforms to the sinus of Vansalva;
- "straight commissural" to support the valve.

It has three eyelets on the inflow ring for passage of guide sutures (see Figure 2.19).

In order to perform its implantation, Perceval THV must be collapsed without compressing the leaflets and be inserted into the heart by a valve delivery system[5].

Such valve utilizes the "memory" of the metal stent which deploys and places the valve with no suture required unlike the conventional prosthetic heart valves. Moreover, it can be implanted by minimally invasive incision such as ministernotomy and minithoracotomy, compared to the previously PHVs[6].

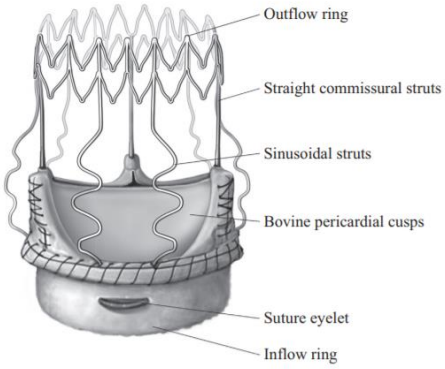

Figure 2.19. Perceval Aortic THV

Both the porcine and bovine tissues used to produce the THVs are usually fixed in low concentrations of glutaraldehyde (GA) to reduce their antigenicity, to stabilize the tissues against the proteolytic degradation, that would otherwise occur following implantation into the recipient, and to improve their mechanical properties. The GA is a chemical crosslinking agent that cross-link proteins thanks to covalent bound's creation with its aldehyde group and the lateral group ($-NH_2$) of the amino acid lysine[7]. Moreover, both types of tissues of the THVs are also subjected to post-treatment of detoxification to improve biocompatibility impaired by the toxicity of GA, thanks to neutralization of the remaining aldehyde groups. In addition, those treatments remove phospholipids and they seem to minimize the progressive calcification of the THVs, partly caused by the GA itself, and hence improve their longevity (see Figure 2.20).

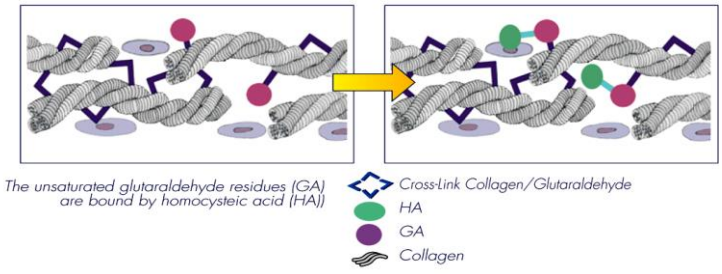

Figure 2.20. Fixation and detoxification treatment on THVs

2.2 TISSUE HEART VALVE (THV) STERILE BARRIER

THVs are sterile Medical devices, according to Medical Device Regulation and to Directive 93/42/EEC, which must be properly packaged at the end of their productive cycle.

Packaging for terminally sterilized medical devices must ensure that the medical devices can be sterilized and remain sterile under storage and transport conditions until the packaging is damaged or opened. The term "sterile barrier system" was introduced in 2006 to describe the minimum packaging required to perform the unique functions required of medical packaging: to allow sterilization, to provide an acceptable microbial barrier, and to allow for aseptic presentation.

THV sterile barrier, also known as primary packaging of THV, is used in two plants, Saluggia and Vancouver for packaging of Perceval Aortic, Pericarbone More Mitral and Solo Smart Aortic valves.

As shown in Figure 2.21, the THV sterile barrier consists of:

- jar (1) that contains the storage fluid surrounding the THV;
- holding collar, also known as retainer shelf (2), or Solo Smart holding collar which allows attachment of the THV and its position's maintenance;
- silicone sealing ring, also known as gasket (4);
- lid (3) that is screwed to the jar pressing the proper gasket assuring the retaining of fluid.

Figure 2.21. THV sterile barrier

In this work only jar, holding collars and lid are considered, manufactured by injection molding technique by an external supplier.

The scopes of THV sterile barrier are:

- to contain the biological prosthetic valve, hanging in the storage fluid;
- to allow the sterilization and neutralization treatments of the THV;
- to maintain the sterility of the medical device preventing the microbiological contamination and guarantees the absence of storage fluid leakage until the packaging opening at the point of use;
- to provide the protection of the medical device during storage and shipping.

2.2.1 THVS' STERILIZATION AND NEUTRALIZATION TREATMENTS

Solo Smart aortic, Pericarbon more mitral and Perceval aortic THVs after their manufacture are assembled manually into the THV sterile barrier to perform the THV primary packaging. The lid, the two type of retainer shelves and jar of THV sterile barrier must be sterilized after their double packaging in sterile bags, by steam sanitization via autoclave or by ethylene oxide, and then they are used to perform the primary packaging of the THV. The manufacture and the packaging of the THVs as well as the sterilization of the equipment used to perform both the operations must be achieved in ISO 6 clean room according to UNI EN ISO 14644-1, i.e. 352.000 particles of diameter $0{,}5\ \mu m$ per m^3. It is a room with a controlled environment in term of pression, moisture and particle pollution, and its operation is based on the principle of forced recirculation of super-filtered air in a sealed room. The personnel working in such rooms must wear sterile and disposable gloves, gowns, shoe covers, head covers, and masks and must be properly trained.

The primary packaged THVs are then treated in order to perform their sterilization and neutralization. The sterilization is achieved filling the jars with Glutaraldehyde (GA) solution in temperature, followed by rinsing. After that, a neutralization treatment is performed in order to eliminate from the tissue free aldehyde groups, known to reduce the durability in vivo of the valve. After neutralization, rinsing is performed and then the jars with the THVs are filled with an antimicrobial sterile buffered solution (called STERIDET) and closed with lids. The primary packaged THVs are then stored in the magazine, read to be sold.

Device's sterility is maintained over time by jar's integrity and the proper screwing of the lid to the jar. The use of an antimicrobial storage solution, i.e., STERIDET, provides an

additional margin of safety for long-term storage of the valve, according to common practices for biological prostheses.

In the next chapters, the material of the THV sterile barrier's components and their manufacturing technique are described in order to comprehend the criticality of the products.

2.3 PRODUCTION OF THV STERILE BARRIER

2.3.1 RAW MATERIAL

The selection of proper material for each component of a medical device is crucial to ensure the performances of the object along with the budget restrictions. Particularly, the material's choice is done evaluating several factors such as its mechanical properties, chemical properties, physical properties, rheological properties, biocompatibility, stability, processability and cost.

The components of THV sterile barrier are made of high strength thermoplastic polymers: a particular kind of polycarbonate (PC), is used for the jar and the two type of holding collars, and a particular kind of polyoxymethylene (POM), is used for the lid.

These materials have been recently developed and have characteristics like soft metals. They have excellent mechanical, physical and chemical properties due to primary chain's composition and they have food contact compliance with FDA & EU requirements.

They are supplied in a granulated form and can be formed in desired shape by opportune processing techniques, among them injection molding technique because above a certain temperature these materials become pliable and moldable.

2.3.1.1 JAR & RETAINER SHELFS' MATERIAL

The jar and retaining shelfs' material is a biocompatible polycarbonate with high performances. Polycarbonates (PCs) are thermoplastic homopolymers obtained from step-growth condensation polymerization reaction. They have the following structure general formula:

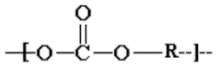

Figure 2.22. Structure general formula of PC

in which there is carbon bounded to three oxygen atoms. The characteristics of PC depend on its molecular weight and R group. Commonly, R is an aromatic diol.

It is needed for the polymerization's reaction an organic phase and an aqueous one. For the most common PCs, among them the PC used in the production of THV sterile barrier's components, the first phase is composed by 2,2-bis(4-hydroxyphenyl) propane also known as bisphenol A (BPA) in basic aqueous solution; the second one contains phosphagen (or diphenyl carbonate) in dichloromethane. The polymerization takes place at the interface of the aqueous solution and the organic one and produces chloride ions, which are by-products:

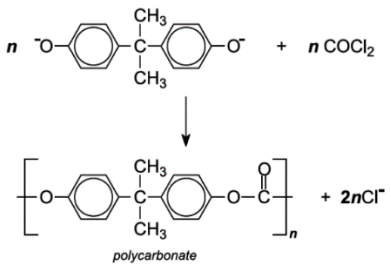

Figure 2.23. Polymerization's reaction of PC

The chemical composition of BPA based PCs influences several properties such as the crystallinity degree and some optical properties.

The sterically hindered molecular structure limits the rotation's freedom of bonds of primary polymeric chain; consequently, the packing of the macromolecules is difficult, and the crystallization does not occur spontaneously.

Regarding optical properties, the aromatic group provides BPA based PCs of a high refractive index. The good transparency and the absence of pigment allow the light permeation in the visible spectrum. In particular, the resin used has Refractive Index of 1586 and exhibits a Light Transmission of 88%.

PC has a good resistance to several substances such as mineral acids, aliphatic hydrocarbons, petrol, fats, oils, alcohols (except methyl alcohol) and water at temperature below of 70°C (above this temperature occurs the chemical decomposition by the water).

Concerning hygroscopy, the Humidity Absorption Index gives quantitative information on capacity of polymer to absorb moisture from the environment.

The Humidity Absorption of the resin used is 0.35%.

The biodegradability is very low: it is difficult for enzymes to reach the carbonate bond due to hulking phenyl groups.

According to polymerization process, BPA based PCs exhibit different average molecular weights ranging from 20000 g/mol to 200000 g/mol.

The average molecular weight influences several properties of the polymer such as mechanical one, the processability and the crystallization kinetic.

The mechanical properties increase if the average molecular weight increases until the reaching of about 22000 g/mol of molecular weight; beyond such value there is a plateau: even if average molecular weight increases the mechanical properties remain constant; nevertheless, the material's processability results harder. Thus, it is important to have a PC with reasonable average molecular weight in order to satisfy more specs.

The PC used have tensile stress at yield of 62 MPa with a tensile strain at yield of 7 %; the tensile stress at break is 68 MPa with a tensile strain at break of 130%; the Young's Modulus is 2370 MPa; therefore, this material has good toughness and stiffness. Concerning tribology, the material has Taber Wear Index of 10 mg/1000 cy and it has low fatigue strength.

It has Melt Flow Rate (MFR) of 10 g/10 min at the temperature of 300°C; high MFR indicates a low material viscosity when it is processed; it is recommendable to have MFR high enough in order to process material by Injection molding technique. The Mold Shrinkage ranges from 0.5% to 0.7%, thus the final object is mostly faithful to the mold's dimensions.

Regarding thermal properties, the PC used exhibits a Vicat B Softening Temperature of 141°C; this is the value of temperature at which the specimen is penetrated to a depth of 1 mm by a flat-ended needle with a 1 mm^2 of circular cross-section, pushing with a load of 50 N. It represents the temperature above which the material loses all load-bearing properties. It is useful for biomedical applications having a high Vicat B Softening Temperature, because it is given the possibility to sterilize the PC components with steam via autoclave in which temperature of about 120°C is reached, without losing mechanical properties and original shape of the objects. They can be sterilized also by EtO[8].

2.3.1.2 LID'S MATERIAL

The lid's material is a polyoxymethylene copolymer (POM-C). It is a biocompatible thermoplastic copolymer with high performances.

POM is a formaldehyde-based polymer; the polyformaldehyde (i.e., the homopolymer of polyacetal) is a thermally unstable material that decomposes on heating to yield formaldehyde gas. Hence, it is developed a copolymer in order to stabilize polyformaldehyde.

The Celanese route for production of POM-C (see Figure 2.24) is realized by reaction of trioxane, a cyclic trimer of formaldehyde, and a cyclic ether (e.g., ethylene oxide).

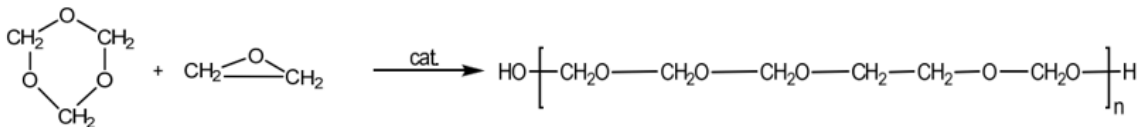

Figure 2.24. Celanese route for production of POM-C

The improvement of thermal and chemical stability of the copolymer versus the homopolymer is the result of randomly distributed oxyethylene groups; these groups offer stability to oxidative, thermal, acidic and alkaline attack and good resistance to hydrolysis until the water temperature is below 60°C.

The copolymer is then hydrolyzed in order to have oxyethylene end; that offers a further improvement of polyacetal's thermal stability.

POM has crystallinity about 80% due to its regular molecular structure. The homopolymer (POM-H) has crystallinity degree higher than copolymer (POM-C); greater is crystallinity degree, better are mechanical properties in terms of hardness and fatigue strength. Otherwise POM-C has better chemical stability due to oxyethylene groups and lower melting temperature, reflecting an easier processability.

Regarding the resin used, it exhibits tensile stress at yield of 64 MPa along with a tensile strain at yield of 9% at the temperature of 23°C; the tensile strain at break is 30% and the tensile modulus is 2850 MPa at the temperature of 23°C. Thus, it has good toughness and stiffness. It has Charpy impact strength of 180 kJ/m^2 at the temperature of 23°C. Concerning tribology, the material has excellent wear resistance.

The resin used is intrinsically opaque white, due to its high crystallinity degree.

Concerning hygroscopy, the Water Absorption of the resin used is 0.65% and Humidity absorption is 0.2%. Hence, the material absorbs low quantity of moisture.

It has Melt Volume Rate (MVR) of 8 cm^3/10 min at the temperature of 190°C, so it can be processed by Injection molding technique. The Mold Shrinkage is 2%, and this shrinkage may occur in the mold while the material is cooling and/or after processing.

Regarding thermal properties, the resin used exhibits a Vicat B Softening Temperature of 150°C. It has melting temperature of 166°C that represents the temperature above which the material pass to an amorphous and fluidic state and all mechanical properties are lost. Below the temperature of -40°C the material is characterized by high strength, hardness, rigidity and low toughness.

The material can be sterilized via autoclave without decomposition and also by EtO[9].

2.3.2 INJECTION MOLDING

Lid, the two types of retainer shelves and the jar are manufactured with Injection molding technique, which is one of the most common industrial manufacturing processes to produce thermoplastic parts.

The advantages of this process are:

- production of finished products in one cycle that, do not usually need to be additionally processed and have rather articulate geometries and tight tolerances;
- possibility of production of relatively small size objects with high level of accuracy;
- high production volume and low cycle's time;
- low cost production;
- minimum waste;
- high automation;
- versatility in processing different raw materials.

The disadvantages are:

- high cost of the equipment, therefore it is required a high initial investment;
- high encumbrance (the equipment has a certain "footprint");
- necessity to produce different molds when a different geometry is request;
- high competitivity.

2.3.3 INJECTION MOLDING MACHINE

Injection molding is performed by the injection molding machine (IMM), also known as press. The majority of machine are horizontally oriented (see Figure 2.25) as for the one used to produce THV sterile barriers' components at external supplier. Injection molding machine is composed by the following units:

- the control unit and control cabinet, that allow the machine operator to set, control and monitor process parameters;
- the injection unit, which is defined as the set of components that allow the polymer's plasticization and its injection in the mold. The principal ones are the feed hopper, the reciprocating screw with nonreturn valve, the nozzle, the barrel with heaters, the motor and the gears for screw rotation;
- the mold unit, that is composed by the tie bars, the stationary and moving platens, as well as the molding plates that comprehend the cavity, the vent holes, the sprue, the runner and the gate system, the ejector pins, and the cooling system. The mold, thanks to the action of cooling system, serves as a heat exchanger causing the thermoplastic material solidification into the shape and dimension of the mold's cavity itself;
- the clamping unit, that serves to open and close the mold, to move other mold units' components, and to create the force to hold the mold in order to avoid its opening;
- the motor unit with either hydraulic, electric or hybrid system, which provides the power to open and close the mold, realizes and holds the clamping force, rotates and translates the reciprocating screw, moves the ejector pins and carry away the finished parts[10].

The use of hydraulic, electric or hybrid motor defines the whole press, that can be classified as Electric IMM, Hydraulic IMM or Hybrid IMM.

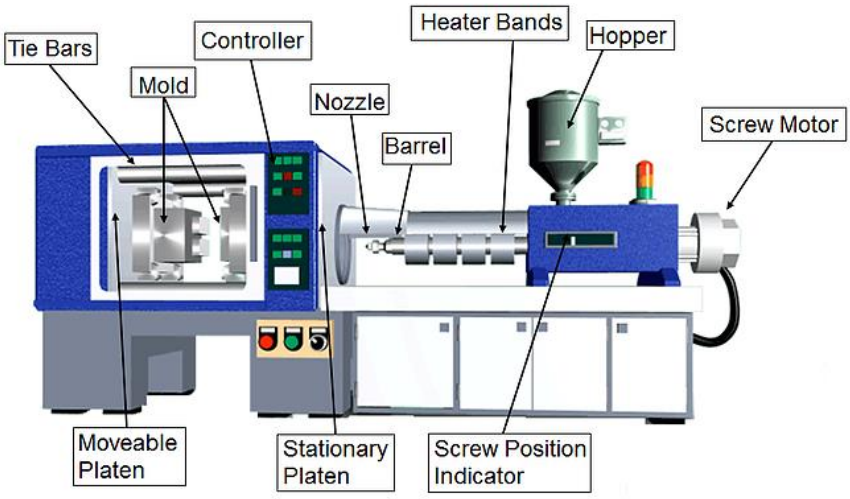

Figure 2.25. Injection molding machine

The external supplier uses an electric IMM which is adjacent to an ISO 7 clean room. Right after the products are manufactured, they are moved thanks robotic arms and belt into the clean room where it is performed visual inspection in order to discard defective parts. The products that pass the inspection are double packaged ready be delivered to LivaNova.

Figure 2.26. Visual instepction of molded products

2.3.3.1 FOCUS: ELECTRIC VS. HYDRAULIC INJECTION MOLDING MACHINES

In injection molding machines with an all-oil hydraulic system, the hydraulic components are motors, pumps, hydraulic accumulators, directional valves, fittings, tubings, and oil reservoirs. The electrical energy is converted into mechanical one that pressurize the motor oil. The pressure from the oil provides the power to turn the screw to plasticate the raw

material, inject the melt into the mold cavity or cavities, close the mol clamp, hold the clamp tonnage, release the clamp, and eject the molded parts.

Electrical injection molding machines provides decentralized power generation for the press' functions with individual electrical drivers which are the actuator themselves, converting the electrical energy into mechanical one. They use servo drives and main-spindle drives[11].

Advantages of hydraulic press respect electric IMM:

- the oil that provides the power to drive the components has also the function to remove the heat from the mold and to reduce the friction between the mechanical joints and hence, there is the possibility to not install additional cooling and lubrification systems;
- the cost of acquisition is about 10-20% less[12];
- the capacity is higher. With the same volume of the motor, hydraulic press supplies more power;

Disadvantages respect the Electric IMM:

- higher electrical energy consumption;
- the oil is highly inflammable and is environmentally hazardous and thus, needs a proper disposal that comports additional costs;
- the higher downtime and maintenance labor costs. The oil must be replaced after 8000-9000 working hours because it loses its initial viscous characteristics and the components that houses the oil must be constantly monitored because if non-visible leakages of oil occur, the production's efficiency is compromised, the parts can be contaminated and there is the risk of inflammable jets;
- the efficiency of the process (η_{tot}) is lower due to the friction losses;
- the impossibility to install sensors inside the hydraulic components entails that the variables associated to the process parameters are not real-time monitored but can be only predicted, affecting negatively the reproducibility and the control of the process;
- high noise, that could bother the IMM operators lowering their attention and hence lowering the production's efficiency;

The Electric IMM compensates the shortcomings of hydraulic IMM:

- the electrical energy used is lower, particularly it is cut the power use by 50% to 90%;

- the elimination of oil and hence of the disadvantages brought;
- the maintenance costs are eliminated;
- low noise (below 70 dB);
- high capability of the process[11];
- the repeatability and the precision of the process, and the product's quality are improved by the introduction of CNC system and pressure direct or indirect sensors near the mold;
- the cycle time is lower.

The disadvantages of Electric IMM:

- the higher cost of acquisition due to the sophisticated technology used;
- in case of breakdown of the electric motors it is necessary its whole substitution, while for hydraulic presses it is possible change single components of the system;
- the limited capacity.

For these reasons the Electric IMM may be best suited for small precision components and medical products which require precision, accuracy, consistency and repeatability. Moreover, they assure the sterility of the products due to the absence of oil and they guarantee the traceability of the process thanks to CNC system[12].

2.3.4 PREPROCESSING OF RAW MATERIAL

Thermoplastic raw materials are supplied from the plastic's manufacturer in granules that are generally cylindrical shaped, and they have the size of 3-4 mm. The granules are supplied in 25 kg bags in most cases. Raw materials for production of THV sterile barrier's components are exclusively composed by virgin polymers.

All the polymeric materials during the synthesis, transport and storage phases have the tendency to retain moisture that reaches an equilibrium value with the environment depending on type of polymer, temperature and moisture of the air, size of granule and many other factors. Related to the ability to absorb the water molecules present in the surrounding environment, plastic materials can be divided into hygroscopic and non-hygroscopic ones. POM and PC are hygroscopic polymers. When hygroscopic granules are exposed to the atmosphere, the water molecules spread and accumulate into them according to the absorption process. This phenomenon is governate by the Fick's second law:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

where C is the concentration of the water molecules, which depend on the time t, on the spatial coordinates x of the granule and D, i.e. the diffusion coefficient of the humidity into the plastic material that is calculated by Arrhenhius equation:

$$D = D_0 \exp\left(\frac{-U}{kT}\right) \tag{2}$$

where D_o is a constant depending on the kind of material, U is the activation energy, K is the Boltzmann's constant and T is the temperature.

The absorbed water molecules bind to polymer molecular chains by weak interaction thanks to the presence of polar functional groups on the chains themselves.

The presence of moisture in the granules is one of the main causes of quality problems in injection molding's process of plastic materials. It leads to product' deficiencies through three different mechanism:

- at the melting temperature of the polymer the trapped water becomes vapor, that comes out from granules and condenses on the relatively cooler wall of the mold. The external wall of the final product as a result of this process is characterized by black streaks, dieseling, splay, embedded bubbles and open bubbles;
- the water molecules by binding to polymeric chains, cause the reduction of intermolecular bonds increasing the chains' mobility, and hence act as a plasticizer that lowers the glass transition temperature of the polymer. The cooled product consequently, exhibits a deterioration of mechanical properties, particularly lower Young modulus, hardness and mechanical resistance.
- at the melting temperature of the polymer the water molecules can cause the hydrolytic reaction with the polymer chains, which leads to the split of the chains and hence to a lowering of the molecular weight as well as the formation of by-products. Therefore, there is a variation of chemical and rheological properties of the final object. This mechanism occurs in those polymers produced by condensation reaction such as polycarbonates.

The supplier of plastic materials gives the Max Moisture content % in the raw material's datasheet that represents the upper limit of moisture in the granules allowing the quality of

final product. In order to reach such percentage of moisture it is almost impossible to not perform the dehumidification of the hygroscopic raw material before its processing.

As well as a dry granule which is placed in a humid environment absorbs moisture until achieving a balance, a humid one which is placed in a dry environment releases moisture until an equilibrium point. Therefore, fixed the value of the desired humidity percentage it is necessary to choose air with a proper dew point, which defines the drought of the air. Dehumidification is performed by blowing heated dried air through the granules for certain time in order to remove the water from the polymer chains transformed into vapor by the air itself. Variables that influence dehumidification's process are:

- the initial humidity of granules. If it increases the time of the process increases too;
- the final request humidity of granules;
- the air's temperature. If it increases, the dehumidification time decreases therefore it has to be as high as possible without overcoming the softening temperature of the polymer. Moreover, particular attention should be paid in the maintenance of uniformity of temperature. As shown in the Fick's second law (2) a difference in temperature of the granules leads to different diffusion constants and consequently different levels of dehumidification between the granules;
- the air's flow rate. If it increases, the process time decreases;
- dimension and shape of the granule. Process time increases if there is an increase of dimension as well as if there is an increase of the surface-to-volume ratio. If there are granules with different dimensions, the drying time must be related to the bigger granule;
- process time[13].

POM granules needs 3 to 4 hours of dehumidification with dried air at the temperature of 120° to 140° in order to achieve the Maximum Moisture content of 0.15%. For PC granules the dehumidification time is about 2/4 hours, the Temperature is 120° and the Maximum Moisture content is 0.2%.

The dehumidification system is composed by two parts:

- the hopper (or hoppers) that is a cylindrical container which is insulated in order to reduce the dispersion of the heat toward the outside and it ends with a discharge outlet. In the dynamic dehumidification the material is poured from the upper side and

extracted from the lower one. During the transit, the material is insufflated by heated and dried air and the time it needs to cross the hopper determines the treatment's duration. The hopper is connected to the dryer;

- the dryer is a hot and dehumidified air's generator which is equipped with a blower to insufflate the air into the hopper.

The hopper-dryer is sized according to the shape of material thermoplastic, the hourly amount of material required, and the initial amount of material's moisture compared to the final desiderated one.

Figure 2.27. Hopper-drier system used by the external supplier

2.3.5 PROCESSING: THE INJECTION MOLDING'S CYCLE AND PROCESS PARAMETERS

The preprocessed polymeric granules are transformed into finished product by the injection molding process, that can be divided in five principal phases:

1. closing of the mold. The molding plate with empty cavities is closed and it is ready to receive the melted compound. Mold must be closed with a considerable clamping force as the injected melt pressure within the mold is very high.
2. injection or mold filling phase. The preprocessed thermoplastic material is placed inside the hopper and thanks to gravitational force it is leaded inside the barrel reaching the reciprocating screw. The latter begins to rotate in order to convey the granules along its threads until the anterior zone of the barrier, in front of the screw

itself. Along the direction the material's flow the reciprocating screw is divided in three zones:

- the feeding zone, that includes the 50% of the screw's length. In such zone the granules of material are conveyed from the hopper to the middle region of the barrel;
- the compressing (or transition) zone, that includes the 25% of the screw's length. In this region begins the "plastication" of the thermoplastic material, which is melted thanks to the heat that is produced by the heater bands placed on the external lateral surface of the barrel and by friction of compressed material along the screw's threads (autogenous heating). In this zone the thermoplastic material reduces its viscosity and flows forward thanks to the driving force of the screw which mixes and homogenizes the thermal and viscous distributions of the polymer;
- the metering zone, that includes the 25% of the screw's length and it is where the material is completely melted.

When the molten material reaches the screw tip, it goes through a check valve. After passing the screw tip, the molten material, also known as "the shot", remains into the anterior zone of the barrel because the injection nozzle is closed. The shot is the volume of material that is used to fill the mold cavity, but also to compensate the part's shrinkage. Moreover, it provides a cushion (about 10% of the total shot volume), which remains into the barrel to transfer pressure from the screw to the mold cavity, preventing the screw from bottoming out.

The reciprocating screw is moved backwards by the pressure (backpressure) performed by the molten material filling up in front of the screw. When the volume of the shot is enough, the reciprocating screw stops. In order to proceed to the injection of the molten plastic into the pre-heated mold, the reciprocating screw moves forward without rotating performing high pressure (injection pressure) to the shot. As a result of this movement the valve in the screw tip closes preventing the retrogression of the molten material, which is forced to pass through the nozzle brought at molten temperature, preventively opened. The molten plastic flows through the sprue, the runner and the gate channels and completely fills the mold cavity.

3. Solidification or packing phase.

Once completely filled any interstice of the mold's cavity, holding pressure to the molten has to be maintained for a certain time (holding time) in order to provide additional material from barrel that compensates the part's shrinkage, caused by decreasing of density of the solidifying polymer. This phase ends when the injection point solidifies, preventing the screw from adding extra material into the cavity.

4. Cooling phase.

In this phase the part continues the solidification, but the shrinkage is no more compensated by the addition of extra material.

5. Mold opening and part's ejection phase.

The mold is freed from its content by opening of movable half of the mold and by extraction of the cooled part performed by the ejectors. After that, the mold is closed in order to start another cycle.

The duration of each phase, expressed as the percentage of the cycle time, is shown in Figure 2.28.

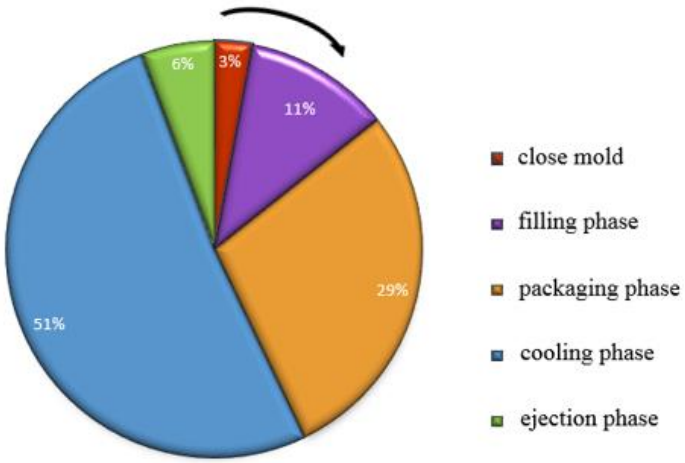

Figure 2.28. Breakdown of injection molding process

In the datasheet of the raw material, recommendations are given concerning the processing of the preprocessed granules, particularly the setting of some process temperatures.

For POM resin used it is indicated a melt temperature of 190-230°C and a mold temperature of 60-120°C. For the PC resin used it is recommended a melt temperature of 280-310°C, a nozzle temperature of 270-290°C and a mold temperature of 80-110°C.

The process parameters are summarized in the table below[14]:

Temperature	Time	Speed	Pressure
Melt	Ejection	Injection	Holding pressure
Mold's surface	Mold's closure	Screw	Injection
Oil if present	Mold's opening	Mold's closure	Cavity-pressure
Environment	Cooling	Mold's opening	Nozzle
Barrel	Cycle	Ejection	
Nozzle	Holding time		

Table 2.1. Process parameters

2.3.5.1 DIFFERENCES IN PROCESSING BETWEEN AMORPHOUS (PC) AND SEMI-CRYSTALLINE (POM) THERMOPLASTICS

The main differences between the amorphous and semi-crystalline materials observed during injection molding are:

- Melting and solidification. Amorphous thermoplastics exhibit a progressive softening over a wide temperature span, whereas the semi-crystalline materials rapidly change from the solid melt condition over a quite narrow temperature band. Conversely, when amorphous materials are cooled, they slowly solidify over a wide range of temperature, as against the semi-crystalline plastics, which change from melt to solid over a narrow range of temperature.
- Shrinkage. Amorphous thermoplastics display very low shrinkage when they solidify, particularly for PC resin used, it ranges from 0.5% to 0.7%. Semi-crystalline materials shrink more, indeed the POM resin used exhibits 1.8% of percentage shrinkage.

  The higher shrinkage with the semi-crystalline materials is due to the repeat units along the molecular chains being of such a form that they can pack very closely together in an ordered manner. By using of appropriate molding conditions it is possible to vary the extent of the crystalline areas. For example, when there is a high mold temperature, cooling rates are slow allowing more time for the molecular chains to disentangle themselves and take up their crystalline formation. This results in a greater proportion of the material being in its crystalline state (higher crystallinity) giving a product with superior mechanical strength and dimensional stability, but with relatively high shrinkage, that may lead the part out of dimensional specifications. If

the same material is molded in a cold mold, the more rapid cooling will inhibit the formation of crystalline areas. The resulting lower level of crystallinity will give the product inferior mechanical properties, and a lower shrinkage. This is accompanied by a tendency for dimensional instability and distortion during later service due to after-shrinkage[15].

2.3.5.2 THE INFLUENCE OF PROCESS PARAMETERS ON DEFECTS OF THE MOLDED PART

Ordinary defects of molded parts are:

- Short shot, also known as incomplete shots.
  The part results incomplete and hence it does not present the auspicate geometry. This is an aesthetical, dimensional and functional defect and it is caused by any factors that increase the resistance of the flow, or that prevents the filling of the mold with enough material. There is an increase of the viscosity of the molten induced by the variations of process parameter, hence not enough molten is injected into the mold's cavity and premature solidification of the injection point occurs.

  Particularly, an increase of viscosity of the molten is a consequence of too low melt temperature that can be tuned by the speed of the screw, the backpressure and the temperature profile of the barrel. Moreover, a too low mold temperature causes the premature cooling of the molten flowing and thereby prevents the front of flow to move on. An injection speed and injection pressure too low may lead to this defect. The injection pressure must be as high as possible to assure the complete filling of the mold but must not overcome the 70%-85% of the maximum pressure that the press can provide. Another cause of the defects is that the holding pressure and/or and holding time are too low. …..

- Dieseling, also known as gas burns.
  The part exhibits black spots distributed on the surface. It is an aesthetical defect and it alters the superficial characteristic of the parts. It is caused by the gas in the mold's cavity that is compressed between the walls of cavity and the flow of molten and according to the general gas equation, it overheats reaching the degradation temperature of the polymer. The gas may be present in the mold's cavity itself and/or is released by the material if not properly preprocessed. This problem can occur when the melt temperature is too high and hence the viscosity of the molten decreases and

with the same injection pression the molten fills the mold too fast. In such condition as well as when the injection speed is too high the eventual gases located in the mold's cavity have not time to be vented and therefore, they are compressed. Another cause of this defect is the excessive backpressure that introduces air in the molten that may be too much for vent holes of the mold.

- Weak parts, also known as degraded material.
  The parts exhibit poor mechanical properties, even though they result intact. This is a functional defect and it occurs when there are polymeric chains with low molecular weight in the material, which are generated during processing due to the reaction with the water molecules and the polymer's chains if the material is not correctly preprocessed and/or excessive mechanical and/or thermal stress to the material. Particularly, the thermal stress occurs when there is a melt temperature and/or a screw speed and/or backpressure are too high. The excessive holding time is also a parameter that leads to severe stress conditions.

- Burns, also known as black streaks.
  Black burns are present within and outside the part. The defect causes aesthetical imperfection of the part as well as its mechanical weakening. It appears during the injection phase when the molten is overheated until the degradation temperature and/or when the additives have a degradation temperature below the melt one. The main cause that leads to the presence of this defect is an excessive melt temperature. A too high screw speed can also cause the degradation of the materials due to the excessive heat produced by friction's phenomena. Another cause regards the injection speed: if too high, there is an excessive production of heat generated by friction between the molten's flow and the injection point and/or the mold's walls. Moreover, a quite marked degradation occurs due to a too long permanence time in the barrel.

- Flash, also known as parting line remnants.
  The parts have burrs near the junction parts of the mold, or near the vent holes. This defect impairs the aesthetical as well as the geometry of the molded object. It occurs every time the molten come out from the mold's cavity that arises when the mold is not able to contain the molten and/or when the material is too fluidized.
  During the injection phase if the closing of the mold is performed with a too low clamping force and/or if the injection pressure is too high, the molten's flow generates a force that can distance the two mold's plates. Nevertheless, high clamping force

leads to other kind of defects, i.e. short shot and dieseling, so it must be tuned considering these two aspects. Moreover, if the injection phase has an excessive duration, extra material is forced to enter inside the cavity that compresses the molten which fills mold's cavity and hence molten may leaks out.

One of the causes of having a molten too fluidized is the unproper preprocessing of material, since the presence of water can lead to reduction of the molecular weight and hence the lowering of the molten viscosity during its processing. Another cause is the set of injection speed at a too high value that increases the shear stress to the molten lowering its viscosity because it is a non-Newtonian fluid. Moreover, excessive melt temperature also causes a decrease of the viscosity of the molten, as well as excessive screw speed and/or backpressure that in turn affect the melt temperature itself. A too high mold temperature can also lower viscosity of the molten inside the mold's cavity.

- Silver streaks, also known as moisture streaks.

  The defect appears when the gases originated from the molten remain trapped inside the mold's cavity and once they contact the cooler walls of the mold, they condensate and cause silver stripes on the surface of the part, impairing its aesthetical and its surface finishing. The gases usually can be water moisture originated by the unproper dry treatment of the material and volatile substance from additives that are generated when the molten reaches a temperature over their vaporization temperature. This last situation happens when injection speed as well as melt temperature and nozzle temperature are too high.

  If the mold temperature is low the gases condense further, enhancing the defect.

- Bubbles, also known as trapped gas.

  The part is characterized by the presence of bubbles which can be distributed or concentrated in a region of the part. This defect impairs the aesthetical a well as the mechanical properties of the molded object. It appears when the volatile substances eventually present in the molten remain trapped inside it. The volatile substances commonly are water vapor when the material is badly preprocessed, gases originates from additives when it is reached their vaporization temperature and gases originated from the molten degradation. The latter may occur when there is a too high melt temperature.

  The backpressure must be as high as possible in order to compress and compact the molten in order to release the volatile substance from it.

A too low injection speed leads to a too viscous molten which is difficult to compact, on the other hand a too high injection speed causes turbulence in the molten's flow and air remains trapped within the material.

A too low mold temperature can cause the defect because the material nearest to the walls of the mold cools quickly, in contrast to the material in the internal regions of the mold' cavity that solidify slower and this situation may lead to not uniform shrinkage of the various sections of the part and thus the generation of bubbles.

- Flow lines.

  The surface of the part present imperfections due to irregularity of the flow of molten into the mold. This defect is an aesthetical one and it impairs the surface finishing of the parts. The main cause is the weak pressurization of the molten when it is within the mold (low cavity pressure). The too low melt temperature as well as the too low mold temperature lead to a premature cooling of the molten when it contacts the mold' walls and thus the mold is not filled with the sufficient quantity of molten needed to compact the material. In order to ease the filling of the mold the injection speed as well as the backpressure must be increased because the molten becomes less viscous.

  In the cooling phase if the holding pressure and the holding time are too low there is the impairment of the correct filling of the mold.

- Weld lines, also known as knit lines.

  The surface of the part has imperfection due to the inhomogeneous weld joints between the flow lines of the molten. This defect is an aesthetical defect and it impairs the surface finishing as well as the mechanical properties. The main cause is the improper pressurization of the molten within the mold's cavity. The considerations for the process parameters are the same for the flow lines[14].

- Residual stress.

  The part looks apparently normal. This is a defect impairs the mechanical properties. Excessive residual stress originates due to residual deformation of the part, which consists of intramolecular and intermolecular deformation.

  There are two sources of residual stresses. First, due to viscoelastic nature of the molten, flow-induced stresses develop during the injection and holding phases. When in molten state, polymer molecules are unstressed, and they tend to an equilibrium, random coil state. During processing, the polymer is sheared and elongated, and the molecules are oriented in the flow direction. If solidification occurs before the

polymer molecules are fully relaxed to their state of equilibrium, molecular orientation is locked within the molded part. They can be caused by a too high injection speed. The second cause of residual stresses is the non uniform temperature distribution of the part during cooling phase. When the polymer starts to cool, the external surface layers start to shrink, while the bulk of polymer at the core is still hot and free to contract. Later when the internal core cools, its contraction is constrained by the external layers since they are already rigid. This leads to thermally-induced stress. Usually the stress distribution is tensile in the core and compressive at the surface areas[16]. These stresses can be caused by a too low mold temperature. Generally, residual stress in the part tend to change due to stress relaxation.

Residual stresses can be a factor of deformation of the part, based on the plastic viscoelasticity characteristics, that impairs dimensional stability, may leading to distortion of part and/or causes crazing and reduce the Environmental Stress Crazing resistance and/or deterioration of optical and/or creep and other change in mechanical properties[17].

- Crazing, also known as stress cracking.

  The outer surface of the part is characterized by cracks. This is an aesthetical and functional defect that impairs the surface finishing as well as the mechanical properties. Crazing can appear even if no external load is applied to the part or the internal/external load is below the Yield straight of the material. It can occur right after the part is molded, when the residual stresses accumulated during processing are excessive. The cracking of a plastic material is a response to stress that occurs through disentanglement of polymer chains overcoming inter-molecular forces like van der Waals forces, hydrogen bonding between polymer chains. If the residual stresses are high, crazing can occur after the part have just been molded even if no external load is applied. Indeed, when plastic material is subjected to constant load maintained over time, which can be the residual stress, it deforms continuously (creep), until it is reached the fracture of the part. Moreover, Environment Stress Cracking (ESC) of the part with high residual stress level may occur when the part come in contact with aggressive chemical agent over time, which reduces the time of crazing. The chemical agent that causes ESC do not react with the polymer, but, due to its high solubility or compatibility with the polymer, simply enters the free volume of the plastic and disentangles the linkages between the molecules, which increases the polymer's chain

mobility and hence reduces the glass temperature and yield stress of the of the polymer which leads to crazing at lower stresses. The ESC failure depends on the synergistic effect of residual/external stress on the part, the time of exposure and the type and of chemical solvent which comes in contact with the material, the morphology of the material, and the environmental condition, particularly the temperature. Both Creep rupture and ESC of polymeric materials are also influenced by temperature, cyclic loading, fatigue, stress concentration, etc.. Amorphous polymers are more susceptible to ESC than crystalline polymers because of greater free volume in amorphous polymers[18].

- Warped part, also known as distortion.

  The part results permanent distorted with an altered geometry.

  The main cause is the not uniform and/ or the excessive shrinkage of the part. The shrinkage is mostly influence by the pressure and the temperature of the material during the cooling phase. If the melt temperature as well as the mold temperature are too low the molten that firstly contact the mold's walls has greater shrinkage respect other part's region due to the sudden cooling that impairs its proper compaction. Moreover, if the nozzle temperature is too low the molten becomes more viscous and fills the mold's cavity too slow impairing its compaction.

  Another cause of the defect is the presence of excessive residual stresses in the finished part, which are not properly relaxed during processing. The residual stress, as previously said can cause deformation of the part.

  A too low cycle time, particularly too low cooling time, causes the defect because the interior zones of the part have not solidified, and they cool after processing leading to shrinkage of the part.

- Delamination, also known as layering.

  The part is characterized by a series of overlapping layers in certain zones.

  This is an aesthetical defect and it impairs harshly the mechanical properties. It appears because of the improper cohesion of the molten's molecules. This may be caused by the presence of water vapor between molecules originates by not appropriate preprocessing of material and/or of additives incompatible with the polymer.

If the mold temperature is too low, the zones of the molten nearest to the mold's walls solidifies too fast and does not proper weld with the remaining molten. A similar situation appears when the injection speed is too low.

If the melt temperature is too low there are portion of the molten still in the solid state, thus during cooling phase they shrink and separate from the molten originating the defect.

- Jetting.

  In the surface of the part near to the injection point there are threadlike protrusions. This is an aesthetical defect that impairs the mechanical strength of the part, indeed the protrusions are not welded to the adjacent material. It is caused when the part of the molten pass through the injection point too fast and it cools before the mold's cavity is completely filled. The process parameter mainly leading to this condition is a too high injection speed. The improper tuning of melt temperature as well as the nozzle temperature also causes the defect: if too high there is an increase of molten viscosity and hence it flows too fast. Moreover, a too high mold temperature may cause the premature cooling of portions of the molten.

- Pitting, also known as orange peel.

  The part is characterized by irregular surface near the gate. This is an aesthetical defect that impairs the surface finishing of the part. It is caused by the impaired adherence of the molten to the walls of the mold during injection phase. This condition occurs when there is a too low melt temperature and/or a too low mold temperature and/or a too low injection speed.

- Pin marks.

  The part is characterized by surface hollows in correspondence of the ejection points. This is an aesthetical defect. It is caused by a too low cooling time that leads to an incomplete cooling of the part that is still deformable[14].

2.3.6 POST PROCESSING

Usually, parts coming from injection molding process are ready to use and post-processing is limited to trimming away the runner system. Sometimes, the annealing treatment can be performed on the finished parts, particularly when they are formed by semi-crystalline polymers. The benefits deriving from annealing are:

- dimensional stability through acceleration of post-molding shrinkage. In this way the mold temperature can be reduced during processing, which, as previously said, accelerate the crystallization;
- relaxing parts' internal stress and hence improve the resistance to crazing;
- improvement of mechanical properties, particularly increase of tensile strength, flexural strength, and glass transition temperature of the parts, while decreasing its elongation;
- improvement the heat resistance.

The annealing is achieved by putting parts in the proper medium under certain temperature between the melting temperature and the glass transition temperature, then maintaining the temperature for a certain time before slowly cooling down with a cooling speed that the greater is, the thinner is the part[19].

2.3.6.1 ANNEALING OF THE LID

Lid is made by a kind of POM-C, which have a high degree of shrinkage after processing, depending on the temperature of the mold, as previously said, which is maintained at 185-200°C. With this condition the shrinkage phenomenon continues after 24 hours and can even take up to a month after the part is molded. Furthermore, shrinkage is also amplified by steam sterilization. This results in a shrinkage around 0,3-0,4 mm on the diameter, i.e. about 0,4%. A decrease in the diameter of this entity in some case cause difficulties in screwing the lid to the jar, impairing the efficacy of THV sterile barrier. Therefore, in order to overcome this shortcoming, the diameter of the die and of the threaded male of the mold have been increased of 0,4 mm to achieve the diameters centered at the desired value. Moreover, the lid is subjected to the annealing treatment, performed no later than 2 day after the part is molded to give dimensional stability to the part.

The annealing is done putting the lids in a ventilated oven in temperature for about one hour, after that the samples are cooled until they reach the room temperature.

2.4 PROCESS VALIDATION

We focus on ensuring that the THV sterile barrier is a safe, a functional and an effective product. Four components of this object, particularly the lid, the two type of retaining shelfs, and the jar, are manufactured with injection molding technique by the external supplier and then assembled to perform the sterile barrier.

As previously said, the THV sterile barrier is a critical device, being in indirect contact for most of its time with the THV. For this reason, the external supplier is compliant to ISO 9000 and to ISO 13485. The latter specifies the requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet costumer/regulatory requirements and which normatively references to the ISO 9000. In the section 7.5.6 of the ISO 13485 "Validation of process for production and service provision", it is declared that the organization shall validate every production process where the resulting output cannot be or is not verified by subsequent monitoring or measurements and, as a consequence, deficiencies become apparent only after the product is in use. Process validation represents not only the substantial but also the formal demonstration, through documented and objective evidence, that a specific process has the capacity to consistently provide a product which is compliant to predetermined requirements, i.e., the process has a good capability. In other words, validating a process means ensuring that the outcome of this process, when it operates within specified limits, will meet the specifications required during the routine production.

The injection molding process for the manufacturing of the four components of THV sterile barrier has been already validated, but since the external supplier has made a change of the injection molding machine, i.e. substitution of the hydraulic press with and electric one, the output of process could be altered and hence it is necessary to revalidate the injection molding process.

In general, the validation of a process comprehends the following operative phases:

- Installation Qualification (IQ), which verifies that the equipment has been delivered, installed and configured in accordance with the manufacturer's specifications or installation checklist;
- Operational Qualification (OQ), whose main purpose is to challenge the process and to establish objective evidence that the process meets predetermined requirements

throughout all anticipated operating ranges including worst case conditions. OQ should consist of worst-case testing of process to establish that the process, when executed at the allowable extremes, produces parts that meet all requirements;

- Performance Qualification (PQ), which aims to demonstrate that the process will consistently produce acceptable product under normal operating conditions, i.e. it has acceptable performance. Challenges should be representative of situations that are encountered during routine manufacturing operations. A sufficient amount of PQ runs should be conducted to establish repeatability. PQ runs should be conducted per routine manufacturing procedures and be executed by trained manufacturing staff

3 MATERIALS AND METHODS

3.1 VALIDATION TECHNICAL PROTOCOL

The validation technical protocol is a document that establishes how the validation of the process under examination will be conducted, why it is carried out and which are its scopes. This protocol must also contain a series of information such as:

- identification of the equipment that is used in the validation;
- identification of the personnel and its qualifications;
- duration of the study;
- the use of specific methods, procedures and acceptance criteria;
- requirements that the product has to exhibit;
- statistical methods for data collection with rationale for sample sizes.

The validation technical protocol is always accompanied by the process "FMEA" (Failure mode and risk Analysis), an analysis of the risks for the patient, caused from an improper management of the process and which must be minimized through validation.

We developed the validation technical protocol (TP-10787) describing the Installation Qualification (IQ), the Operational Qualification (OQ) and Performance Qualification (PQ) for the validation of the molding process producing four of the components of the THV primary packaging (jar, lid , Solo Smart retainer shelf and retainer shelf), with a new injection molding machine. The change of the press does not affect the material, the pre-process parameters, the molds, the operators, the process management, and the environment, which remain the same of the validated injection molding process with the old press and hence will be not considered in the current validation, because it has already been assessed that they are compatible with a production that meets specifications. Otherwise, with the new press there is a change of process parameters, thus the current validation activities (inspections/verifications) will be focused on the evaluation of the effects that the new process parameters have on:

- dimensional
- mechanical
- aesthetical

- functional

characteristics of molded parts.

Moreover, the process capability analysis of the injection molding process will be performed.

The process can be considered validated when the parts molded during validation pass all the planned inspections/verifications, thus showing that the requirements set in the pertinent drawings/specifications are met.

3.1.1 INSTALLATION QUALIFICATION

Installation Qualification is done, in this case, by the external supplier and it will be completed verifying the installation documentation provided by the supplier in agreement with the supplier installation protocol and by the equipment manufacturer (e.g. technical assistance service report and safety testing of electrical components). When IQ results passed, validation can continue with the OQ phase.

3.1.2 OPERATIONAL QUALIFICATION

In the Operational Qualification the main process parameters are defined. The supplier then defines the extreme values of these parameters, which are used in the molding runs for the OQ activities (OQ runs). In this way parts are produced in the worst process conditions and by means of proper inspections/verifications, described in the next chapters, it is evaluated if these parts are acceptable in term of aesthetical, geometrical, mechanical and functional characteristics and hence that process parameters ranging between their extreme values are associated to a process that produces a performant output.

If all parts pass all the inspections with no failures, the parameters ranges are considered correct and the OQ is passed; otherwise, if failures occur, the ranges of the values of the process parameters need to be fine-tuned. In this case, OQ runs with the new parameters' ranges are performed and all the parts must pass all the inspection.

When the OQ is completed, validation can continue with the PQ phase.

3.1.2.1 OPERATIONAL QUALIFICATION MOLDING RUNS

Operational Qualification is completed defining for jar, lid, retainer shelf and Solo Smart retainer shelf the influence of the main process parameters on the process outputs with dedicated runs. On the basis of the specifications of the raw material and the parameters

defined during the validation of the old injection molding machine, melt temperature, holding pressure and holding time are chosen as critical process parameters with the nominal values and relative tolerance ranges showed in the Table 3.1.

The barrel melt temperatures and the holding times are set with ranges overlapping the ranges validated for the old machine. The definition of the holding pressure is done to compensate the change in the screw diameter of the new injection molding machine (35 mm) respect to the value of the old one (40 mm). Both the injection molding machines are characterized by the same screw length to screw outside diameter ratio (L/D=22), moving the setup values of the pressures towards lower values respect to the ones used on the old equipment in order to maintain unchanged the dynamic of the injection process obtaining comparable molded parts. The pressures for the lid molding are maintained higher than the ones used with the old equipment to facilitate the degassing of the air from the plastic material due to the geometry of the mold and of the component itself.

Component	**Melt temperature [°C]**			**Holding time [s]**			**Holding pressure [bar]**		
	Nominal value	**Tol. -**	**Tol. +**	**Nominal value**	**Tol. -**	**Tol. +**	**Nominal value**	**Tol. -**	**Tol. +**
Jar	310	300	320	6	5	7	700	650	750
Retainer shelf	300	290	310	4	3	5	700	650	750
Lid	210	200	220	8	7,50	8,50	950	900	1000
Solo Smart retainer shelf	300	290	310	4	3	5	700	650	700

Table 3.1 Process parameters tolerance ranges and nominal value

The parts used in the OQ phase must be molded challenging the process, hence the three process parameters are set at their extreme values. Since there are 2 extreme values, i.e. the minimum (tol.-) and the maximum (tol.+) for each process parameters, 2^3 molding condition (OQ runs) must be performed in order to have all the possible combination of the values of process parameter, as shown in Table 3.2.

All the parts molded are visually inspected by the supplier and no defect have been found.

Molding condition	Melt temperature [°C]	Holding time [s]	Holding pressure [bar]
1	Max. value	Max. value	Min. value
2	Min. value	Max. value	Min. value
3	Max. value	Max. value	Max. value
4	Min. value	Min. value	Max. value
5	Min. value	Min. value	Min. value
6	Max. value	Min. value	Max. value
7	Min. value	Max. value	Max. value
8	Max. value	Min. value	Min. value

Table 3.2. Combinations of values of process parameters

3.1.2.2 DIMENSIONAL AND VISUAL INSPECTION

The dimensional inspection and the visual inspection of the parts from the OQ runs shall be passed, assessing that parts are conform from the geometrical and aesthetical point of view, respectively. To pass the dimensional inspection, the critical quotes of the four components shall be inside the tolerance ranges, defined in the drawing of the components (Attachment 1). The critical quotes that have to be checked and measured are:

- thread diameter (A) and total height (B), for the jar;
- holder groove (A) and thickness (B), for the retainer shelf;
- external diameter (A) and total height (B), for the lid;
- total height in holder position region (A), for Solo Smart Retainer shelf.

Equipment needed to perform the dimensional inspection are:

- Calibrated 150-mm digital caliper with accuracy of 0,02 mm and resolution of 0,01 mm;
- Johansson gauges and dial indicator with 10 mm range and with graduations of 0,01 mm;
- SmartScope ZIP, which is a OGP multi-sensor metrology system that can perform the inspection automatically once the routine measurement is created It has a resolution of 0,0001 mm.

To pass visual inspection, no unacceptable aesthetical defects shall be present. Common aesthetical defects coming from injection molding process and their acceptability or unacceptability will be defined in Chapter 3.2 and 4.1.

Conditions to perform the visual inspection are defined in the Table below.

Condition	Requirements
Viewing distance	45cm
Viewing angle	Direct with rotating particular
Inspection points view	Only one side for the retainer shelves Inside and outside for the lid Inside and outside for the jar
Lighting intensity	Fluorescent ligth, 800-1200 LUX
Inspection time	More than 5 seconds for retainer shelves More than 10 seconds for the lid More than 10 seconds for the jar

Table 3.3. Visual control conditions

The same samples are used both for dimensional and visual inspection. The minimum number of sample size for each component type is 59, as per LivaNova procedure (significance of 5%). 8 sample from each OQ runs for every components are inspected.

3.1.2.3 RESIDUAL STRESS VERIFICATION

The mechanical characterization of the parts molded when the process is challenged, is evaluated assessing the residual stress level of the parts themselves. As previously said, too high residual stresses can cause the sudden crazing of the parts, even if the stresses are under the Yield strength of the material and no external stress is applied, hence it is important to assess if the parts molded with the new process parameters have acceptable residual stress level, to assure their reliability over time. The verification of residual stresses is performed only for the components in PC, i.e. jar, retainer shelf, Solo Smart retainer shelf. This because the material of the lid, which is in POM-C, which is a semi crystalline polymer, is subjected to the annealing treatment, that drastically reduces the residual stress of the part. There are several methods to evaluate the residual stress level of molded part, which can be destructive or no destructive test. At LivaNova is currently used a procedure (TP-10061), based on the solution soaking method, which is a destructive test. With this method, the presence and relative magnitude of residual stresses are indicated by the crazing of the sample after its

immersion in an aggressive chemical agent. The specified chemical agent is calibrated in order to cause the Environmental Stress Cracking of the part in a defined time (exposure time) when a specified residual stress level is present.

The current method used at LivaNova for the evaluation of residual stresses in PC is shown in Table 3.4; this method is recommended by the resin producer and it is used only in molding validation.

% Toluene/n	% Propanolo	Exposure time (min)	Residual stress (PSI)	Residual stress (MPa)
10	90	3	2900	20
33	67	3	1450	10
33	67	15	1015	7

Table 3.4. Resin producer method for residual stress evaluation

It is evaluated the residual stress level starting from the highest one (2900 PSI) and ending with the lowest one (1015 PSI). The sample size consists in one sample coming from every molding condition for each residual stress level evaluated

The procedure is based on the following steps:

- a 500 ml beaker is filled with 300 ml of solution composed by n-Toluene and Propanol with the proper proportion residual stress level indicated in the table 6.5;
- one jar, one retainer shelf and one Solo Smart retainer shelf are placed in the beaker, assuring the solvent covers completely the samples;
- after the exposure time of the correspondent residual stress level, the samples are extracted from the beaker;
- the samples are rinses with isopropyl alcohol and dried with compressed air and then they are visually inspected in order to evaluate if cracks are present.

The samples which do not show any cracks in their surfaces in the condition of 1450 PSI, are considered conform relatively to them mechanical properties, having residual stress level lower than 10 N/mm^2.

It must be noticed that amorphous polymers, such as PC, when exposed to strong solvents may incur in solvent-induced crystallization, because the chain's polymer acquired sufficient mobility and tend to align in order to give rise the thermodynamically favored state of the

plastics. The areas of the PC part that crystallize change their optical properties, becoming opaque[20].

In this work we develop an alternative solution soaking method (Table 3.5) to evaluate residual stress level, elaborated referring literature and old procedure used at LivaNova and designed to saving time and money. In this method the same acceptance criteria for the residual stress level of the current procedure are used, as well as the evaluation of the same three stress level. As stated in the current procedure the sample size consists in one sample coming from every molding condition for each residual stress level evaluated.

The equipment needed to perform the solution soaking test are:

- solvents, particularly methanol and ethyl acetate;
- isopropyl alcohol;
- two glass crystallizer (2l);
- glass stirrer;
- graduated cylinder with subdivision of 1 ml;
- stainless steel forceps;
- timer;
- compressed air

Moreover, the test must be performed wearing gloves, gowns, head covers, and masks and under laminar flow condition.

% Methanol	% Ethyl acetate	Exposure Time (min.)	Residual stress (PSI)	Residual stress (MPa)
93,4	6,6	3	2900	20
75,2	24,8	3	1450	10
67,3	32,7	3	1015	7

Table 3.5. Alternative procedure for residual stress evaluation

Jars, Solo Smart retainer shelves and retainer shelves corresponding to 8 different molding runs are used to evaluate each of the three levels of residual stresses, for a total of 24 jars, 24 retainer shelves and 24 Solo smart retainer shelves. 8 jars, 8 Solo Smart retainer shelves and 8 retainer shelves are no treated, serving as the control. The residual stress levels is evaluated starting from the highest one and ending with the lowest one.

For the evaluation of residual stress level of 2900 PSI, 1868 ml of methanol and 132 ml are mixed with ethyl acetate to fill a glass crystallizer with 2 l of capacity and homogenized using

a glass stirrer. Another 2 l glass crystallizer is filled with 2 l of isopropyl alcohol. The correct volume of every solvent is measured using borosilicate glass graduated cylinder with subdivision of 1 ml. Using stainless steel forceps, four jars, four retainer shelves and four Solo Smart retainer shelves are placed simultaneously in the crystallizer containing the solution of methanol and ethyl acetate, making sure the solution covers completely the samples. After 3 minutes of immersion the samples are all extracted and inserted into the crystallizer with the isopropyl alcohol to perform the rinse of the objects. The samples then are extracted from the crystallizer and dried with compressed air. Other four jars, four retainer shelves and four Solo Smart retainer shelves are treated in the same way, using the same solutions. After the treatment the samples are visually inspected.

For the evaluations of residual stress level of 1450 PSI and 1015 PSI, the same equipment and procedure are used for 8 samples of jars, retainer shelves and Solo Smart retainer shelves, representing the 8 molding conditions, but in this case the solution is made mixing 1504 ml of methanol and 496 ml of ethyl acetate and 1346 ml of methanol and 654 ml of ethyl acetate, respectively.

3.1.2.4 LEAK TEST AND OPENING TEST

The functional characterization of the components is assessed performing the leak test considering only the jars and lids from the OQ runs. This because the main important functions of THV sterile barrier, as previously said, are to shield the THV from the external environment guarantying the preservation of the aseptic condition of the medical device hosted over time and the avoidance of leakage of storage fluid. The correct tightening of the lid to the jar is one of the condition to have these functions. Therefore, the leak test is performed screwing the lid to the jar, filled with STERIDET (without THVs) to get the final configuration of the THV primary packaging in the worst condition of tightening, i.e. at the minimum allowed torque (1.8 Nm, worst condition for potential leakage). No leakage shall occur from the samples to consider the barrier function effective and hence the test passed. The equipment used to perform the leak test are illuminator and leak tester.

After that, the opening test is performed on the same samples used in the leak test; the test is done to exclude possible difficulties in opening the jar before the client use. To perform the test the jars are closed with the lid at the maximum torque and then they are manually opened to evaluate the torque required for the lid opening. The acceptable torque for opening ranges

from 1,8 Nm to 3,5 Nm. The equipment used consists in a calibrated torque meter retaining the jar and its embedded software for data acquisition.

Figure 3.1. Equipment needed to perform opening test

The minimum number of sample size for each “jar and lid” system is 59, as per LivaNova procedure (significance of 5%). 8 sample from each OQ runs for every components are inspected.

3.1.3 PERFORMANCE QUALIFICATION

Performance Qualification (PQ) is conducted in order to evaluate the performance and the capability of this process in routine production conditions, i.e., when the parameters are set to their nominal value, which is contained inside the previously specified range. Therefore, lots (subgroups) are molded in this condition (PQ runs) and part of the samples are subjected to PQ activities, which are described in the next chapters.

PQ is passed when all the PQ activities are passed. Passing the PQ phase, the validation of injection molding process is successfully concluded.

3.1.3.1 PERFORMANCE QUALIFICATION RUNS AND INCOMING INSPECTION

3 performance qualifications lots of retainer shelf, jars, and lids are molded subsequently. The PQ runs are performed setting the holding pressure and holding time at their nominal value defined in the OQ phase. The melt temperature is varied for each run with step of 5°C in order to have difference in the three lots. A summary of the critical parameters used in the PQ runs is reported in Table 3.6.

The PQ phase for the Solo Smart retainer shelf is not performed because it is molded using the same mold of retainer shelf with only different version of the central insert and the same process parameters.

Component	Lot	Quantity	Melt temperature [°C]	Holding time [s]	Holding pressure [bar]
Jars	1909030165	163	305	6	700
	1909030166	163	310	6	700
	1909030167	163	315	6	700
Retainer shelf	1909030168	163	295	4	500
	1909030169	163	300	4	500
	1909030170	163	305	4	500
Lid	1909030171	163	205	8	950
	1909030172	163	210	8	950
	1909030173	163	215	8	950

Table 3.6. Process parameters used in the PQ runs

3.1.3.2 INCOMING ISPECTION

The incoming inspection comprehends a series of inspections/verifications conduced in collaboration with the Quality Control (QC) staff of LivaNova, which is deputed to the acceptance of the products during the routine production. Particularly, visual inspection, dimensional inspection and leak test of the PQ parts are performed, with the same conditions described in the OQ phase. It is used the Acceptable Quality Level (AQL) statistical tool to decide the sample size and to set the maximum number of nonconformities allowed to consider a lot of production as acceptable. 13 sample for each 3 injection PQ lots of every component are taken to perform visual inspection, dimensional inspection and leak test. The sample size of 13 is relative to the size indicated in the AQL table, having a general inspection of First level and the lot size between 151 and 280 parts. The relative AQL is 1%. i.e., if only 1 part of the 13 ones is considered not acceptable, then the whole lot is rejected.

3.1.3.3 CAPABILITY ANALYSIS: CPK AND PPK INDEXES

In a process is usually clearly identifiable a measurable property of the component, called Critical to Quality (CTQ), which must meet the requirements previously specified. It is usually known the nominal value and the specification limits of this characteristic. The

intrinsic and ineliminable variability of the production process causes swings of the value of this property respect to the nominal value. When the process in in statistical control, i.e., the process is stable, the distribution of the values of the properties can be described with a fair approximation, by the normal distribution $X: N(\mu, \sigma)$, in which μ is the mean and σ is the standard deviation of the distribution. From the normal distribution it can be defined the natural tolerance limits of the process: the Upper natural tolerance limit (UNTL) and the Lower natural tolerance limit (LNTL), which include, in case of normal distribution, the 99.73 of values of the variable; in other words only the 0.27 % of the output of the process is not contained into the natural tolerance interval: UNTL-LNTL.

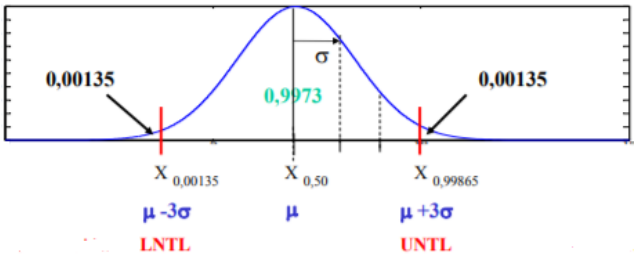

Figure 3.2. Normal distribution of CTQ

The limits of specification for the CTQ do not depend by the intrinsic variability of the process, instead they are defined in the design phase and they comprehend the Lower specification limits (LSL) and the Upper specification limit (USL), which creates the specification interval: USL-LSL. An element is defined nonconforming if the measure of the value of the CTQ is out of the USL-LSL interval.

As previously said, the process capability is the ability of the process to produce elements that meet specifications, i.e. inside the specification interval. It is evaluated with regard to the CTQs of the outputs of the process. Process capability analysis is a set of activities that, using statistical techniques, allows to quantify the capability of the process and it can be conducted following different methods, among them quantitative and adimensional measures called capacity indexes. Particularly we use the Process Capability Index (Cpk) and the Process Performance Index (Ppk). They are indexes that measure how a process is running to its specification limits in relation to the natural variability of the process taking into account the position of μ with respect to the USL-LSL interval.

The Cpk represents the potential that the process has to produce parts within specification interval, presuming there is no variation between subgroups. To calculate this index certain hypothesis must be satisfied:

- the process is in statistical control;
- the distribution of values of the CTQ can be described by normal distribution;
- the specification limits are known.

The index is defined as follow:

$$Cpk = \min(Cpu, Cpl), \tag{3}$$

Where $Cpu = \frac{ULS-\mu}{3\sigma_{Within}}$ and $Cpu = \frac{\mu-LSL}{3\sigma_{Within}}$

The Ppk index is used to assess if the process output is effectively capable to meet CTQs, i.e., the performance of the process, and the same hypothesis relative to Cpk must be satisfied to calculate it, with the exception that the process can be no stable.

The Ppk index is defined as follow:

$$Ppk = \min(Ppu, Ppl), \tag{4}$$

Where $Ppu = \frac{ULS-\mu}{3\sigma_{Overall}}$ and $Ppu = \frac{\mu-LSL}{3\sigma_{Overall}}$

The only difference between the two indexes is that the Cpk is calculated using the Within Standard Deviation, which is the average of the subgroup standard deviation, and the Ppk using the Overall Standard Deviation which represents the variation of all data of each subgroups, assessing the capability of the process for the short term and long term, respectively[21].

The capability analysis is conducted only for the critical quotes, which represent the CTQs, of jar and lid, because as previously said, they represent the most critical components of THV sterile barrier to perform its primary function.

The minimum sample size is of 35 individuals, which ensures a good approximation of the measurements to the normal distribution and hence the value of the indexes can be considered meaningful.

The acceptance criteria to pass the capability analysis assuring the process capable in the short term and in the long term, respectively are:

- Cpk > 1.33;
- Ppk > 1.33.

Firstly, the measurements of the critical shares of jar and lid for samples for each batches are collected, using the same tools used in the OQ phase.

After that, potential within capability index (Cpk) and overall capability index (Ppk) are calculated from measurements of each critical shares.

The values of these indexes are obtained using Minitab software.

Minitab firstly checks the normality of the distribution, which is one of the hypotheses assuring the significance of Cpk and Ppk, as previously said.

The normality of the distribution is verified by the "Normal probability plot". It is formed by plotting the sorted data, which are collected from measurements (x-axes), vs. the percentiles of the series of data (y-axes); if the data are consistent with a sample forming normal distribution, the data points of the normal probability plot should lie close to a straight line. The further the points vary from this line, the greater the indicator of departure from normality[22]. To determine whether the data do not follow the normal distribution, is useful refer to the statistical hypothesis test, which is executed by Minitab in parallel with the normal probability plot. The assumption of statistical hypothesis test is called null hypothesis (H_0), i.e. data follow a normal distribution. A violation of test's assumption is called first hypothesis (H_1), i.e. data do not follow a normal distribution. The statistical hypothesis test returns a value called p-value, a number used to quantify the result of the test, which consists in either rejects or fails to reject the H_0. It is compared the p-value to the significance level (α), which is 0.1 in our case. A significance level of 0.1 indicates that the risk of concluding the data do not follow the normal distribution -even if they follow it- is 10%.

- If p-value > α: fail to reject the null hypothesis, i.e. it cannot be concluded the data do not follow the normal distribution;
- If p-value $\leq \alpha$: reject the null hypothesis; i.e. the data do not follow the normal distribution[23].

Minitab then plots the capability histograms with vertical bars, that show the distribution of the data relative to the measurements of one critical share. Each bar on the histogram represents the frequency of data within the interval and on the graph the USL and the ULS are represented. On the graph, two normal distribution curves (within and overall curves) are also showed that are generated using the process mean and different estimations of process

variation, i.e. the within-subgroup standard deviation for dashed within curve and the overall standard deviation for the continuous overall curve[24].

From the visual examination of the graph obtained, it can be done some qualitative evaluations:

- more the histogram bars fit the continuous curve, more the distribution of the data can be considered normal. If the bars vary greatly from the curve, the data may not be normal distributed and the capability estimation may not be reliable for the process.;
- the continuous overall curve and the dashed within curve should be closely aligned. Substantial difference between the two curves may indicate that the process is not stable or that there is a significant amount of variation between the subgroups;
- ideally, the spread of the data is narrower than the specification limits spread, and all the data are inside the specification limits. Data that are outside the specification limits represent nonconforming items;
- evaluate whether the process is centered between the specification limits or at the target value;
- The obtained curves should be as tight as possible (small overall standard deviation and within standard deviation), that indicates a small intrinsic variation of the process.

In parallel Minitab calculates the Cpk and Ppk values of the process and display them together with the graph.

For all the indexes evaluation the confidence level is 95% (significance of 5%), i.e. there is the 95% of confidence that the actual value of the capability index is contained within the confidence interval[25].

3.2 ACCEPTANCE CRITERIA FOR AESTHETICAL DEFECTS

It is necessary to establish if the components and/or the totality of THV sterile barrier are acceptable in several situations:

- at the validation inspections;
- at external supplier inspections. The external supplier receives from LivaNova the criteria to consider the product suitable or not;
- at quality control inspections (incoming inspection), when the components are delivered to LivaNova's acceptance laboratory;
- at final packaging inspections, where the THV sterile barrier housing the THV in the storage fluid is once more checked before the sealing.

There are different critical aspects depending on the conditions that are considered, hence the relative controls on THV sterile barrier performed are also different; nevertheless, the visual inspection is executed every time, also during the validation activities.

For this reason, a standard and improved visual inspection procedure is developed concerning four THV sterile barrier components: Jar, Lid, Retainer shelf and Solo Smart Retainer Shelf. Particularly, we focus on how to treat their aesthetical defects coming from the injection molding process. They are identified and they are defined as acceptable, with the eventually restriction in terms of size, or not acceptable. The acceptance criteria are expressed on the basis of the "Cosmetic specifications of Injection molded parts © 1994 The Society of the Plastic Industry, Inc. Publication Number: AQ-103" and following a risk base approach: Process FMECA. The fulfilment of such procedure is useful for both companies.

For the four components then is defined on the basis of the defects

3.2.1 PROCESS FMECA

Process FMECA (Failure Mode, Effects and Criticality Analysis) is an inductive, bottom-up technique to evaluate processes, by determining potential sources of failure and how these failures affect the performance of the process.

It is described each failure mode early. The question "How could this component or process step fail to complete its intended function?" is posed and the engineer is trying to anticipate how the component/process step might fail to meet its output requirements.

In our case Failure modes regard aesthetical defects of THV sterile barrier's components.

After failure modes identification, the possible effects associated to each failure mode are defined. Since a failure mode can have more than one effect, all potential independent effects must be identified and described. We rate the Potential Effect Severity on a scale of 1 to 4.

Qualitative estimation	**Numeric rating**	**Definition**
Catastrophic	4	Death or severe permanent dysfunction
Critical	3	Major surgery or significant hospitalized treatment required Patient recovery Slight permanent dysfunction
Major	2	Hospitalized treatment required without surgery Condition is reversible Complete patient recovery Additional or lengthened surgical procedure required during primary surgery Impacts “quality of life”
Negligible / Minor	1	Minor treatment required Patient not hospitalized Condition is reversible. Full patient recovery No impact of “quality of life”

Table 3.7. Potential Effect Severity

After the failure mode and effects assessing, the possible causes associated with each postulated failure mode are identified. Since a failure mode can have more than one cause, all potential independent causes must be identified and described. Possible causes of aesthetical defects of molded parts can be related to the process parameters, the material, as discussed in the chapter 4.2.4, but also the press, the pre-process parameters, the mold, the operators and the process management, the environment, and other items.

The Potential Failure Mode Occurrence then is defined based on the historical aesthetical defects found in THV sterile barrier’s components examined at incoming inspection, on a scale of 1 to 6.

Qualitative estimation	Numeric rating	Quantitative estimation	Class description
Almost Always. It's almost sure that it may happen	6	$P > 10^{-1}$	The failure mode is expected to occur more frequently than 10 times per 100 device population
Frequent. May reasonably happen	5	$10^{-2} < P \leq 10^{-1}$	The failure mode is expected to occur between 1 and 10 times per 100 device population
Probable. Same chances to happen or not to happen	4	$10^{-3} < P \leq 10^{-2}$	The failure mode is expected to occur between 1 and 10 times per 1000 device population
Occasional. It's unlikely that it may Happen	3	$10^{-4} < P \leq 10^{-3}$	The failure mode is expected to occur between 1 and 10 times per 10000 device population
Rare. A few chances that it may Happen	2	$10^{-5} < P \leq 10^{-4}$	The failure mode is expected to occur between 1 and 10 times per 100000 device population
Improbable. Almost zero chances that it may happen	1	$P \leq 10^{-5}$	The failure mode is expected to occur between 0.1 and 1 times per 100000 device population

Table 3.8. Potential Failure Mode Occurrence

After that, it is identified the Probability of Detection of the Potential Failure Mode on a scale of 1 to 6. The assessment of the Probability of Petection is done on the basis of the information given by the staff performing the incoming inspection.

Qualitative extimation	Numeric rating	Quantitative extimation
Uncertain	6	$P > 10^{-1}$
Remote	5	$10^{-2} < P \leq 10^{-1}$
Occasional	4	$10^{-3} < P \leq 10^{-2}$
Moderate	3	$10^{-4} < P \leq 10^{-3}$
High	2	$10^{-5} < P \leq 10^{-4}$
Certain	1	$P \leq 10^{-5}$

Table 3.9. Probability to Detect the Failure Mode

Finally, the RPN (Risk Priority Number) is calculated for each Failure Mode by the product of the numeric rating of Potential Effect Severity, Potential Failure Mode Occurrence and Probability of Detection. The range of RPN is given, that establishes the level of acceptance of a Failure Mode.

RPN levels	
$1 \leq RPN \leq 36$	Acceptance range
$37 \leq RPN \leq 66$	Tolerable range
$72 \leq RPN \leq 144-$	Not Acceptable

Table 3.10. RPN levels

Despite the RPN value, if there is a numeric rating of Potential Effect Severity of 3 or 4 the aesthetical defect is considered not allowed.

4 RESULTS

4.1 RESULTS OF ACCEPTANCE CRITERIA FOR AESTHETICAL DEFECTS

4.1.1 RISK PRIORITY NUMBER (RPN) EVALUATION

Defects of injection molded parts have been examined considering their presence on the THV sterile barrier components and a value of Risk Priority Number RPN has been assigned on the basis of process FMECA analysis, as shown in Table 4.1.

RPN in the range 1÷36 is considered acceptable (green highlighted). Severity score of 3 and 4 are considered critical/catastrophic leading to consider the defects not acceptable (such defects were highlighted in orange in table 3 and 4).

RPN EVALUATION				
Aesthetical defects	**Occourence**	**Severity**	**Detection**	**RPN**
hanging burrs	2	4/particles detachment risk leading to embolism	4	32
Embedded foreign particles	5	2/embedded particles no risk of detachment	3	30
embedded black spots	5	2/ embedded particles no risk of detachment	3	30
outcrop particles and black spots	1	4/ particles detachment risk leading to embolism	4	16
pin marks	2	2/no risk, presence only on the retainer shelves	2	8
cracking	1	4/ particles detachment risk leading to embolism	2	8
external scratches	2	2/ no risk of particles detachment	3	12
flash	2	4/ particles detachment risk leading to embolism	3	24
mismatch	1	2/identified during leak testing	3	6
bubbles	3	4/ particles detachment risk leading to embolism	3	36
warping , pulling	1	3/ impairment of the function of barrier and hence loss of sterility	3	9
surface delamination	2	4/ particles detachment risk leading to embolism	2	16
flow/weld line	3	2/aestetic defect not leading to risks	3	18
short shots	1	3/loss of sterility	3	9
pitting, pits	1	3/ loss of sterility	3	9

Table 4.1. Common aesthetical defects and relative RPN evaluation

The bubbles defect must be split in two: open and embedded ones. According to “Cosmetic specifications of Injection molded parts © 1994 The Society of the Plastic Industry, Inc. Publication Number: AQ-103”, open bubbles are not allowed, but embedded and surface not open bubbles are acceptable with size up to 0,65 mm for grade 1 components or 0,75 mm for grade 2 components. However, it is conducted an analysis in order to evaluate their effective grade of severity. Such aesthetical defects are usually found in the bottom of jar, on internal side.

Figure 4.1. Open bubble

4.1.2 EVALUATION OF EMBEDDED BUBBLE DEFECT ON JAR

Collecting a series of jars that present embedded bubbles and subjecting them to several tests in order to assess the defect’s effective criticality. The tests aim to simulate conditions of distribution of the THV sterile barrier. If no detachment of material from all the tested jars occurs at the end of these tests, then the embedded bubbles are not defects with a grade of severity over 2 and hence, within certain limits, they are considered acceptable.

4.1.2.1 MATERIAL AND METHODS

For the evaluation of the embedded bubble defect, 17 jars, presenting one, two or three defects for a total of 27 defects, are collected at Saluggia and Vancouver. Defects show dimensions ranging from less than 1 mm to about 3 mm. Some defects are identified before the packaging of the THV, particularly on 2 jars, and some of them are identified with the THV inside, during final packaging inspection, on 15 jars.

We treated the 15 samples identified during packaging final inspection as follow:

- photographic mapping of the defects at time zero, at different magnifications, i.e., 10X, 20X and 40X, if the defect is sufficiently large, and 10X and 80X, if it is very small;

- Performing of the simulated distribution test, which comprehends the transportation simulation test, thermal shock test and the accelerated aging test. Tests are performed according to the following conditions/parameters:
  - jar filled with final storage solution and closed with the lid;
  - no valve in the jar since there is no contact between the valve and the jar bottom, thus the presence of the valve does not affect the test outcome;
  - shaking at least 16 hours on a shaker at 200 rpm (transportation simulation test);
  - store in a fridge 4-8 °C for 4 hours (thermal shock test);
  - placing from the fridge to the oven at 70°C for a total time of 7 weeks, equivalent to 4 years natural ageing (accelerated ageing test). The accelerated ageing at 70°C for 7 weeks, was calculated according to ASTM F-1980-16 with following equation (Arrhenius equation):

$$AAT = \frac{RT}{Q10^{\left[\frac{TAA-TRT}{10}\right]}} \quad (5)$$

    Where:

    - *AAT*: Accelerated Ageing Time in days;
    - *RT*: Real Time Aging in days;
    - *TAA*: Accelerated Aging Temperature;
    - *TRT*: Room Temperature, typically between 20°C and 25°C;
    - *Q10*: Reaction Rate Factor equal to 2, a conservative value generally used for medical devices or related devices.

    Therefore, with *Q10*=2, *TAA*=70°C, *TRT*=20°C, RT=4 years corresponding to 1461 days, the Accelerated Aging Time (*AAT*) is 46 days.
- photographic checking of the mapped defects at the end of tests;

The 2 samples identified before the packaging of the THV is performed, are treated as above but after a simulated sterilization and neutralization step, which is named STAN cycle. Samples are filled manually with the solutions and vigorous agitation on a shaker was used, then the sample were drained manually.

The distribution tests are performed at LivaNova laboratories.

4.1.2.2 RESULTS OF THE TESTS

From the photographic mapping of the defects, it was noticed that the aspect of the defects was similar to a thin film bubble with different morphologies:

- very small and adherent to the jar surface;

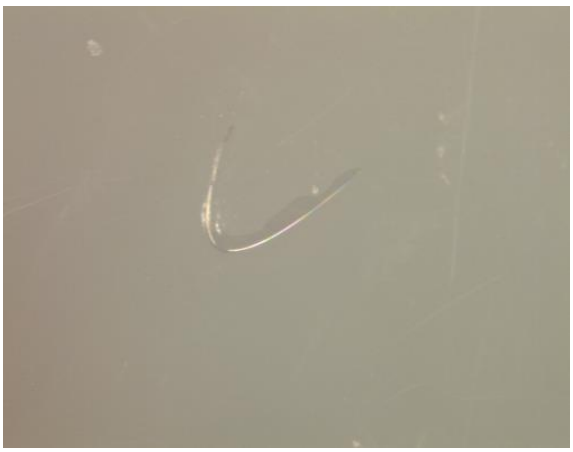

Figure 4.2. Small defect (magnification 80X)

- larger and with the appearance of a close, inflated bubble.

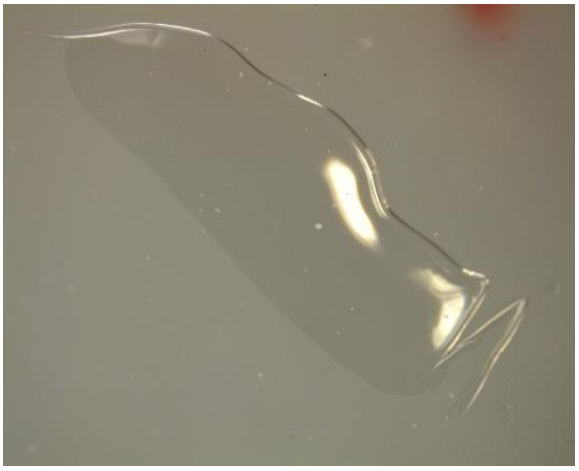

Figure 4.3. Large defect (magnification 40X)

The results of the tests in terms of changes of detected defects are summarized in Table 6.6.

Sample n°	Quantity of defects	STAN cycle	Outcome
1	2	Done before	One unchanged; one with a collaPSIble point
2	1	Done before	Unchanged
3	3	Done before	All unchanged
4	2	Done before	All unchanged
5	1	Simulated	Unchanged
6	1	Simulated	Unchanged
7	2	Done before	All unchanged
8	2	Done before	One unchanged; one with a collaPSIble point
9	2	Done before	One unchanged; one with a collaPSIble point
10	1	Done before	CollaPSIble point
11	2	Done before	All unchanged
12	1	Done before	CollaPSIble point
13	1	Done before	CollaPSIble point
14	2	Done before	All unchanged
15	1	Done before	Unchanged
16	1	Done before	Unchanged
17	2	Done before	All unchanged

Table 4.2. Samples used for the tests and outcomes

The majority of the defects were completely unchanged after distribution tests.

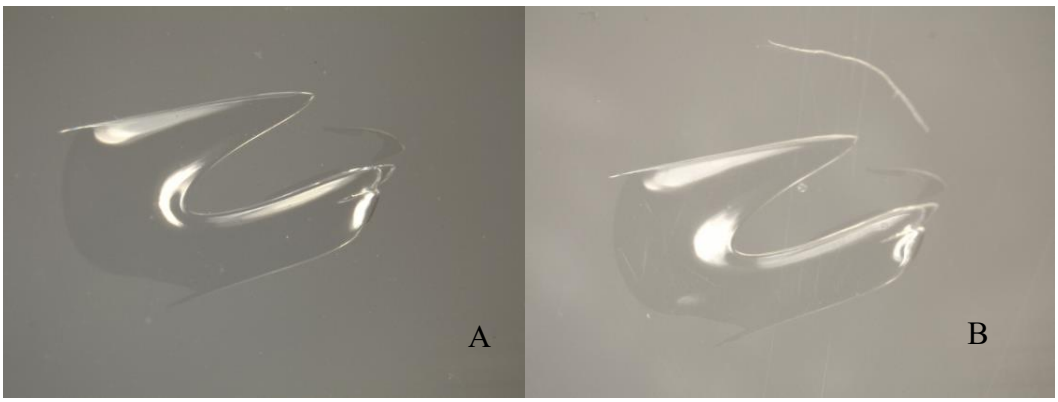

Figure 4.4 Bubbles defect before (A) and after tests (B), magnification 40X

Some defects with the initial appearance of an inflated bubble resulted with a “collapsed” point on their surface after the accelerated aging test. No film detachment was noticed.

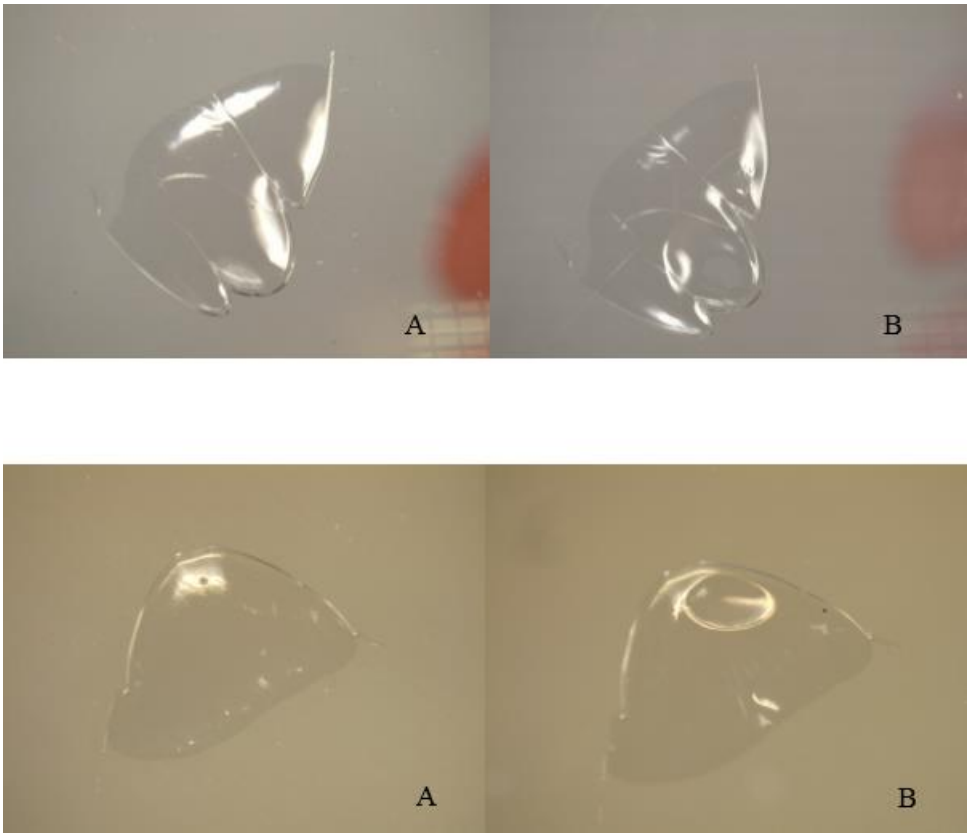

Figure 4.5. Bubble defects before (A) and after (B), magnification 40X

4.1.2.3 SUMMARY OF THE TEST’S OUCOMES AND CONCLUSION

The analyzed defects appeared to be stable through distribution test. Few defects showed a change in their morphology, particularly the partial collapse of the film of the bubbles on the jar surface, but there was not loss of material. The bubbles’ collapse was probably an artifact of the accelerated aging test due to the long exposure of the samples at the temperature of 70°C. Therefore, it was concluded that the risk of detachment of material was negligible and as a consequence these defects had not a grade of severity as high as the open bubbles. For this reason, we assigned a severity grade of 2 to embedded bubbles and we adopt the size restriction to assess the defects as acceptable according “Cosmetic specifications of Injection molded parts © 1994 The Society of the Plastic Industry, Inc. Publication Number: AQ-103”.

A B

4.1.3 VISUAL ACCEPTANCE CRITERIA FOR STERILE BARRIER'S COMPONENTS

We defined for lid, jar and the two retainer shelves the visual acceptance criteria regarding most common aesthetical defects affecting these components, and we listed them in three different tables (one for each component). In the tables are shown:

- in column "AQ-103", the requirements suggested by the publication "Cosmetic specifications of Injection molded parts © 1994 The Society of the Plastic Industry, Inc. Publication Number: AQ-103" were displayed. Particularly, if the defect is not allowed or allowed and the eventual dimensional limit;
- in the column "Integration", the requirements not foreseen by the above-mentioned publication, that were added following a risk based approach (FMECA analysis) were included: defect leading to an harm of severity with grade 3 or 4 were not allowed.

The jar were classified as GRADE 1 according to 'AQ-103' since it is clear transparent, with a highly polished surface, and in contact with medical application fluids; the surface identification was assessed of type A, indeed all surfaces are visible and the most critical surface is the inner one.

Aesthetical defects	**S**	**RPN**	**AQ-103**	**Integration**
Embedded and not open surface bubbles	2	18	< 0,65 mm	-
Open bubbles	4	36	-	None allowed
Embedded black spots	2	30	< 0,65 mm	-
Outcrop black spots	4	16	-	None allowed
Flashes and hanging burrs	4	32	None allowed	-
scratches	2	12	< 2,54mm	-
Short shot	3	9	None allowed	-
Cracking	4	8	None allowed	-
Surface delamination	4	16	None allowed	-
Warped parts	3	9	None allowed	-
pitting	3	9	None allowed	-
Flow line, weld line	2	18	Allowed	-

Table 4.3. Common aesthetical defects of jar and their acceptance criteria

The lid were classified as GRADE 2, according to 'AQ-103' since it is clear translucent, and have low grade of polish with a textured surface; the surface identification was assessed of type A, all surfaces are visible and the most critical surface is the inner one.

Aesthetical defects	**S**	**RPN**	**AQ-103**	**Integration**
Embedded and not open surface bubbles	2	18	< 0,76 mm	-
Open bubbles	4	36	-	None allowed
Embedded black spots	2	30	< 0,76mm	-
Outcrop black spots	4	16	-	None allowed
Flashes and hanging burrs	4	32	None allowed	
sctratches	2	12	< 3.81mm	-
Short shot	3	9	None allowed	-
Cracking	4	8	None allowed	-
Surface delamination	4	16	None allowed	-
Warping, pulling	3	9	None allowed	-
Pitting, pits	3	9	None allowed	-
Flow line, weld line	2	18	Allowed	-

Table 4.4. Common aesthetical defects of lid and their acceptance criteria

The two kind of retainer shelves were classified as GRADE 2 according to "AQ-103" since they are clear translucent, have low grade of polish with a textured surface; the surface identification was assessed of type A.

Aesthetical defects	S	RPN	AQ-103	Integration
Embedded and not open surface bubbles	2	18	< 0,76mm	-
Open bubbles	4	36	-	None allowed
Embedded black spots	2	30	< 0,76mm	-
Outcrop black spots	4	16	-	None allowed
Flashes and hanging burrs	4	32	None allowed	-
scratches	2	12	< 3.81mm	-
Short shot	3	9	None allowed	-
Cracking	4	8	None allowed	-
Surface delamination	4	16	None allowed	-
Warping, pulling	3	9	None allowed	-
Pitting, pits	3	9	None allowed	-
pin marks	2	8	< 0,1mm	-
Flow line, weld line	2	18	Allowed	-

Table 4.5. Common aesthetical defects of retainer shelves and their acceptance criteria

4.2 RESULTS OF MOLDING PROCESS VALIDATION

4.2.1 INSTALLATION QUALIFICATION

The correct installation of the equipment was verified by the supplier in agreement with the supplier installation qualification protocol. The presence of manufacturer's documents on the installation of the equipment at the supplier site (e.g. technical assistance service report and safety testing of electrical components) had been verified. In the Table below the activities conducted by external supplier in installation qualification are summarized.

Activity	**Responsibility**	**Outcome**
Verify that the personnel involved in the validation process are trained on the reference validation and control procedures	External supplier	Conform
Verify that the molds have been installed within the time allowed and that they respect the characteristics of the project	External supplier	Conform
Verify that the raw materials have the required characteristics and that they are in compliance with the specifications	External supplier	Conform
Verify the alarm and safety system of the press	External supplier	Conform
Verify the correct cleaning of the press, the equipment and emptying the line	External supplier	Conform
Verify that all the maintenances of the equipment (press, belt, etc.) are present	External supplier	Conform
Verify that all the tools used during the various validation phases are calibrated	External supplier	Conform
Verify that the updated drawings of the components are present	External supplier	Conform

Table 4.6 IQ verifications

4.2.2 OPERATIONAL QUALIFICATION

4.2.2.1 DIMENSIONAL AND VISUAL INSPECTION: JAR

8 samples for the 8 molding runs were inspected in order to measure the critical shares of the jar, i.e. the thread diameter (A) and the total height (B). The reference was the jar drawing in the Attachment 1, in which nominal values and respective tolerance of the critical shares are shown. The measurements were taken using the dial indicator for the total height and the caliber for the thread diameter.

JAR							
Share (mm)		**A**			**B**		
		Nominal value	**Tol. +**	**Tol. -**	**Nominal value**	**Tol. +**	**Tol. -**
		64,8	0,15	0,15	64,7	0,3	0,3
Run	**Sample n°**	**Detected (mm)**					
1	1	64,78			64,67		
	2	64,82			64,68		
	3	64,81			64,68		
	4	64,78			64,67		
	5	64,79			64,69		
	6	64,78			64,68		
	7	64,79			64,67		
	8	64,81			64,67		
2	1	64,73			64,69		
	2	64,76			64,70		
	3	64,75			64,69		
	4	64,75			64,71		
	5	64,80			64,70		
	6	64,69			64,68		
	7	64,77			64,68		
	8	64,73			64,68		
3	1	64,82			64,70		
	2	64,80			64,72		
	3	64,83			64,72		
	4	64,84			64,71		
	5	64,83			64,71		
	6	64,81			64,72		
	7	64,82			64,71		
	8	64,79			64,72		

JAR							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol. -
		64,8	0,15	0,15	64,7	0,3	0,3
Run	Sample n°	Detected (mm)					
4	1	64,79			64,67		
	2	64,74			64,66		
	3	64,78			64,65		
	4	64,74			64,65		
	5	64,76			64,67		
	6	64,75			64,65		
	7	64,76			64,65		
	8	64,75			64,66		
5	1	64,79			64,64		
	2	64,76			64,64		
	3	64,76			64,64		
	4	64,79			64,63		
	5	64,79			64,63		
	6	64,78			64,64		
	7	64,75			64,65		
	8	64,77			64,63		
6	1	64,80			64,65		
	2	64,81			64,65		
	3	64,78			64,64		
	4	64,79			64,63		
	5	64,78			64,64		
	6	64,81			64,65		
	7	64,80			64,65		
	8	64,79			64,64		
7	1	64,81			64,72		
	2	64,78			64,74		
	3	64,81			64,74		
	4	64,83			64,75		
	5	64,82			64,72		
	6	64,83			64,73		
	7	64,76			64,73		
	8	64,80			64,73		
8	1	64,76			64,64		
	2	64,77			64,64		
	3	64,77			64,64		
	4	64,78			64,65		
	5	64,76			64,64		
	6	64,78			64,64		
	7	64,77			64,64		
	8	64,76			64,64		

Table 4.7. Measurements of the critical shares of the jars

All the values of the critical shares detected of each sample were within the tolerance range, hence the dimensional inspection of the jar was considered passed.

Visual inspection of the same samples was also performed referring to the acceptance criteria described in the chapter 4.1. All the samples resulted free from aesthetical defects, thus the visual inspection relative to jar was passed.

4.2.2.2 DIMENSIONAL AND VISUAL INSPECTION: LID

8 samples for the 8 molding conditions (runs) were inspected in order to measure the critical shares of the lid, i.e. the external diameter (A) and the total height (B). The reference was the lid drawing in the Attachment 1, in which nominal values and respective tolerance of the critical shares are shown. They were taken using the dial indicator for the total height and the OGP system for the external diameter.

LID							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol. -
		70	0,5	0,2	15	0,2	0,2
Run	Sample n°	Detected (mm)					
1	1	70,17			15,13		
	2	70,17			15,13		
	3	70,18			15,12		
	4	70,17			15,13		
	5	70,16			15,12		
	6	70,17			15,12		
	7	70,17			15,13		
	8	70,17			15,12		
2	1	70,18			15,12		
	2	70,18			15,13		
	3	70,19			15,12		
	4	70,17			15,12		
	5	70,17			15,14		
	6	70,13			15,10		
	7	70,17			15,11		
	8	70,17			15,10		
3	1	70,20			15,10		
	2	70,20			15,16		
	3	70,21			15,16		
	4	70,21			15,11		
	5	70,21			15,12		
	6	70,21			15,11		
	7	70,20			15,11		
	8	70,21			15,11		
4	1	70,20			15,11		
	2	70,21			15,11		
	3	70,23			15,11		
	4	70,22			15,11		
	5	70,21			15,11		
	6	70,22			15,11		
	7	70,21			15,11		
	8	70,21			15,11		
5	1	70,21			15,11		
	2	70,21			15,11		
	3	70,21			15,11		
	4	70,21			15,11		
	5	70,21			15,11		
	6	70,21			15,11		
	7	70,21			15,11		
	8	70,22			15,12		

LID							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol. -
		70	0,5	0,2	15	0,2	0,2
Run	Sample n°	Detected (mm)					
6	1	70,20			15,11		
	2	70,21			15,11		
	3	70,21			15,11		
	4	70,21			15,10		
	5	70,21			15,10		
	6	70,21			15,11		
	7	70,21			15,11		
	8	70,21			15,11		
7	1	70,19			15,10		
	2	70,19			15,11		
	3	70,19			15,10		
	4	70,19			15,10		
	5	70,19			15,10		
	6	70,19			15,10		
	7	70,19			15,11		
	8	70,17			15,11		
8	1	70,20			15,12		
	2	70,20			15,12		
	3	70,18			15,12		
	4	70,20			15,11		
	5	70,20			15,12		
	6	70,21			15,12		
	7	70,21			15,11		
	8	70,21			15,12		

Table 4.8. Measurements of the critical shares of the lids

All the values of the critical shares detected of each sample were within the tolerance range, hence the dimensional inspection of the lid was passed. Visual inspection of the same samples was also performed referring to the acceptance criteria described in the chapter 4.1.

All the samples resulted free from aesthetical defects, thus the visual inspection was passed.

4.2.2.3 DIMENSIONAL AND VISUAL INSPECTION: RETEINER SHELVES

For both the Solo Smart Retainer shelf and the Retainer shelf, 8 samples for the 8 molding conditions (runs) were inspected in order to measure the critical share, i.e. the total height in holder position region (A) for the Solo Smart retainer shelf and the holder groove (A) and the thickness (B) for the retainer shelf. The references were the Retainer shelf and the Solo Smart Retainer Shelf drawings in the Attachment 1, in which nominal value and respective tolerance of the critical share are shown. The measurements were taken using the caliber for the critical shares.

SOLO SMART RETAINER SHELF				
Share		**A**		
		Nominal value	**Tol. +**	**Tol. -**
		2,9	-	0,1
Run	**Sample n°**	**Detected (mm)**		
1	1	2,86		
	2	2,85		
	3	2,85		
	4	2,84		
	5	2,85		
	6	2,85		
	7	2,84		
	8	2,86		
2	1	2,86		
	2	2,85		
	3	2,84		
	4	2,86		
	5	2,85		
	6	2,85		
	7	2,85		
	8	2,85		
3	1	2,84		
	2	2,87		
	3	2,86		
	4	2,85		
	5	2,85		
	6	2,85		
	7	2,86		
	8	2,85		

SOLO SMART RETAINER SHELF				
Share		A		
		Nominal value	Tol. +	Tol. -
		2,9	-	0,1
Run	Sample n°	Detected (mm)		
4	1	2,82		
	2	2,82		
	3	2,83		
	4	2,83		
	5	2,84		
	6	2,84		
	7	2,85		
	8	2,83		
5	1	2,84		
	2	2,85		
	3	2,84		
	4	2,84		
	5	2,85		
	6	2,85		
	7	2,85		
	8	2,84		
6	1	2,84		
	2	2,84		
	3	2,85		
	4	2,85		
	5	2,84		
	6	2,83		
	7	2,85		
	8	2,84		
7	1	2,87		
	2	2,86		
	3	2,85		
	4	2,85		
	5	2,84		
	6	2,85		
	7	2,86		
	8	2,85		
8	1	2,83		
	2	2,85		
	3	2,85		
	4	2,83		
	5	2,84		
	6	2,84		
	7	2,84		
	8	2,84		

Table 4.9. Measurements of the critical shares of the Solo Smart retainer shelves

RETAINER SHELF							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol. -
		7,3	0,1	-	2,9	-	0,1
Run	Sample n°	Detected (mm)					
1	1	7,29			2,86		
	2	7,29			2,86		
	3	7,3			2,86		
	4	7,3			2,87		
	5	7,3			2,87		
	6	7,3			2,86		
	7	7,3			2,87		
	8	7,3			2,86		
2	1	7,3			2,86		
	2	7,3			2,86		
	3	7,3			2,86		
	4	7,3			2,87		
	5	7,3			2,87		
	6	7,3			2,86		
	7	7,3			2,86		
	8	7,3			2,87		
3	1	7,3			2,87		
	2	7,29			2,86		
	3	7,29			2,86		
	4	7,3			2,87		
	5	7,3			2,87		
	6	7,3			2,87		
	7	7,29			2,86		
	8	7,29			2,87		
4	1	7,27			2,85		
	2	7,28			2,86		
	3	7,28			2,86		
	4	7,28			2,86		
	5	7,27			2,85		
	6	7,27			2,85		
	7	7,27			2,85		
	8	7,28			2,86		
5	1	7,27			2,84		
	2	7,28			2,85		
	3	7,28			2,85		
	4	7,28			2,85		
	5	7,27			2,84		
	6	7,28			2,85		
	7	7,28			2,85		
	8	7,27			2,85		

RETAINER SHELF							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol. -
		7,3	0,1	-	2,9	-	0,1
Run	Sample n°	Detected (mm)					
6	1	7,27			2,85		
	2	7,28			2,85		
	3	7,28			2,85		
	4	7,28			2,85		
	5	7,27			2,86		
	6	7,29			2,86		
	7	7,28			2,85		
	8	7,27			2,85		
7	1	7,3			2,86		
	2	7,29			2,86		
	3	7,29			2,86		
	4	7,3			2,87		
	5	7,3			2,87		
	6	7,29			2,86		
	7	7,3			2,88		
	8	7,3			2,87		
8	1	7,27			2,85		
	2	7,28			2,85		
	3	7,28			2,85		
	4	7,28			2,85		
	5	7,29			2,86		
	6	7,28			2,85		
	7	7,28			2,85		
	8	7,28			2,86		

Table 4.10. Measurements of critical shares of the retainer shelves

All the values of the critical shares detected of each sample were within the tolerance range, hence the dimensional inspection was passed.

Visual inspection of the same samples was also performed referring to the acceptance criteria described in the chapter 4.1. All the samples result free from aesthetical defects, thus the visual inspection was passed.

4.2.2.4 RESIDUAL STRESS EVALUATION: JAR AND RETEAINER SHELVES

The samples treated with the solution to evaluate if the residual stress level is 2900 PSI were visually inspected, and a minor opacity was noticed around the injection point, respect the control samples; this situation was the same for the the samples of all molding conditions. The following figures refer to the jar, retainer shelf and Solo Smart retainer shelf of the 8th injection molding condition.

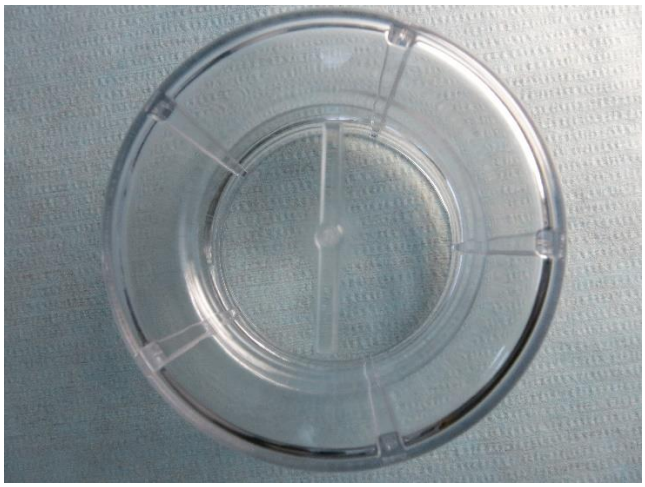

Figure 4.6. Visual inspection of jar, 2900 PSI

Figure 4.7. Visual inspection of Solo Smart retainer shelf, 2900 PSI

Figure 4.8. Visual inspection of retainer shelf, 2900 PSI

A further inspection of the samples of the 8th molding condition was conducted with the OGP system, in order to detect imperfections that cannot be seen by the naked eye. It was noticed clearly opacity around the injection point.

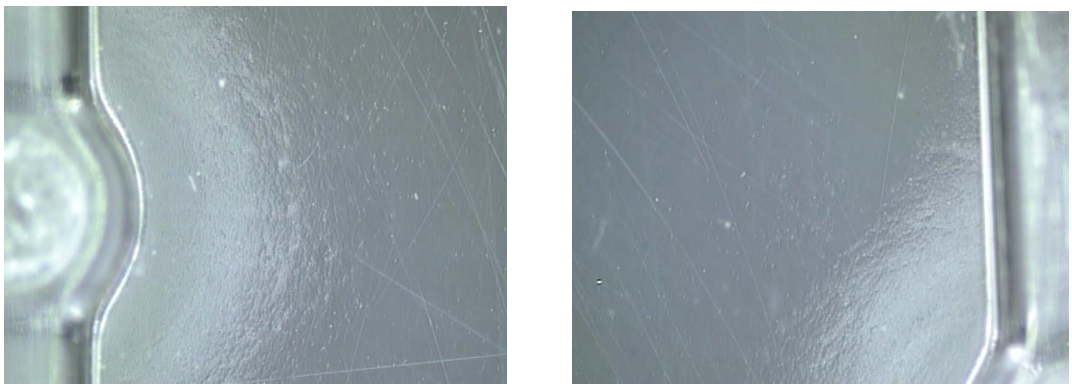

Figure 4.9. OGP inspection of jar, 2900 PSI

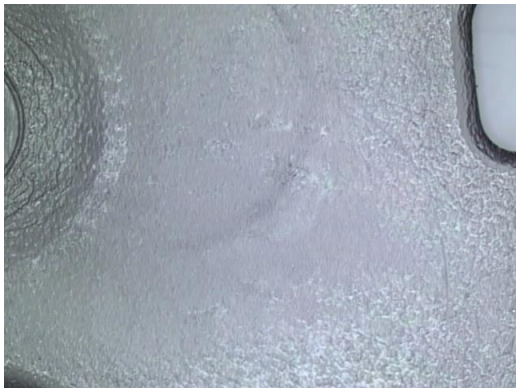

Figure 4.10. OGP inspection of Solo Smart retainer shelf, 2900 PSI

Figure 4.11. OGP inspection of retainer shelf, 2900 PSI

Since no cracks were present in all the samples, it could be concluded that they had residual stresses lower than 2900 PSI.

The samples treated with the solution to evaluate if the residual stress level is 1450 PSI were visually inspected and opacity near the injection point was noticed in all the samples referring to different molding conditions. The figures below refer to samples of the third molding condition.

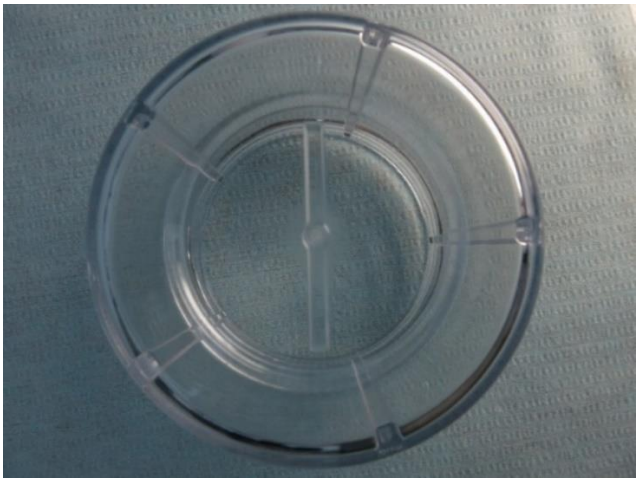

Figure 4.12. Visual inspection of jar, 1450 PSI

Figure 4.13. Visual inspection of retainer shelf, 1450 PSI

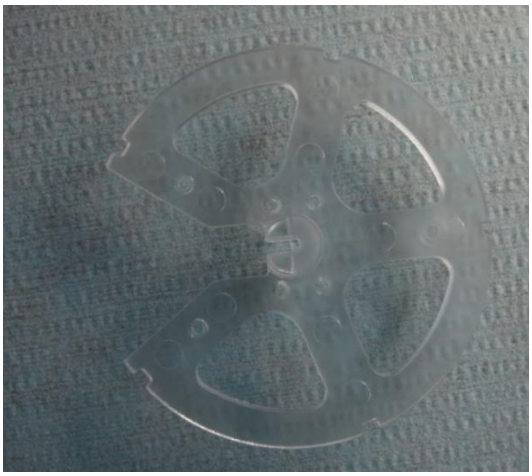

Figure 4.14. Visual inspection of Solo Smart retainer shelf, 1450 PSI

Inspection using the OGP system was also conducted for the samples of third molding condition, which confirmed the presence of opacity around the injection point of the samples.

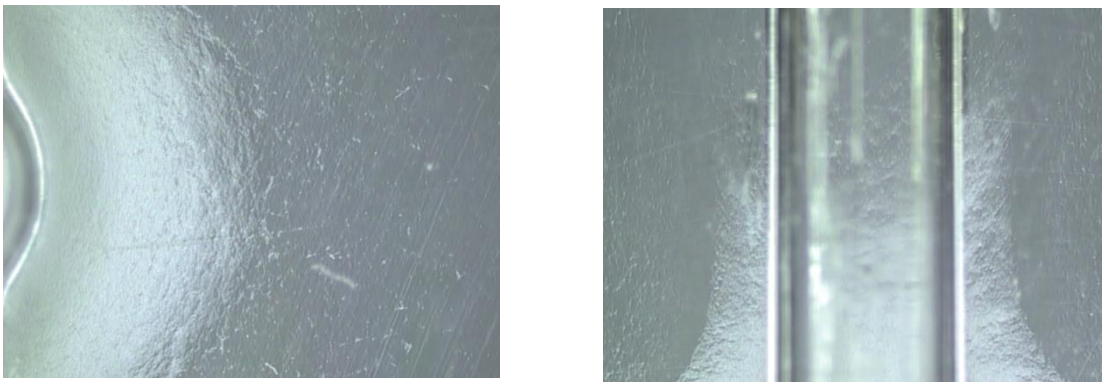

Figure 4.15. OGP inspection of jar, 1450 PSI

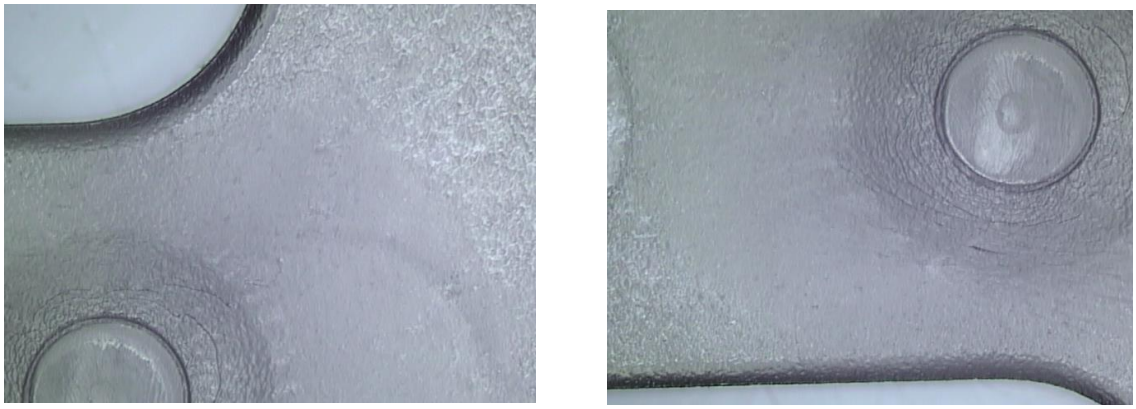

Figure 4.16. OGP inspection of retainer shelf, 1450 psi

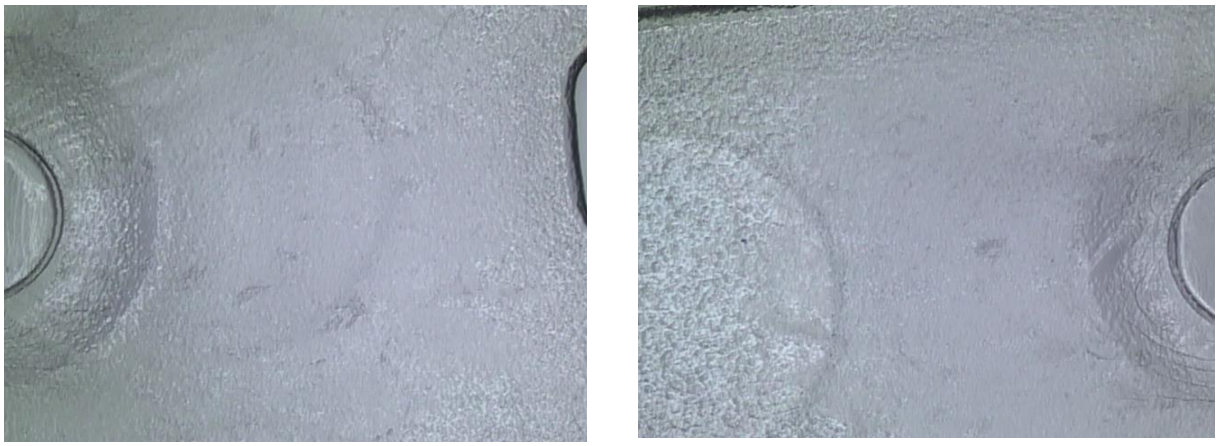

Figure 4.17. OGP inspection of Freedom Solo retainer shelf, 1450 psi

All the sample treated had no cracks and hence the residual stress level was considered as lower than 1450 PSI.

The samples treated with the solution to evaluate if the residual stress level is 1015 PSI were visually inspected and relevant opacity near the injection point was noticed in all the samples referring to different molding conditions. The figures below refer to samples of the first molding condition.

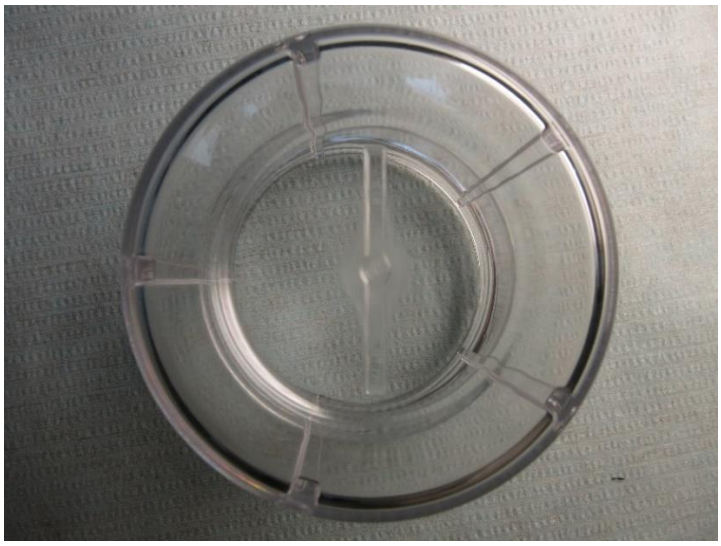

Figure 4.18. Visual inspection of jar, 1015 PSI

Figure 4.19. Visual inspection of Solo Smart retainer shelf, 1015 PSI

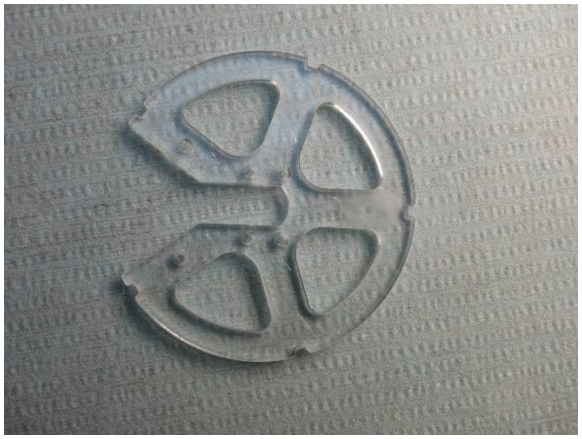

Figure 4.20. Visual inspection of retainer shelf, 1015 PSI

With the OGP system the sample of the first condition are further inspected and it was seen a circumscribed ring of opacity all around the injection point.

Figure 4.21. OGP inspection of jar, 1015 psi

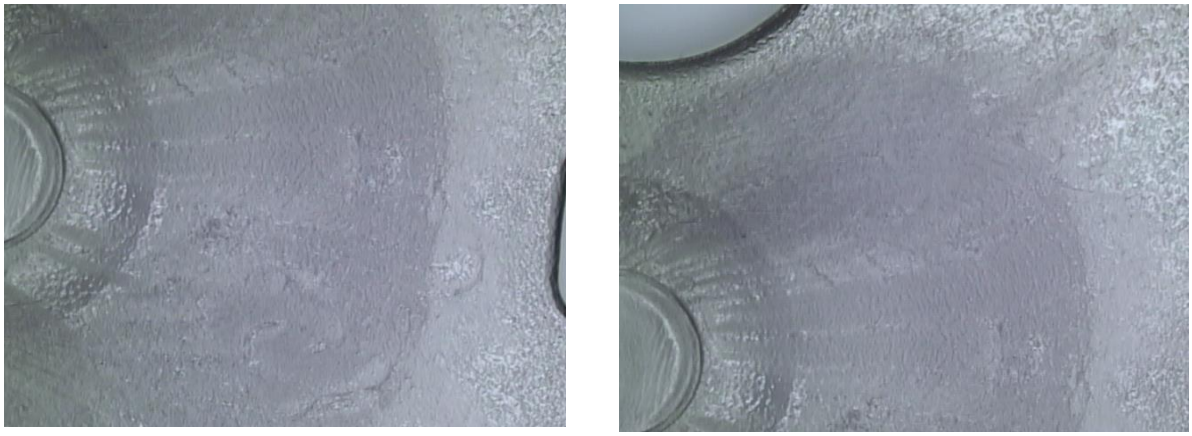

Figure 4.22. OGP inspection of retainer shelf, 1015 psi

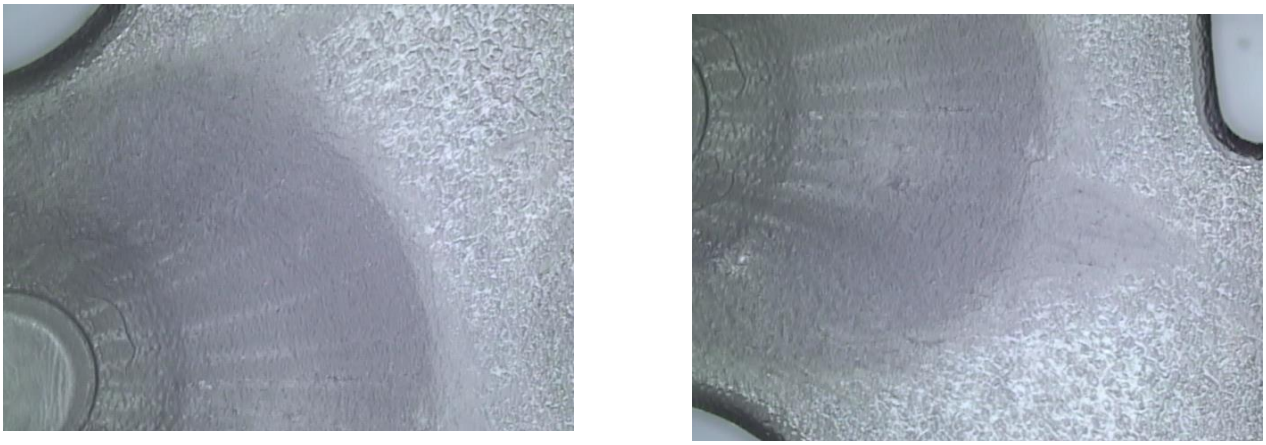

Figure 4.23. OGP inspection of Freedom Solo retainer shelf, 1015 psi

Nevertheless, no cracks were present in this condition too, verifying that residual stress level do not exceed 1015 PSI for all the samples.

The residual stress test was successfully passed indeed the parts have residual stress level lower than 1015 PSI, below the acceptable limit of the test (1450 PSI); the parts showed a opacity near the injection point that progressively increased, as the solution becomes more aggressive, due to the solvent-induced crystallization, which was considered an artifact of the test conditions without relations with the stress residual levels.

4.2.2.5 ALTERNATIVE METHOD VS CURRENT ONE

This alternative method was conducted in parallel with the current one, and the same outcomes was found, i.e. the conformity to the test: residual stress level lower than 1015 PSI; This new method allows saving solvents' amount and time, thanks to the use of 2-liter crystallizer filled with 2 liter of solution in which four jars, four retainer shelves, four Solo Smart retainer shelves at time are treated, instead of 500 ml beaker filled with 300 ml of solution that allow the treatment of one jars, one retainer shelves, one Solo Smart retainer shelves at time. In addition, the use of methanol and ethyl acetate instead of propanol and n-Toluene represents the vantage to save money, indeed the first solvents are more economical. In the Table 4.11 quantitative data are showed to support the savings discussed above considering the treatment of the samples in the 8 molding conditions for the three residual stress levels, used in the validation.

Procedure	**Total exposure time (min.)**	**Total volume of solvent (l)**	**Total cost of solvents (€)**
Current	168	7,2	216,22
Alternative	18	6	79,45

Table 4.11. Comparison between times and costs of two methods

The shortcoming of this alternative method is that the ethyl acetate is minimally absorbed by the PC during the treatment. This may lead to an alteration of the concentration of the solution used and hence to an error in the assessment of residual stress level of the sample. An improvement in order to bypass this limitation, could be the replacement of the solvent every time the samples have been exposed to it. Nevertheless, in this way there is an increase of the total amount of volume of solvent used, to 12 liters and hence of the total cost of solvent which become 158,9 €. However, respect to current procedure there is still a saving in total costs and exposure time.

4.2.2.6 LEAKAGE TEST AND OPENING TEST: LID AND JAR

8 jars and 8 lids for each of the 8 molding runs were coupled in order to produce 64 samples to be subjected to the leak test.

Lid	Jar	Outcome
1	1	pass
2	1	pass
3	1	pass
4	1	pass
5	1	pass
6	1	pass
7	1	pass
8	1	pass
1	2	pass
2	2	pass
3	2	pass
4	2	pass
5	2	pass
6	2	pass
7	2	pass
8	2	pass
1	3	pass
2	3	pass
3	3	pass
4	3	pass
5	3	pass
6	3	pass
7	3	pass
8	3	pass
1	4	pass
2	4	pass
3	4	pass
4	4	pass
5	4	pass
6	4	pass
7	4	pass
8	4	pass
1	5	pass
2	5	pass
3	5	pass
4	5	pass
5	5	pass

Lid	Jar	Outcome
1	3	pass
2	3	pass
3	3	pass
4	3	pass
5	3	pass
6	3	pass
7	3	pass
8	3	pass
1	4	pass
2	4	pass
3	4	pass
4	4	pass
5	4	pass
6	4	pass
7	4	pass
8	4	pass
6	5	pass
7	5	pass
8	5	pass
1	6	pass
2	6	pass
3	6	pass
4	6	pass
5	6	pass
6	6	pass
7	6	pass
8	6	pass
1	7	pass
2	7	pass
3	7	pass
4	7	pass
5	7	pass
6	7	pass
7	7	pass
8	7	pass
1	8	pass
2	8	pass
3	8	pass
4	8	pass
5	8	pass
6	8	pass
7	8	pass
8	8	pass

Table 4.12. Results of leakage test

After leak test, the closure torque was verified unscrewing the samples; the test was performed to exclude possible difficulties in opening the jar before the client use. The mean value of the unscrewing torque was 1.74 Nm with a standard deviation of 0.14 Nm, hence the verification was passed.

4.2.3 PERFORMANCE QUALIFICATION

4.2.3.1 INCOMING INSPECTION

The incoming inspection activities (visual inspection, dimensional inspection and leak test) were successfully completed with a deviation observed during the visual inspection of the jars. The visual inspection of sampled components of the jar showed the presence of some aesthetical defects of not acceptable dimensions referring to the acceptance criteria defined in chapter 4.1. The types of observed defects were already seen on components produced with the old equipment; the defects were not repetitive by their nature and were not strictly connected to the use of the new injection molding equipment under validation. In details

- batch 190930166: one jar with one light scratch on the external surface with length more than 2.54 cm;
- batch 190930167: two jars with one light scratch (length more than 2.54 cm) and one jar with three black spots with dimensions less than 0,65 mm concentrated in a small area (acceptance criteria: single black spot of dimension less than 0.65 mm).

Observed scratches had a length above the limit but are very thin and probably they have been made during handling operations after the injection molding process; they can be considered as a marginal aesthetical defect and do not constitute risks in use. The three black spots that were present on one sample had dimensions clearly below the maximum limit and were not accepted only for aesthetical reasons; the particles were completely embedded in the jar material and did not constitute a risk on the product. The presence of the defects was notified to the supplier in its quality control but it was not considered critical for the purpose of this validation.

4.2.3.2 PROCESS CAPABILITY: JAR

Firstly, measurements of the thread diameter (A) and the height (B) of 13 jars from the three different lots were acquired.

JAR							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol.-
		64,8	0,15	0,15	64,7	0,3	0,3
PQ Lot ID	Sample n°	Detected (mm)					
1909030165	1	64,77			64,64		
	2	64,76			64,65		
	3	64,74			64,65		
	4	64,75			64,65		
	5	64,74			64,66		
	6	64,75			64,64		
	7	64,74			64,65		
	8	64,73			64,64		
	9	64,75			64,64		
	10	64,75			64,67		
	11	64,75			64,65		
	12	64,77			64,64		
	13	64,75			64,67		
1909030166	1	64,73			64,64		
	2	64,74			64,64		
	3	64,76			64,68		
	4	64,75			64,67		
	5	64,75			64,64		
	6	64,74			64,66		
	7	64,72			64,65		
	8	64,75			64,65		
	9	64,73			64,65		
	10	64,74			64,65		
	11	64,75			64,66		
	12	64,73			64,64		
	13	64,78			64,64		
1909030167	1	64,77			64,65		
	2	64,75			64,66		
	3	64,78			64,64		
	4	64,76			64,67		
	5	64,76			64,64		
	6	64,77			64,68		
	7	64,74			64,64		
	8	64,74			64,66		
	9	64,75			64,65		
	10	64,76			64,67		
	11	64,77			64,67		
	12	64,76			64,67		
	13	64,75			64,66		

Table 4.13. Measurements of critical shares (A and B) of jar

All the measurements of the critical shares were inside the tolerance ranges.

After that, the Normal probability plots relative to the measurements of the thread diameter (A) and the height (B) of jar were obtained, as shown in Figure 4.24 and Figure 4.25.

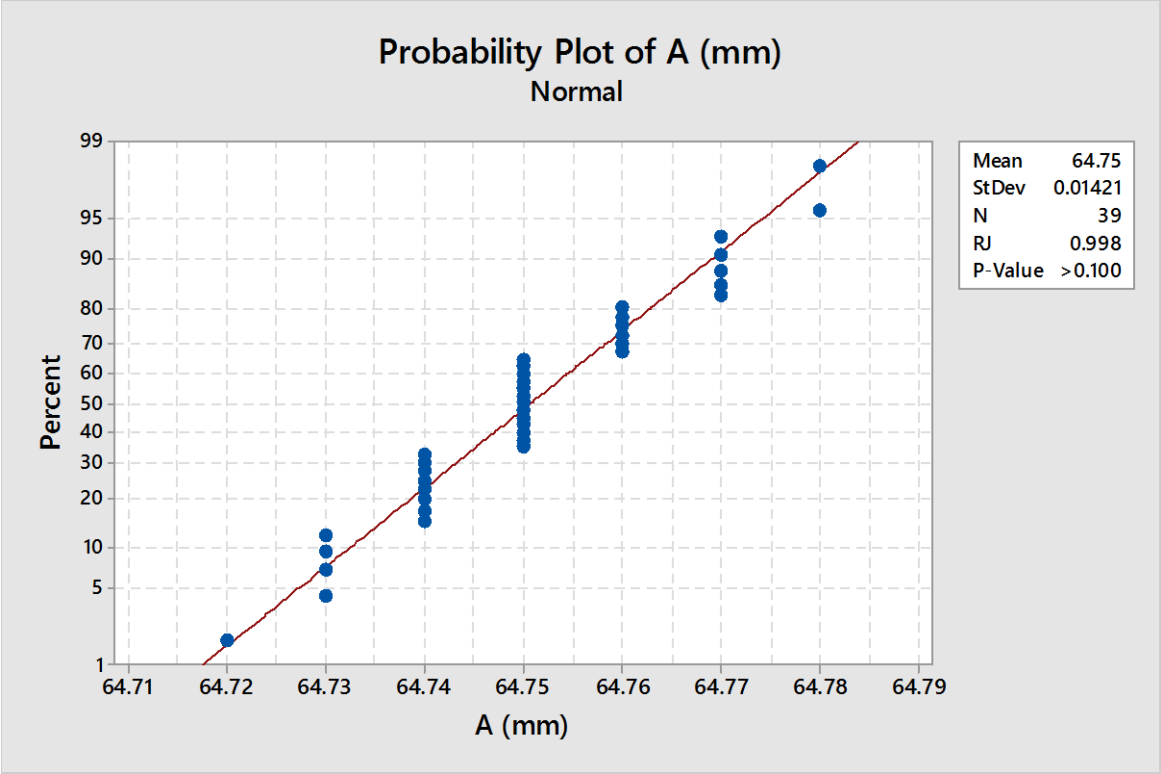

Figure 4.24. Probability plot of the cumulative data relative to the diameter's measurements

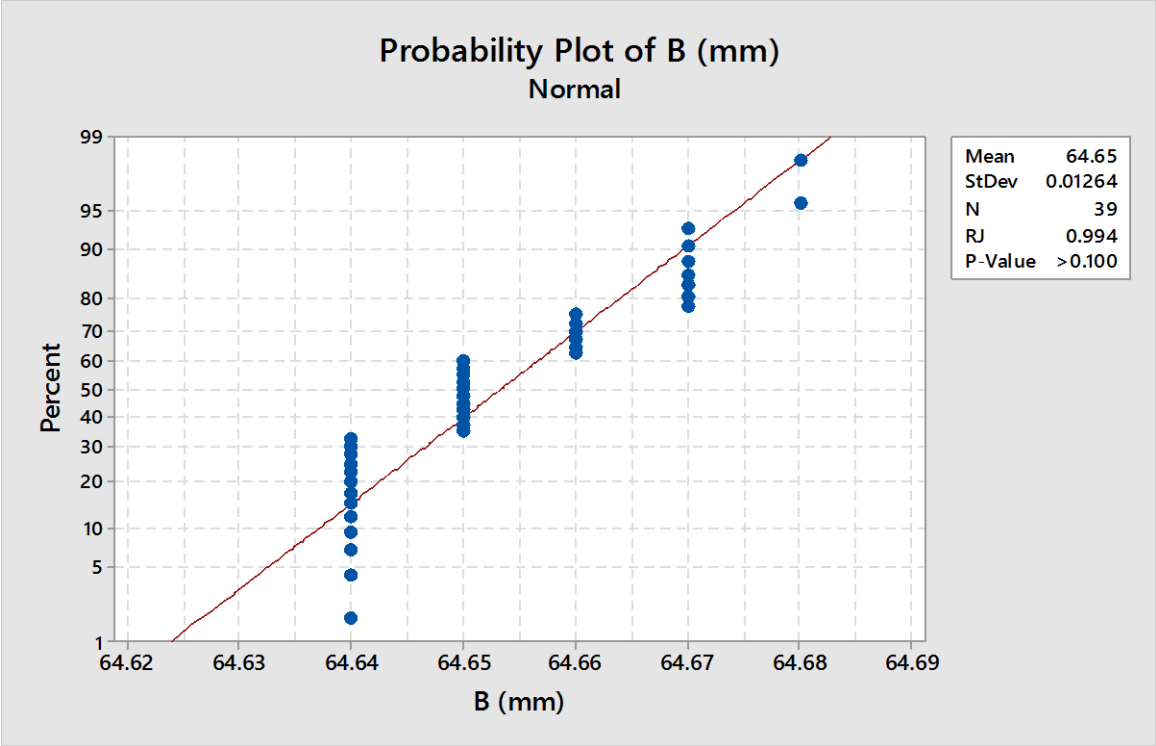

Figure 4.25. Probability plot of the cumulative data relative to the height's measurements

Data points near the straight line and p-value > 0.1 confirmed that it could not be concluded that data were not normally distributed.

After that, the histograms of the data relative to the thread diameter (A) and the height (B) were obtained, as well as the Ppk and Cpk indexes, as shown in Figure 4.26 and Figure 4.27.

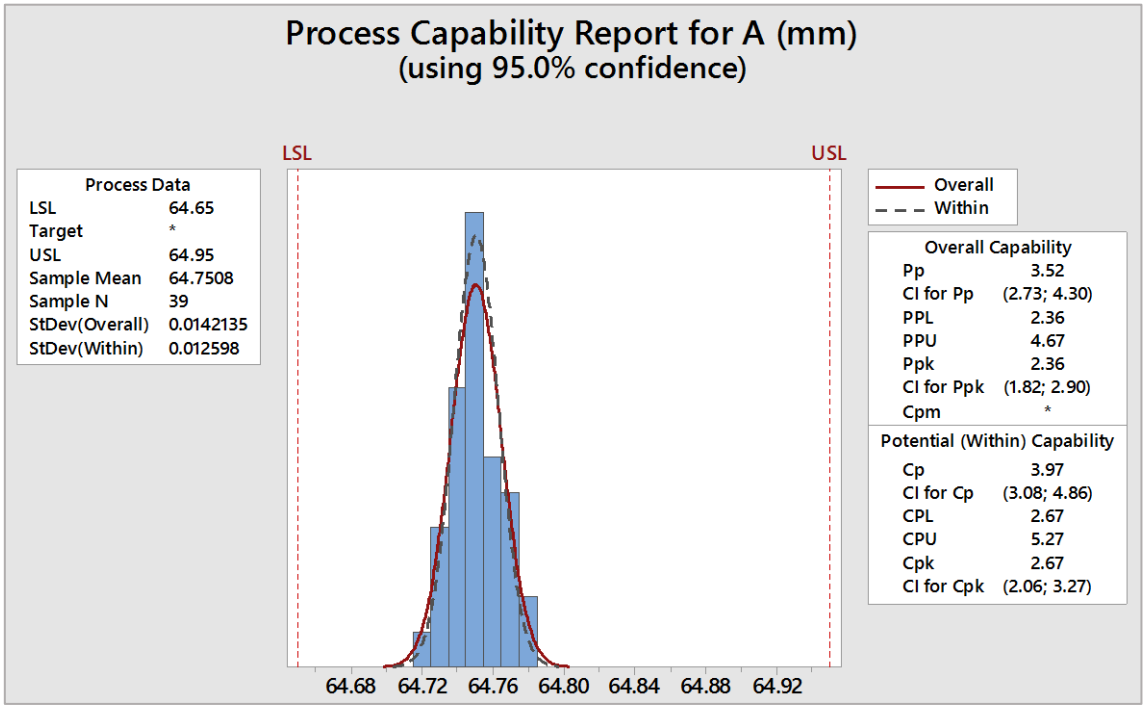

Figure 4.26. Histogram of cumulative data relative to diameter's measurements and Cpk and Ppk indexes

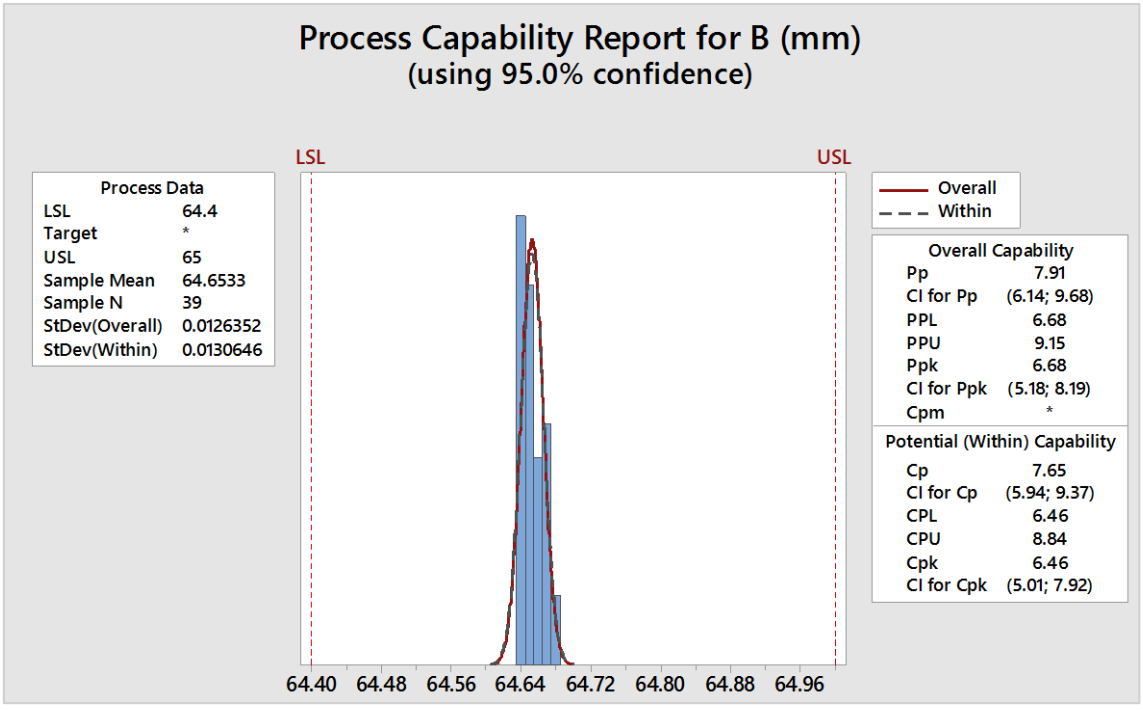

Figure 4.27. Histogram of cumulative data relative to diameter's measurements and Cpk and Ppk indexes

The histograms were contained within the USL-LSL range, as stated when the measurements were collected.

The dashed and continuous curves were similar in both cases, thus the process could be considered stable.

This was confirmed also by the values of Within and Overall Standard deviations which were similar, about 0.0126 and 0.0142, respectively, for the thread diameter and about 0.013 and 0.012, respectively, for the height.

Moreover, the intrinsic variability of the process resulted low, in accordance with the small values of Standard deviation and the narrowness of the two curves relative to the two graphs.

Being the data normal distributed and the process stable, the Cpk and Ppk indexes could be considered meaningful.

Thus, Cpk of 2.67 and Ppk of 2.36 relative to the thread diameter and Cpk of 6.46 and Ppk of 6.68 relative to the height demonstrated that the process was capable in the short and long period, respectively, because the indexes were higher than 1.33.

Moreover, the values of the Cpk and Ppk indexes relative to the A and B critical shares respectively, were similar, confirming the process is stable.

4.2.3.3 PROCESS CAPABILITY: LID

Firstly, measurements of the external diameter (A) and the height (B) of 13 lids from the three different lots were acquired.

LID							
share (mm)		**A**			**B**		
		Nominal value	**Tol. +**	**Tol. -**	**Nominal value**	**Tol. +**	**Tol.-**
		70	0,5	0,2	15	0,2	0,2
PQ Lot ID	**Sample n°**	**Detected (mm)**					
1909030171	1	70,14			15,05		
	2	70,10			15,08		
	3	70,21			15,07		
	4	70,14			15,06		
	5	70,23			15,08		
	6	70,22			15,08		
	7	70,17			15,08		
	8	70,22			15,09		

LID							
Share (mm)		A			B		
		Nominal value	Tol. +	Tol. -	Nominal value	Tol. +	Tol.-
		70	0,5	0,2	15	0,2	0,2
PQ Lot ID	Sample n°	Detected (mm)					
1909030171	9	70,24			15,07		
	10	70,14			15,06		
	11	70,15			15,06		
	12	70,14			15,07		
	13	70,09			15,07		
1909030172	1	70,16			15,02		
	2	70,19			15,06		
	3	70,17			15,07		
	4	70,09			15,04		
	5	70,17			15,04		
	6	70,21			15,04		
	7	70,17			15,05		
	8	70,20			15,03		
	9	70,19			15,07		
	10	70,14			15,05		
	11	70,17			15,05		
	12	70,20			15,07		
	13	70,21			15,04		
1909030167	1	70,10			15,05		
	2	70,17			15,07		
	3	70,22			15,04		
	4	70,14			15,03		
	5	70,08			15,03		
	6	70,19			15,04		
	7	70,09			15,05		
	8	70,23			15,03		
	9	70,20			15,07		
	10	70,14			15,04		
	11	70,09			15,05		
	12	70,11			15,05		
	13	70,12			15,06		

Table 4.13. Measurements of critical shares (A and B) of lid

All the measurements of the critical shares were within the tolerance ranges.

After that, the Normal probability plots relative to the measurements of the external diameter (A) and the height (B) of lid were obtained, as shown in Figure 4.28 and Figure 4.29.

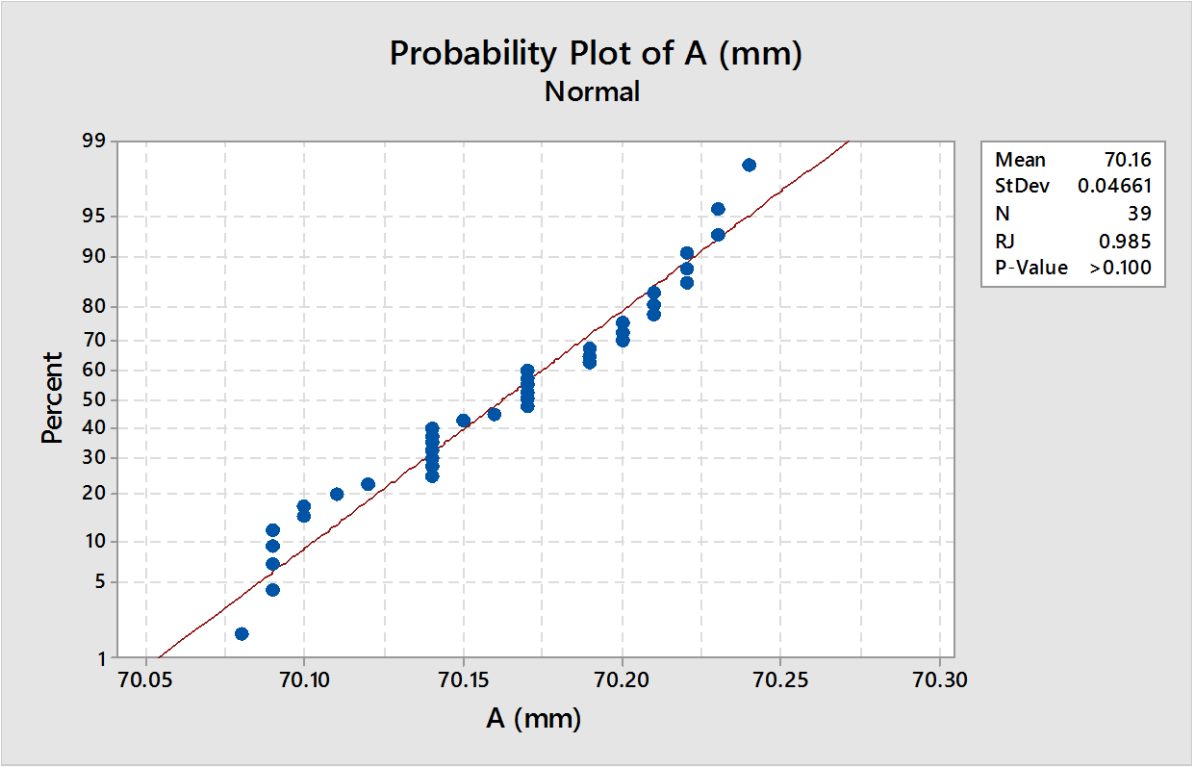

Figure 4.28.Probability plot of the cumulative data relative to the diameter's measurements

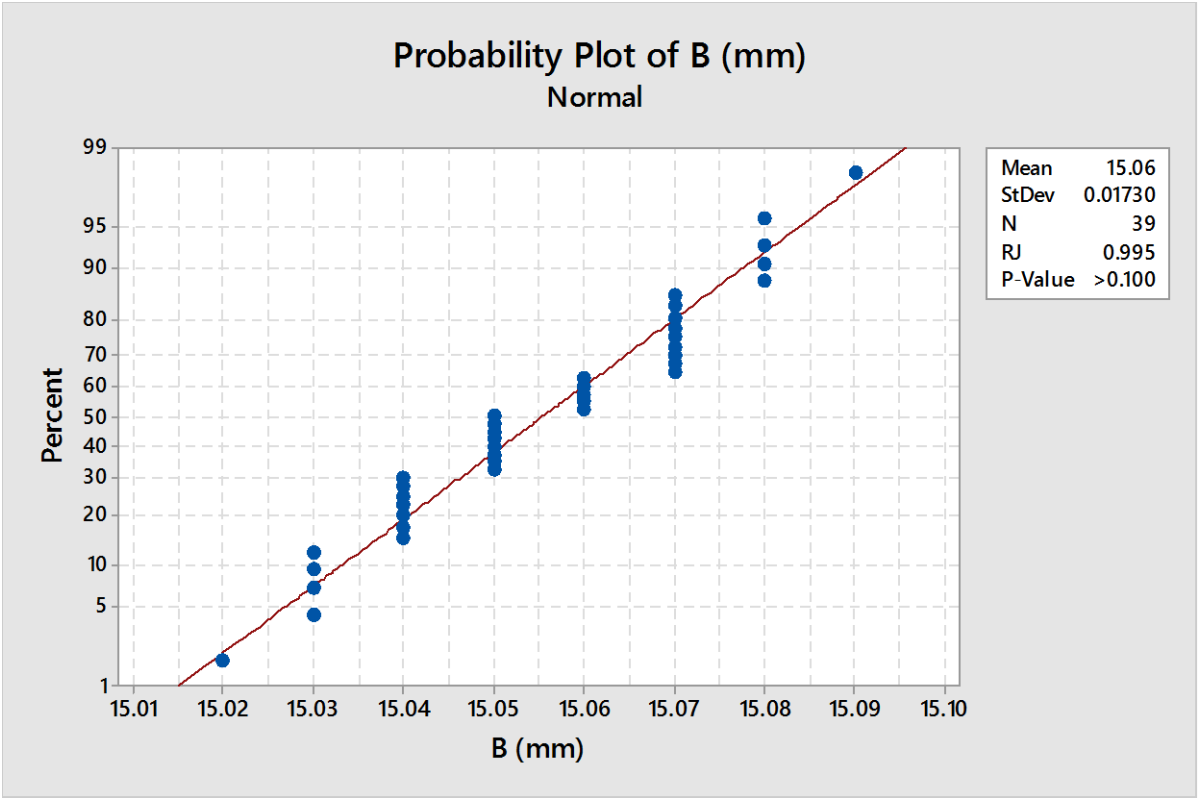

Figure 4.29. Probability plot of the cumulative data relative to the height's measurements

Data points near the straight line and p-value > 0.1 confirmed that it could not be concluded that data were not normally distributed.

After that, the histograms of the data relative to the external diameter (A) and the height (B) were obtained, as well as the Ppk and Cpk indexes, as shown in Figure 4.30 and Figure 4.31.

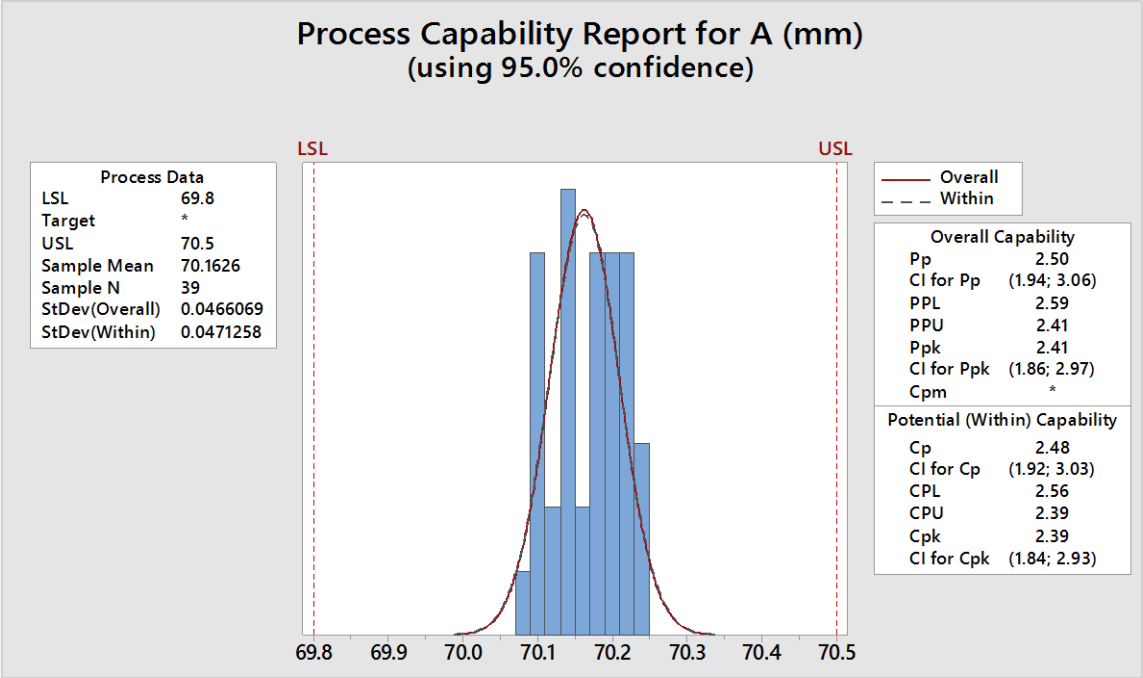

Figure 4.30. Histogram of cumulative data relative to diameter's measurements and Cpk and Ppk indexes

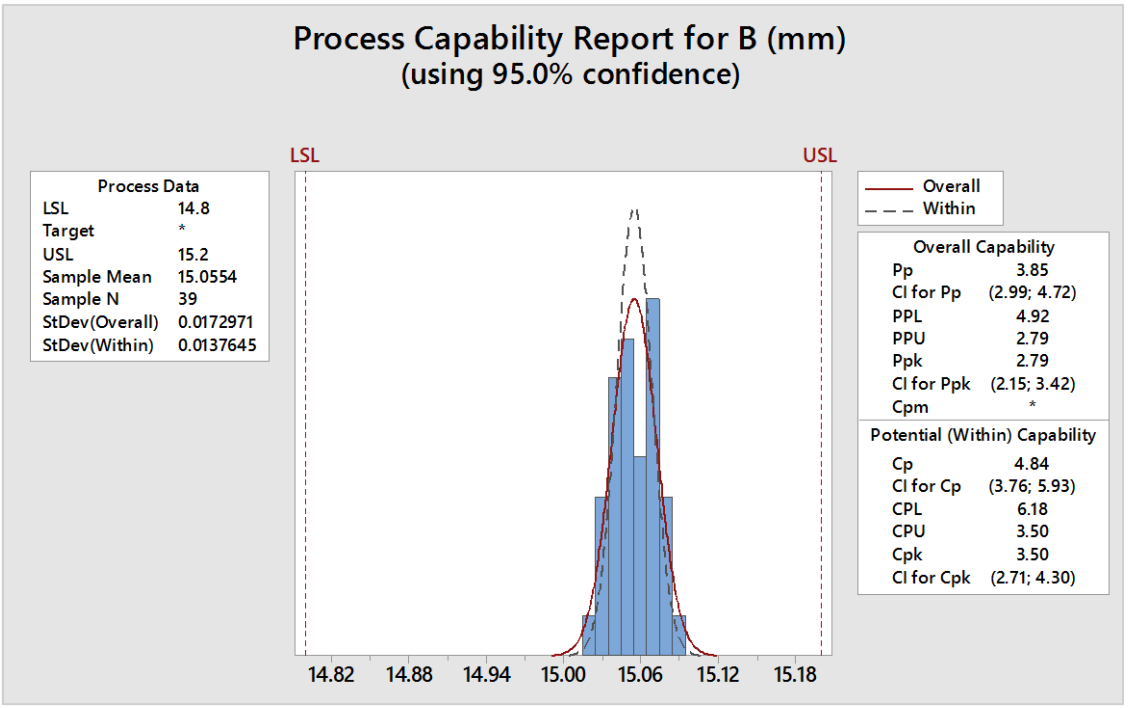

Figure 4.31. Histogram of cumulative data relative to height's measurements and Cpk and Ppk indexes

The histograms were contained within the USL-LSL range, as stated when the measurements were collected.

The dashed and continuous curves were similar in both cases, thus the process could be considered stable. This was confirmed also by the values of Within and Overall Standard deviations which were similar, about 0.047 and 0.0466, respectively, for the external diameter and about 0.014 and 0.017, respectively, for the height. Moreover, the intrinsic variability of the process resulted low, in accordance with the small values of Standard deviation and the narrowness of the two curves relative to the two graphs.

Being the data normal distributed and the process stable, the Cpk and Ppk indexes could be considered meaningful. Thus, Cpk of 2.39 and Ppk of 2.41 relative to the external diameter and Cpk of 3.50 and Ppk of 2.79 demonstrated that the process was capable in the short and long period, respectively, because they were higher than 1.33. Moreover, the values of the Cpk and Ppk indexes relative to the A and B critical shares, respectively, were similar, confirming the process is stable.

4.3 SUMMARY OF THE VALIDATION'S RESULTS

The results of all activities complied with all the requirements of the test protocols.

The planned tests proved that the new injection molding machine installed at the external supplier still guarantees products that meet consistently the specifications and hence injection molding process can be considered validated.

5 CONCLUSIONS

The aim of this work of thesis was to re-validate, according to the prescriptions of the ISO 13485, the injection molding process for the production of jar, lid, and two kind of retainer shelfs which are constituents of the tissue heart valve (THV) sterile barrier, after the change of the injection molding machine from Hydraulic to Electric one. The sterile barrier is the primary packaging of the valve, which comes in indirect contact with it and guarantees the maintenance of its sterility. First of all, the validation technical protocol was developed, in order to describe the main steps of the validation: the Installation Qualification (IQ), the Operational Qualification (OQ) and the Performance Qualification (PQ). The validation protocol also details the inspections that must be performed, their acceptance criteria, the sample size and the equipment needed. For as regards the visual inspection, an improved standardized procedure was defined. It describes the most common aesthetical defects on the THV sterile barrier's components and their acceptance criteria. After that, all the OQ and PQ inspections were performed, and the results were reported. Since all the inspections passed the tests, the validation of the injection molding process with the new equipment was successfully concluded and hence the it was demonstrated that the process is consistent and capable to produce components compliant with the required specifications, assuring that the THV sterile barrier is a safe and effective product.

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