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PRODUCTION REQUIREMENTS OF POLYMERIC MEDICAL DEVICES

Master of Science Thesis

Examiner: Professor Minna Kellomäki
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ABSTRACT

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The medical devices industry has a healthy growing trend nowadays and a promised future. However, a broad range of materials for selection and several specific requirements which concern both the functionality and safety of products are regarded as difficulties by manufacturers who want to set foot in this area. The goal of this thesis is to illustrate a clear pathway from raw material to final products for the manufacturers with production experience of polymeric material based devices.

This thesis is divided into two parts. The first half of this study is a synopsis of a valid production of medical devices. At each processing stage, the requirements and corresponded solutions are generally discussed based on scientific publication, industrial experience and/or related standards and regulation. To emphasis on product validation, the discussion of regulatory issues is infiltrated along the whole medical devices processing procedure. The becoming manufacture can follow this synopsis to evaluate the relevant requirements and solutions.

The Second half of this thesis is focusing on polymeric materials in a material-application manner. As a well-established material category which used in medical devices industry, polymeric materials are preferred candidates due to their processing flexibility, low cost and function diversity. Silicone rubber, thermoplastics and thermoplastic elastomers are three grouped objects with thorough discussion. Subsequently, the possible applications are introduced and categorised by contacting condition with human body. In this part, the commercialized materials and available applications are summarized to provide a direct impression of selection for manufacturers. As the end of comprehensive discussion, two case studies are given to illustrate the practice in reality. In this part, the manufacturer can choose the interested material and move forward to possible application as a fast start-up.

PREFACE

This thesis is sponsored by Teknikum Yhtiöt Oy. Great thanks to my supervisors: Mirva Mustakangas (R&D Director, Teknikum Yhtiöt Oy) and Professor Minna Kellomäki (Tampere University of Technology), I cannot achieve this study without their kind help and advice. Not only have the knowledge been acquired, but also the attitude of dealing with problems is precious experience I have learnt. I also would like to thank my family which is the power to push me moving forward.

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ABBREVIATIONS

General terms:

FDA	Food and Drug Administration
ISO	International Standardization Organization
MHLW	Ministry of Health, Labour and Welfare
SAL	Sterility Assurance Level
API	Active Pharmaceutical Ingredients
DUR	Dose Uniformity Ratio
EtO	Ethylene Oxide
DOE	Design of Experiment
MRI	Magnetic Resonance Imaging

Silicone rubber:

LSR	Liquid Silicon Rubber
PDMS	Polydimethylsiloxane
PDES	Polydiethylsiloxane
PDPS	Polydiphenylsiloxane
RTV	Room Temperature Vulcanized
HTV	High Temperature Vulcanized
FSR	Flourosilicone Rubber
HCR	High Consistency Rubber

Thermoplastics:

PVC-U	Rigid Polyvinyl Chloride
PVC-P	Plasticized Polyvinyl Chloride
UHMWPE	Ultrahigh Molecular Weight Polyethylene
PP	Polypropylene
COC	Cyclic Olefin Copolymers
PS	Polystyrene
PMMA	Polymethyl Methacrylate
PC	Polycarbonate
PU	Polyurethane
PET	Polyethylene Terephthalate
PBT	Polybutylene Terephthalate
PCT	Polycyclohexylenedimethylene Terephthalate
PETG	Polyethylene Terephthalate Glycol
PCTG	Polycyclohexylenedimethylene Terephthalate Glycol
PCTA	Polycyclohexylenedimethylene Terephthalate Acid
PA	Polyamide
PSU	Polysulfone
PES	Polyether Sulfone

PPSU	Polyphenylene Sulfone
PEI	Polyether-Imide
PAI	Polyamide-Imide
PPS	Polyphenylene Sulfide
PEEK	Polyether Ether Ketone
LCP	Liquid Crystalline Polymer
PTFE	Polytetrafluoroethylene
PFA	Perfluoro Alkoxy Copolymer
FEP	Fluorinated Ethylene Propylene Copolymer
PVDF	Polyvinylidene fluoride
PCTFE	Polychlorotrifluoroethylene
ETFE	Ethylene Tetrafluoroethylene Copolymer
ECTFE	Ethylene Chlorotrifluoroethylene Copolymer
ABS	Acrylonitrile Butadiene Styrene
SAN	Styrene Acrylonitrile
ASA	Acrylate Styrene Acrylonitrile
MABS	Methacrylate Acrylonitrile Butadiene Styrene
SBC	Styrene Butadiene Copolymer

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1. INTRODUCTION

Despite worldwide economic slowdown or even recession, the global medical devices industry has continued growing healthily in the past decade. Although developed markets dominate medical devices sales today (US, EU, Japan accounts for over 75% of total sales), the emerging markets such as China, India, and Latin America are seeing 10 to 15% annual growth rates in the medical devices market, expectedly.[1][2] The driving forces in these emerging markets are the breakage of historical barrier which, meanwhile, improving of affordability, accessibility and acceptability.

According to FDA and European Commission's definitions, the term 'medical device' covers a broad range of engineering apparatus, instruments, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory.[46][117] Generally, syringes, medical tubing, blood bags, sutures, these common tools in hospital; ECG machine, CT, MRI, these diagnosis devices; and artificial heart, joint prosthesis, all can be called medical devices. This variety gives manufacturer the opportunity to step into this industry by their familiar approach. For example, a metal forging company can fabricate some metallic parts of medical devices when the specific requirements have been met.

However, some production requirements of medical devices often show their brutality to the newly recruited companies that would hold them back in exploring this area. Therefore, it is necessary to consult and examine the requirements and capacity of the company thoroughly before and during development of new products. A systematic analysis of the pathway from raw material selection to final products can ease the sophisticated consideration procedure of manufacturer, and it is the goal of this thesis study.

Starting with introduction of processing requirements in production plant such as clean room and sterilization, a general procedure of exploiting new medical devices production is discussed. The regulatory issues are often regarded as obstacles to deal with; however, the valid production cannot be achieved without regulatory approval. Therefore, the discussion of regulatory issues should be infiltrated along the whole medical devices processing procedure.

Being a manufacturer of medical devices, which probably as a role of contracted supplier, the material selection would be a challenge. Firstly, the intended use of the device should be clear. Secondly, the material selection would determine the processing condition, and vice versa. Moreover, the material selection can have great influence on the properties of final products. Among numerous material options, plastics and elastomers show their advantage on the nature of low cost, design flexibility, good process-

ability, broad range of physical and mechanical property, biocompatibility, sterilization resistance, etc.[1][43] Nevertheless, this diversity of plastics and elastomers gives the manufacturer difficulty to make decision.

In this study, plastics and elastomers are grouped into three categories: liquid silicone rubber, thermoplastic, and thermoplastic elastomer; while each category has its pros and cons. The silicone rubber has been introduced with many excellent properties including chemical and extreme thermal stability, low surface tension, hydrophobicity and gas permeability with expanded medical application since 1960s and today are one of the most thoroughly tested and important biomaterials.[3] Thermoplastics comprise several synthetic polymer groups: commodity, engineering, and high performance thermoplastic. In this category, processing experience of the certain kind material is a key factor for selection by manufacturer. Thermoplastic elastomers are a series of synthetic polymers that combine the properties of vulcanized rubber with the processing advantages of conventional thermoplastics.[87] In other words, they allow the production of rubber-like articles using the fast processing equipment developed by the thermoplastics industry.

The medical applications of such materials keep improving and diversifying as long as the progressing in material science and technology. The demands from basic function to ergonomic and aesthetic achievement have inspired the designer and manufacturer to presume more efficient, qualified, and exquisite products. For this purpose, the variety of formulation and compounds of polymers are booming all the time. However, for the sake of safety, some products should be made from maturely commercialized material which is recognized by authorities such as FDA or ISO.

2. PROCESSING PROCEDURE SYNOPSIS

On the precondition of existing design concept, a pathway from raw material to final product should be established for manufacturer to achieve a successful production of medical devices. This final product can be either an integrated functionalized system or a component/part of it. Apart from the sophisticated initial concept design phase, a manufacturer or contracted supplier plays an important role to take the design drawing into real product.

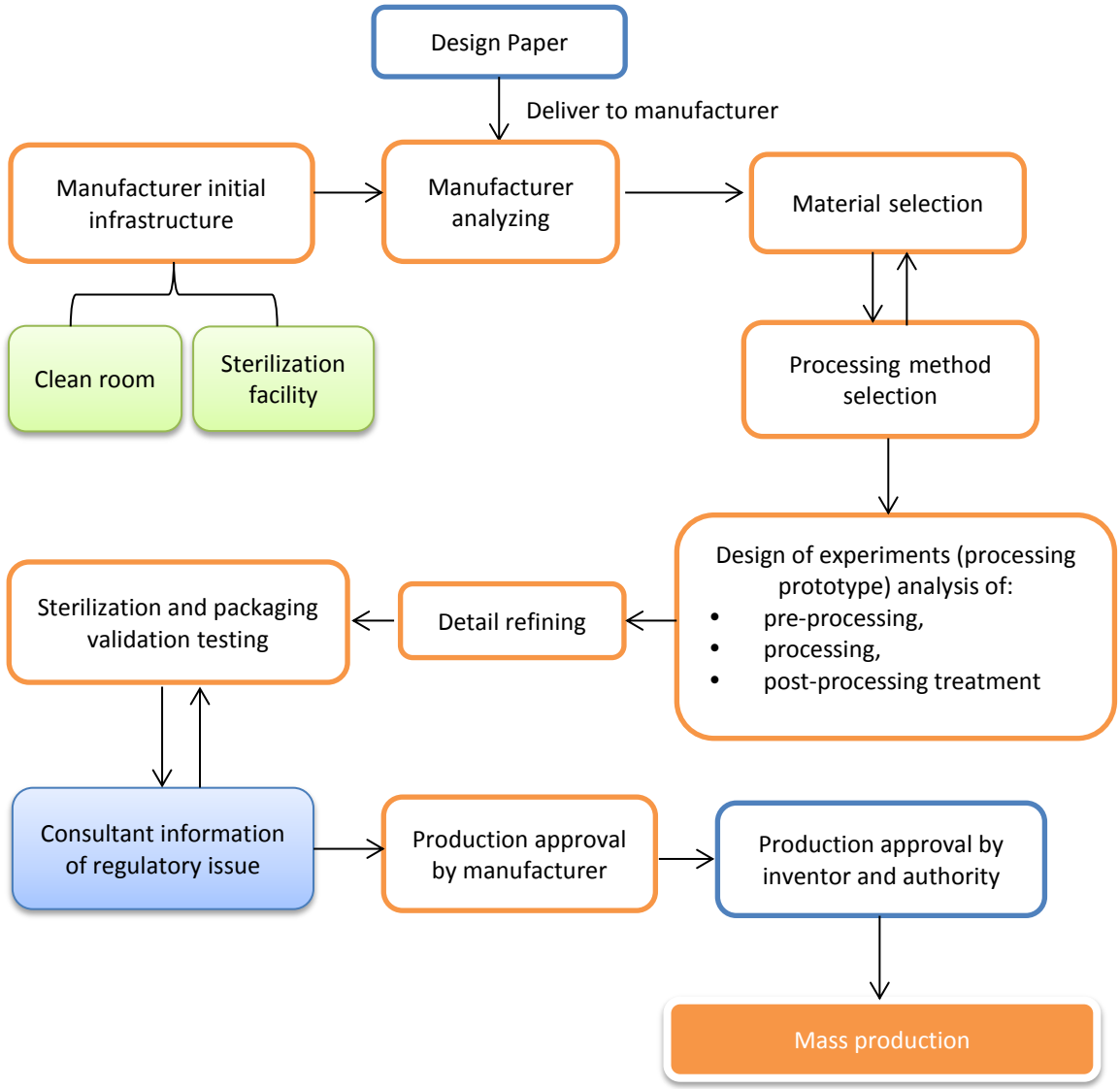


Figure 1: A flow chart of processing procedure of medical devices from raw material to final product

As shown in Figure 1, several steps are involved to achieve a valid production of medical devices. At the beginning, a design paper is done by its inventor. At this stage, the function, dimensional parameters, physical and mechanical properties, and chemical property according to the function should be well defined. The inventor may appoint material and processing method, sometimes, but it is not necessary. Meanwhile, the clean room and sterilization facility is a sign of qualified manufacturer which can draw the interests of inventor (customer) to corporate. However, they are not always a must for some devices design; high precision and consistency is the priority, instead.

With an existing design, a manufacturer starts to analyse the feasible production plan under the regulations from ISO or FDA which equivalent to the designate requirements. In this study, the main applied instructive paper is adopted within European Union Commission in order to get CE mark as a certain purpose.

2.1 Initial infrastructure: Clean room and sterilization facility

In order to achieve the required cleanliness of final product, the contamination is controlled before, during and after production. The clean room can ensure the airborne particles remain in a minimized concentration and restrain the generation of these particles which caused by air flow and operation under controlled environment.[4]

The sterilization is either a physical or chemical approach that eliminates all forms of life, especially microorganisms.[5] Sterilization can be done after packaging or before use which mainly depends on sterilization method and the purpose of device.

It raises the question that when clean room, and/or sterilization is needed. The clean room provides a well-controlled processing environment that allows the manufacture to keep the risk of both inorganic and organic contamination in a low level consistently. However, clean room just can minimize the concentration of contamination; while sterilization eliminates the microorganism existing due to multiplication nature of bacteria: even if one of a billion organisms survives, there is a possibility to rapid multiplication and contamination of the substrate.[5] In other words, sterilization implies an absolute inactivation of organisms. Therefore, the manufacture should make a choice of clean room, and/or sterilization according to the requirements to be fulfilled.

2.1.1 Clean room

In high technological industries, such as electronics, optical and biological industries, the production quality is affected by the airborne particles or dust. Air filter being used in common heating ventilation air conditioning (HVAC) system can never collect these particles, meanwhile, the temperature, pressure, humidity and others factors that make the room suitable for fabrication should be in a controlled manner as well. A matched cleanliness cannot be found in the natural world; therefore, a man-made controlled-environment: clean room, is introduced for such purpose.[6] The demand of clean room for medical devices processing is depended on relevant regulations and requests of a customer. For instance, when the product cannot match the cleanliness level after thor-

oughly washing and sterilization as a result of contamination, a clean room is an option to shoot this trouble. In addition, the clean room keeps the production validation in a consistent trend.[4]

A clean room is defined in the International Organization For standardization (ISO) standard *14644-1 Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness* as:

"room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure are controlled as necessary".[4]

ISO 14644-1 is adopted by the industries except pharmaceutical manufacturers in both the US and EU. Cleanrooms used for pharmaceutical manufacturing have their own standards.[7]

According to this definition, to achieve the minimization of introduction, generation, and retention of particle, an exceptionally large quantity of filtered air is supplied into this room firstly. This air is used to dilute and remove the particle, bacteria and chemicals dispersed from personnel, machinery and other sources within the room; and to pressurize the room and ensure that no dirty air flows into the cleanroom.[4] Meanwhile, the building material of clean room should inhibit the particle generation fundamentally and can be easily cleaned. In addition, personnel are enveloped by specific clothing in clean room to minimize their dispersion of particle and microorganisms.[10]

The building of clean room should be done under consulting experts who are familiar with the practical issue relates to standards. The air cleanliness level by particle concentration is the indicator of the level of a clean room, as shown in Table 1.

According to this classification, for example, an ISO Class 5 clean room contains no more than 832 counted particles with diameter range from 1 to 5 micrometre per cubic meter, no more than 3520 counted particles with diameter range from 0.5 to 5 micrometre per cubic meter, no more than 10200 counted particles with diameter range from 0.3 to 5 micrometre per cubic meter, the rest can be done in the same manner.

It is notable that the first edition of this classification was published in 1999; the newest edition is still in the stage 40.93: Full report circulated: decision for new DIS (draft international standards) ballot. Some modifications have been made in the new edition which is more consistent and scientific, as well as easier to use.[8] Whether using the old version or newest DIS version is based on the consulted verification and confidence level.

Table 1: Air cleanliness classification table by particle concentration[8]
(Reproduced from the new ISO/DIS 14644-1 with permission of ISO)

ISO classification number (N)	**Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes shown below [a]**					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10 [b]	d	d	d	d	e
ISO Class 2	100	24 [b]	10 [b]	d	d	e
ISO Class 3	1 000	237	102	35 [b]	d	e
ISO Class 4	10 000	2 370	1 020	352	83 [b]	e
ISO Class 5	100 000	23 700	10 200	3 520	832	e
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7	c	c	c	352 000	83 200	2 930
ISO Class 8	c	c	c	3 520 000	832 000	29 300
ISO Class 9	c	c	c	35 200 000	8 320 000	293 000

[a] All concentrations in the Table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

[b] These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

[c] Concentration limits are not applicable in this region of the Table due to very high particle concentration.

[d] Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

[e] Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification inappropriate, due to potential particle losses in the sampling system.

Once the clean room is in use, the particle concentration must be monitored routinely or continuously at critical locations during operation and a periodic re-classification should be applied.[8] A particle count is done each and every time a user of the clean room facility is ready to exit the facility. In such a manner, the particle contamination is correlated to amount of use, type of work done and by source of potential contamination. The maintenance of clean room includes: 1) trash removal; 2) replacement of tacky mats; 3) occasional cleaning of all surface of cleanroom. However, the clean room should be completely re-cleaned when the upper limit of acceptable contamination is approaching.[9] The cost of maintenance is composed by material/system consuming and the personnel such as clean room manager.[10]

2.1.2 Sterilization

To eliminate all microorganisms which may arouse interaction by contacting with medical devices, an effective sterilization is applied to the products at certain stage before use if necessary and applicable. The timing of sterilization can be after packaging by manufacturer or before use/reuse in hospital (more generally, the place where the device is intended to functionalize). Efficient sterilization can be achieved by physical or chemical way depends on material type and facility. The common physical approach comprises autoclave (and dry heat), gamma and e-beam irradiation; the chemical way is ethylene oxide (EtO) gas.[13] Due to various molecular composition and sensitivity of

plastic and elastomer, the properties of material are undergoing an irreversible change by exposing to some sterilization conditions. As a result, it is necessary to take material selection into consideration when choosing sterilization method, and vice versa.

The basic requirement for sterilization is to gain effective result without damaging the device. Several indicators like the type and number of microorganisms, the type and amount of organic material that protect the microorganisms, the number and the size of cracks on the device which might be observed during sterilization procedure, and all these can represent the effectiveness of each sterilization method.[11]

According to *ISO 11139:2006 Sterilization of health care products*, the capacity of each sterilization method is defined as sterility assurance level (SAL). It is the probability of a single viable microorganism occurring on an item after sterilization. The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} takes a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.[12]

2.1.2.1 Steam autoclave and dry heat sterilization

As the oldest method, autoclave still plays an important role in medical industry due to its safety and cost efficiency. By applying hot steam under atmospheric pressure, one sterilization cycle can generally be done within half an hour.[13] Two common types of autoclave are differed by different method of removing air from chamber and steam channelling. Gravity-displacement type is done by the pressure that steam-entering chamber exerts on and displace air; while pre-vacuum type removes air by a vacuum pump while steam is injected into the chamber simultaneously.[13] Table 2 summarizes the processing parameters for each cycle.

Table 2: Cyclic parameters of autoclave sterilization[13]

Configuration	Temperature	Time
Gravity-Displacement	121-123 °C	15 - 30 minutes
	132-135 °C	10 - 25 minutes
Pre-vacuum	132-135 °C	3 - 4 minutes

Dry heat sterilization is a choice when the substrate is sensitive to moisture. In the condition that the steam and ethylene oxide gas cannot penetrate, such as anhydrous oils, petroleum products, and bulk powders, this method in a form of hot air can be applied as well. Due to the absence of moisture, the microorganism is destroyed via a slow process of heat absorption by conduction which results in a longer cyclic time (at least two hours) and higher temperature (160-170 ℃).[13] Due to these hazard parameters, its applicable use is limited.

2.1.2.2 Ethylene oxide (EtO) Sterilization

In 1950's, ethylene oxide (EtO) was introduced as an effective, low temperature chemical sterilization method. It is completed in the 50-60℃ range as a cycle of 16-18 hours.[13] As a chemical agent that kills microorganisms, including spores, EtO must have direct contact with microorganisms on the sterilized item. Due to high ignitability and explosibility of EtO, an explosion-proof chamber in a controlled environment is essential to carry the sterilization out.[13]

W. J. Greaves Walker, et al. reported that it was never permissible to regard EtO as practically non-poisonous.[14] For this reason, the EtO sterilized device must be packaged with wraps and be aerated. The aerated time should be long enough to ensure the safety for handling and end using.[13]

2.1.2.3 Irradiation sterilization

Irradiation sterilization eliminates microorganisms via causing microbial death or indirect chemical reaction with an ionizing radiation. This sterilization method has effects on cells and microorganisms depending on three factors: wave-length, dosage, and exposure time. The first use of ionizing radiation can be traced back to 1895 and the method patented in 1921.[11]According to European Pharmacopoeia, the reference dose of 25 kGy is enough to achieve a sterility assurance level (SAL) of 10^{-6}, without any significant rise in temperature.[15]

One key parameter of irradiation sterilization is the dose uniformity ratio (DUR) which is a ratio between the maximum and minimum dose needed to process a product effectively. Due to some plastic and elastomer are sensitive to irradiation, an optimal DUR can prevent unacceptable levels of degradation. Thus DUR is a parameter that must be taken into consideration during sterilization method selection.[16]

At the present, the three main irradiation methods, gamma, X-ray, and e-beam, are differed by irradiation mechanism: radioactive source or electrical source, as shown in Figure 2. The different natures of sources has attributed distinguishable advantage and limitation of each method.[16]

As a highly penetrating and commonly used sterilization method, gamma irradiation is generally used for sterilizing gaseous, liquid, and solid materials, homogeneous and heterogeneous systems and disposable medical equipment. In pharmaceutical field, both active pharmaceutical ingredients (API) and the final dosage forms can be sterilized by gamma irradiation sterilization. Gamma rays are generated with the self-disintegration of Cobalt-60 (^{60}Co) or Cesium-137 (^{137}Cs); and it can be applied on many materials except PVC, acetal and PTFE.[11]

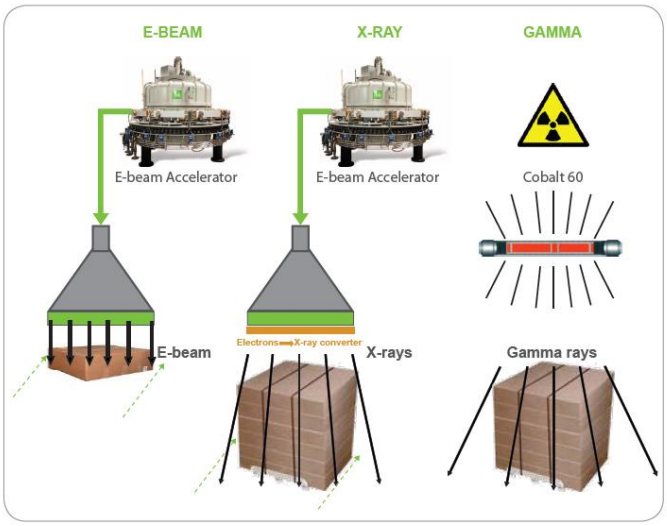


Figure 2: Three main irradiation sterilization method: electrical source and radioactive source[16]

E-beam irradiation method is made by obtaining e-beams from accelerator. Admitted as a safe, non-emissive, and high speed processing, e-beam has been attracting more attention recently in medical device industry. Accordingly, electron-beam dose-rates are much higher than gamma resulting in significantly reduced exposure times (gamma irradiation: 10 to 20 hours exposure[13]; e-beam: 15 minutes[11]). E-beam is by far the cheapest sterilization technology, as well as the most energetic efficiency[16], shown in Figures 3 and 4. If products are compatible, e-beam is the preferred method. Typically, high energy e-beam sterilizes products are packaged in boxes.

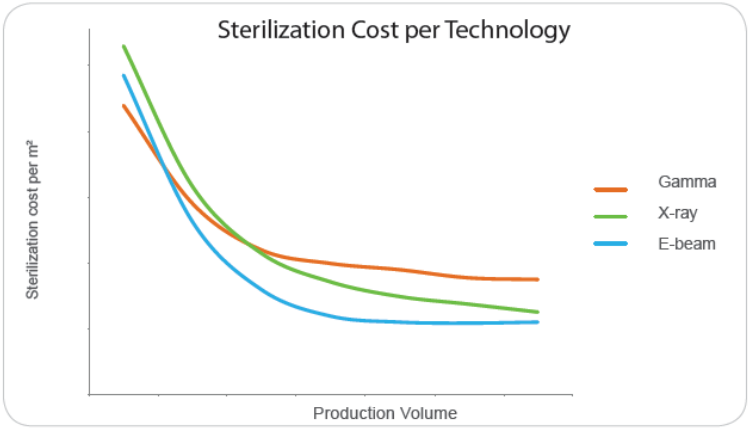


Figure 3: X-ray product sterilization costs decrease faster than gamma when production increases, while the e-beam is the most costless one[16]

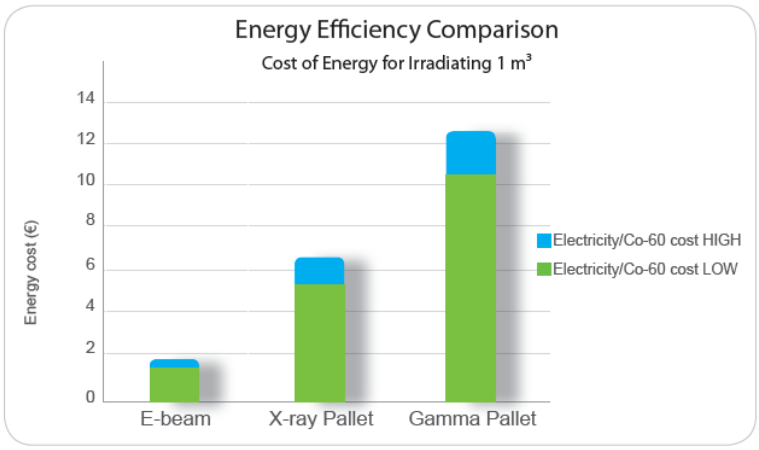


Figure 4: Energy efficiency comparison of each irradiation sterilization method[16]

With a better penetration than e-beam and higher cost efficiency than gamma, X-ray radiation provides an alternative choice when the product wall thickness is incompatible with the e-beam. However, it is not an officially accepted sterilization method for drugs and reused medical devices.[11]

The penetration depth of e-beam has limited its application. A comparison of penetration depth between gamma and e-beam irradiation in same medium is shown in Figure 5.

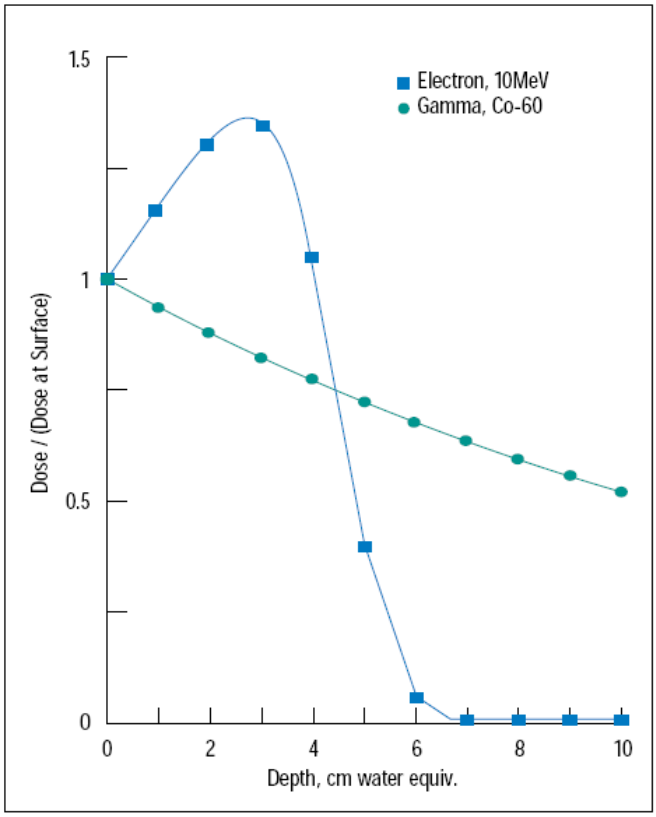


Figure 5: Dose vs. depth comparison of e-beam and gamma sterilization[17]

This graph illustrates the more limited penetration (over gamma) of the e-beam, and this curve is valid for most plastics and objects with the similar density of water. Elec-

tron beams penetrate only about 6 cm in water with normalized dosage, 10 MeV, and about as deeply into 70% isopropyl alcohol/30% water solutions, since the densities are about the same. The dose from gamma irradiation is 60% of the surface dose at the depth where the electron beam dose is virtually zero.[17]

The selection among irradiation sterilization method is mainly based on four aspects: 1) homogeneity layout in their packaging; 2) material / polymer resistance to irradiation; 3) penetration needs; 4) sensitivity of the products. Generally, the preferred method is implied by the raw material supplier.[16] However, the product design may influence the selection by changing geometric dimensions. A general decision pathway is shown in Figure 6 to help the selection procedure.

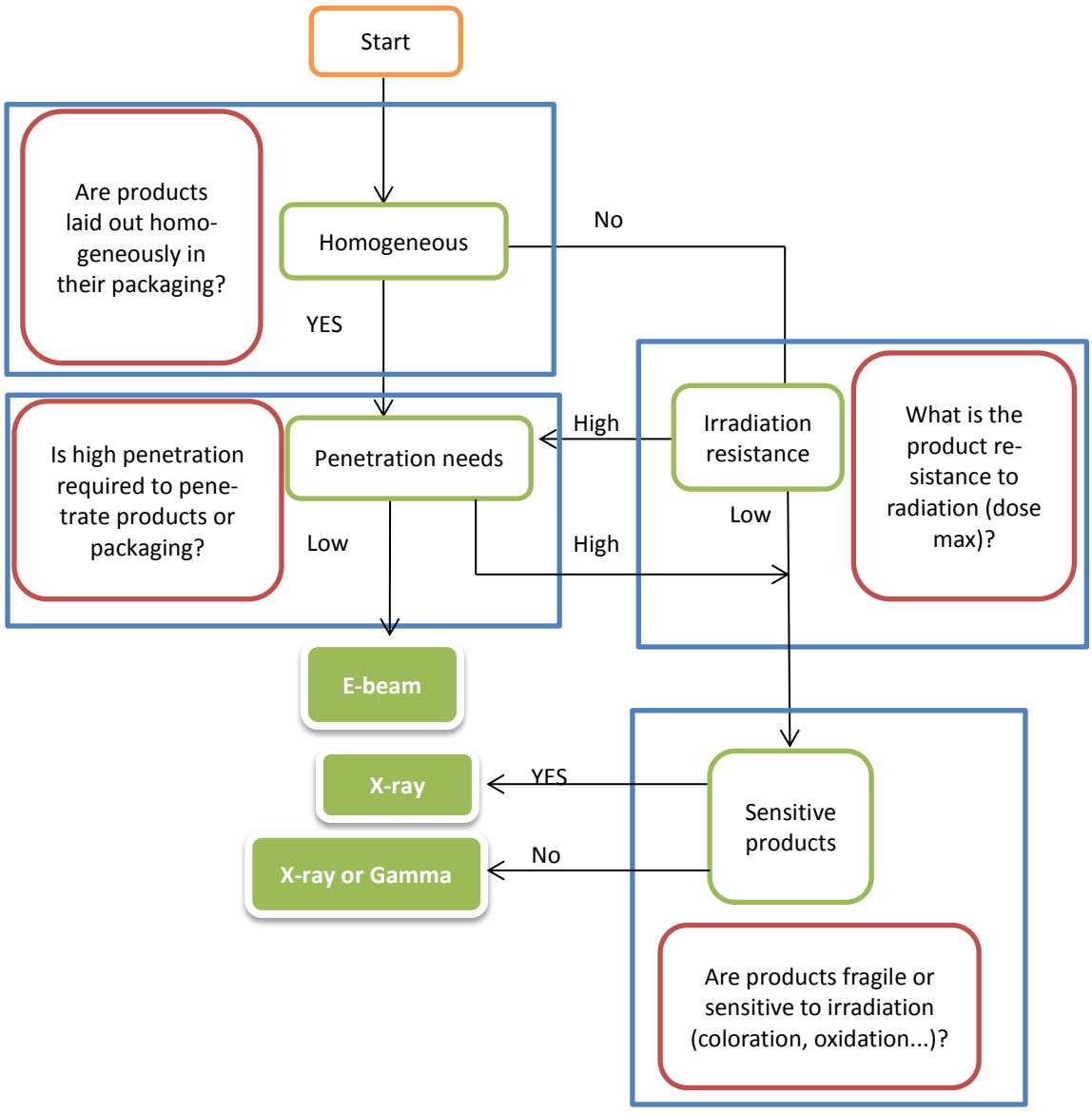


Figure 6: Decision tree for irradiation sterilization method selection[16]

Following this procedure, the suitable irradiation sterilization method for certain product can be identified.

2.1.2.4 Comparison and selection of sterilization methods

Each sterilization method has its limitation, so that there is no absolutely ideal one. Table 3 shows the general advantage and disadvantage of each method. However, as the technology moving on, the new sterilization method might arouse and the weakness of existed method can be improved. Therefore, this table of comparison can only be used for general consideration.

Table 3: Sterilization methods comparison table[11]

Method	Advantage	Disadvantage
Pressured vapor sterilization (Autoclave)	• Maturely commercialized • Nontoxic and safe for the environment • Short processing time	• Harmful to heat and moisture sensitive material
Dry heat sterilization	• Non-toxic and safe for the environment. • Absence of moisture	• Long processing time • High heat
Ethylene oxide (EtO) sterilization	• Maturely commercialized • Moderate temperature • No limit for lumen • Complete penetration depending on the use of the permeable gas.	• Long processing time • Flammable, and explosive • EtO is toxic and carcinogenic, aeration period is required
Gamma radiation sterilization	• Maturely commercialized • High SAL guaranteed • Easy to control • High penetration depth	• Long processing time • Expensive set-up
E-beam sterilization	• Maturely commercialized • Short processing time • High SAL guaranteed • Easy to control • Cost efficiency	• Low penetration depth • Expensive set-up
X-ray radiation sterilization	• Highest penetration depth • High SAL guaranteed • Easy to control	• Not commercialized yet

According to Table 3, the material sensitivity, cost efficiency, sterilization batch capacity should be taken into consideration. More generally, the rules for sterilization selection have been defined as per *Decision Trees for the Selection of Sterilization CPMP/QWP/054/98*, shown in Appendix 1.[18]

According to ISO standard, the term *terminal sterilization* refers the process whereby the product is sterilized within its sterile barrier system.[30] Hereafter, this term is used for this certain case.

The products which intend be sterilized, should be sterilized to clear state in their final containers. It ensures not only the product per se, but also the entire packaging sys-

tem is sterile before open/use. The final result is to achieve no more than 10^{-6} SAL level, by all means. Except the common sterilization method, which including autoclave, dry heat, and irradiation, the formulation filtration and aseptic processing are options as well in some extreme cases. Commercial considerations should not be used as justification for not using terminal sterilization with the highest level of sterility assurance.[18]

The validation of sterilization is obtained by microbial load determination (bio-burden) and sterility testing, before and after sterilization respectively according to *ISO 11737-1* and *-2*.[19] The bio-burden test, shown in Figure 7, is aiming to determine the number of viable bacteria on the product before sterilization. Meanwhile, the test procedure should be conducted via valid tests steps.

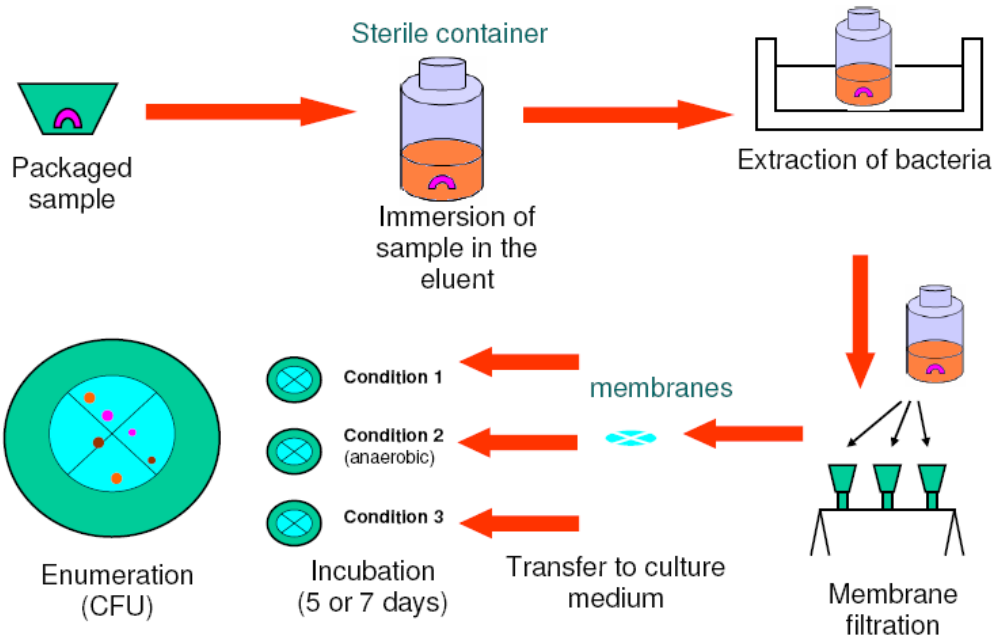


Figure 7: Description of pre-sterilization bio-burden test[19]

After sterilization, the sterility test is applied to detect the presence of viable bacteria on the product (Figure 8). The common used test mediums are trypticase soy broth (TSB) and thioglycollate broth with resazurin (TBR) according to standards.[19] The number of tested samples is decided by consultants as per *ISO 11737-1* and *-2*.

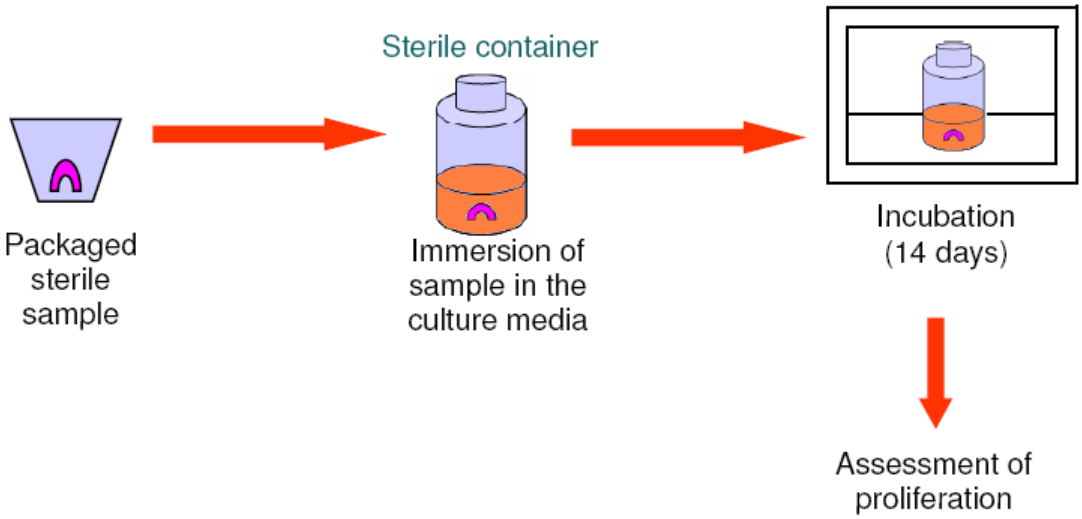


Figure 8: Description of sterility test[19]

The assessment of proliferation can be done via outsourcing or by manufacturer itself. A rapid testing might be achieved by ready-to-use consumable biological indicator under professional instruction.

2.2 Feasible analysis for production

When design paper is delivered to manufacturer, the staffs start to analyse the essential productive elements. To meet the requirements by the nature of products, proper material and processing methods selection is the key to achieve functionality of product. Following with design of experiments to conjecture possible problems in real practice and make revision, a reliable and effective production plan can be established eventually.

2.2.1 Material and processing method selection

By well-defined requirements, locating the suitable material solution for medical device is taken design, processing and performance demands into consideration simultaneously.[20] Briefly, the summary of material and manufacture processing selection is shown in Table 4.

Material characterization refers to composition, mechanical property, thermal property, and electrical property if applicable. The middle column in Table 4 lists the requirements shared by material and processing method selection. The polymeric material offers a good flexibility to design, easy fabrication and sterility integrity[1][43]; however, it raises difficulty for selection due to the ever changing formulation development and variety unless the inventor appoints the certain material. Material and processing method compatibility with the plant's existing manufacturing systems is a reasonable entry point.

Table 4: Material and processing selection criterion[20]

Materials selection		Manufacturing processing
• Mechanical characterization • Shelf life and dimensional stability • Optical clarity • Water vapor transmission Rate, O_2 and CO_2 barrier • Material aging • Biocompatibility • Chemical resistance • Leachables and extractables • Environment friendliness • Lot-to-lot consistency from resin supplier • Supplier technical service	• Processing requirement; Extrusion /molding/ thermoforming, etc. capability • Product components assembly • Compatibility with the plant's existing manufacturing systems • Cost • Sterilization methods and sterilization resistance • Wide processing operation window	• Large-scale manufacturability • High production output rate

2.2.2 Design of experiments

In the industry, the term: design of experiments (DOE) refers an effective method that is to apply a computer-enhanced, systematic approach to experimentation, one that considers all factors simultaneously. Rather than a trial-and-error manner which may neglect something through testing one factor at a time while holding other factors constant, DOE provides information about the interaction of variants and the way the total system works.[21] In this study, polymer manufacturing industry in particular, a DOE analyses the whole production procedure, including pre-processing, in-processing and post-processing treatment, by varying the parameters in each stage.[28] This DOE may involve complicated mathematical modelling, statistic calculation and computer software assistance which is not the concern of this study; instead, all the changeable parameters are considered and discussed.

2.2.2.1 Pre-processing treatment

To fulfil the device design requirement, additives and modifiers are often introduced into polymers due to the property limitation of certain polymeric materials. By incorporation with additives, the properties of formulated plastics and elastomers can be tailored to provide a better processing and end performance.[22] For example, rigid polyvinyl chloride can be made flexible with the addition of plasticizers; the strength of some polymers can be enhanced by mixing with glass fibre; flame retardant can reduce the risk of flammable material; [23] the introducing of tungsten powder can decrease the protein absorption on the surface[64], etc.

Many additives like fillers, toughening agents, lubricants, and stabilizers can be used to improve the physical and mechanical properties. Other properties are modified by more specific additives such as radiopaque additives; nano-additives can be used in small amounts to produce miniature parts and devices that are strong and that incorporate functional characteristics like electrical conductivity, barrier property, radio-opacity

and antimicrobial properties. Stabilizers can be used to improve thermal and radiation resistance.

Additives which should be mixed before processing, the homogeneous dispersion or laid out is crucial. Additives can be incorporated into the polymer at several stages:

1) During the polymerization, which the ready-to-process compounding can be purchased directly;
2) Addition to the raw granulates in pre-processing treatment;
3) In-processing stage;
4) Finishing stage on the product surface.[23]

Additives such as stabilizers are often introduced by raw material supplier, whereas performance-critical additives such as fillers, flame retardants, anticoagulation agents are usually mixed at the compounding stage by device manufacturer via a blender or milling machine.[23] The blending ratio is usually provided by supplier, however, some fillers amount and orientation (lay-out) should be adjusted by user to meet specific purpose. While, the leaching, migration, evaporation and degradation are main issues to be considered which may have potential health risks.[24] New approaches are under development along with the ever developing of polymer technology.

Biocompatibility is the priority of selection of additives. The hazard ingredients which cannot match the safety of final products designation are absolutely banned. Meanwhile, the controversial additives are recommended to be replaced by proven safe alternates if possible. The phthalates, used as plasticizer and solvents, are intensively studied due to the ubiquitous exposure to population and may cause endocrine disorder; bisphenol A, which can be found in epoxy resins, polyester styrene, and polycarbonate, has oestrogenic properties that may influence hormone level; polybrominated diphenyl ethers, a commonly used flame retardant added to a variety of consumer products, is considered pervasive endocrine-disrupting environment contaminants of concern.[25] These controversial additives are still under investigation with more updating information.

Due to moisture sensitivity of both polymer and additives, sometimes, the sufficient drying is applied to ensure the optimal quality and yield. Excess moisture in plastics decreases the strength of the product and causes a poor finish on the surface. The need to dry the plastics depends on the storage conditions of raw material and plastic type. Raw material stored in their unopened original packages is considered to be specifically dried unless the drying is required by supplier. The opened materials should be stored in a clean, dry, and even aseptic environment if applicable.

For hygroscopic polymers, such as PET and nylon which are engineering plastics, the drying process is challenging because of the internal moisture that is absorbed into pellet's or fibre's structure. Effective drying demands that the raw material is warmed up and then exposed to dry air in order to drive off the internal moisture; and during processing, dehumidifying device such as desiccant dryers are used. In contrast, the whole pellet is not required to be heated for non-hygroscopic materials, such as PP and PE. Drying of those materials can be done by exposing to heated air with hot air dryers

to dehumidify the surface moisture from recycling or stored environment.[26] It is strongly recommended that the raw material supplier is consulted for drying recommendations.

Desiccant dryer is the most commonly used dehumidifying device; and its ability to produce dry enough air even for the most hygroscopic materials is highly appreciated. Meanwhile, using a dehumidifying dryer with non-hygroscopic plastics can provide benefits for the user, for instance, some weather related problems with drying can be minimized. The dewpoint range for produced dry air ranges from -10 to -40 ℃, even down to -60 ℃, depending on the dryer type and application.[26] The operating principle of desiccant dryer is quite simple as shown in Figure 9.

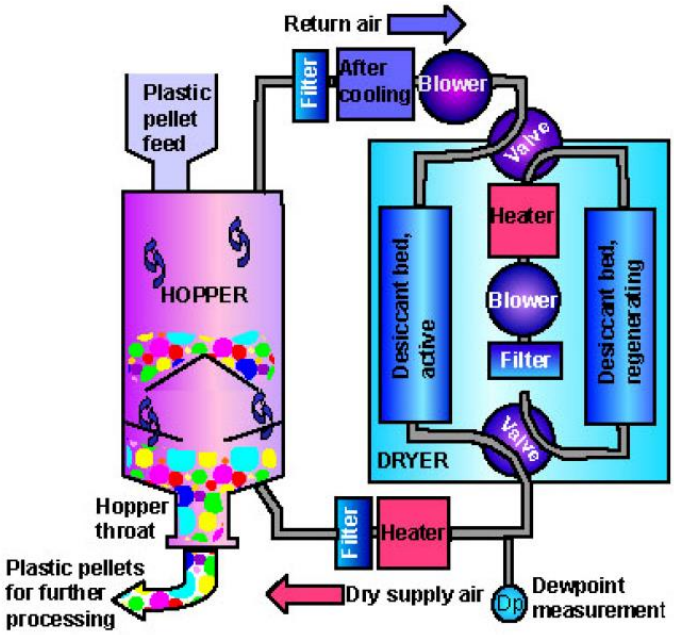


Figure 9: Principle of desiccant dryer[26]

As an indicator of the quality of dry air produced in desiccant dryer, dewpoint should be maintained at a certain level depending on plastics.[26] In order to achieve most reliable data about dryer performance, the dewpoint transmitter is installed before the hopper, illustrated in Figure 9.

2.2.2.2 In-processing parameter

Although some processing parameters and methods are recommended by raw material supplier, this limited information is too general and limited to apply on a specific application. The molding parameters may influence the dimension and microstructure of products directly. These parameters may include additive compounding ratio, feeding speed, barrel temperature, screw speed, nuzzle character, shear rate (depends on the rheology property of material), switchover and holding pressure, cold or hot runner, mold temperature, packing time, cooling time and demolding treatment (draft angle,

etc.). The conventional, experience based trial-and-error method is not only money and time consuming, but also hard to accumulate and pass down the experience. Moreover, there were many uncertain variables besides the working conditions during processing, such as the disturbance of the materials, the influence of ambient temperature etc., which all might influence the product quality.[27]

By the purpose of DOE to find out an effective to analyse the production parameters thoroughly, *Fu-Chen Kung, et al.* have reported an optimization research based on Taguchi method and grey relational analysis.[27] The data were produced by injection molding to find out the optimal level of thin wall part with sufficient tensile strength. The factors which influence on the dimension of thin wall part significantly are injection pressure, injection speed, screw speed, and cooling time. While, the tensile strength of thin wall part is affected by pre-plasticity amount, injection speed, packing time and cooling time. The experiments were conducted five times, and results have proved the reproducibility and reliable (the values all fell within 95% confidence interval). It verified that an optimal processing parameter combination of thin wall part can be received via using grey relational analysis and Taguchi method. Expectedly, this method is applicable for optimization of other processing approach.

Meanwhile, the product design is not always feasible to precise fabrication; therefore, some details should be refined in real production practice. Plastic parts have a tendency to wrap and sink in certain areas, and this is usually overcome by introducing a groove between thick and thin area.[28] A groove functions as a 'defect' that release the imbalance warpage nature of thick and thin are in order to 'lift' the sinking tendency. One example is the difficulty to produce a part with an unsupported wall to remain perpendicular. As shown in Figure 10 (a), a groove can be added that removes the thick area created at the intersection of the perpendicular and main where a supporting rib cannot be designed. A thick area stays hotter for a longer period of time in mold, which increased shrinkage in the part and pulls the wall inward. Another example is shown in Figure 10 (b) that a large-diameter boss with walls for threaded inserts or screw holes for self-tapping screws often too thick to support. A same type of groove feature than Figure 10 (a) can be made around the boss to prevent sinking.

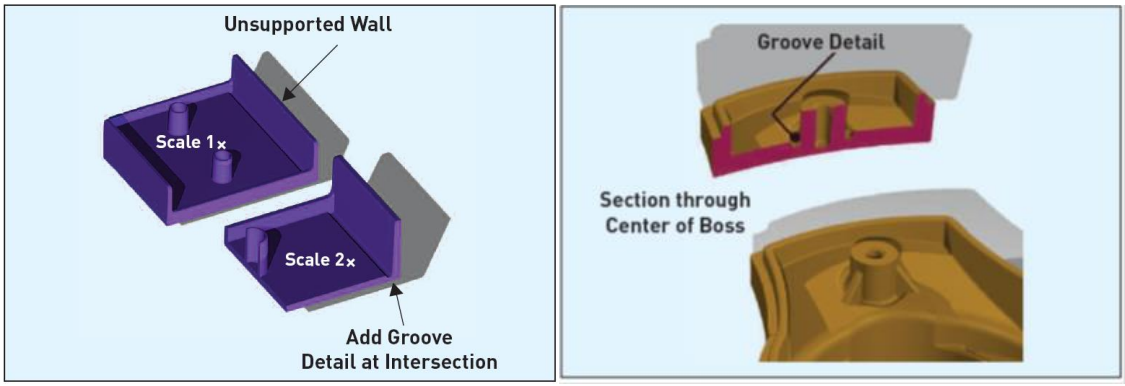


Figure 10: Left (a), an unsupported wall; Right (b), a large-diameter boss[28]

2.2.2.3 Post-processing treatment

The ‘post’ here refers to the timing after mold opening, and before parts assembling. Rather than metal parts are machined into required precision and tolerance, plastic is usually one-step molded except overmolding. This gives plastic the advantages of cost and time efficiency and high production rate; however, the challenge of precise mold design and processing control is raised as well. Usually, mold flash of thermoplastic can be avoided by accurate volumetric filling of the cavity. Considering of thermosets such as silicone rubber, however, it is difficult to prevent the flash due to complicated in-mold curing procedure.[67] In consequence, the trimming is used for these parts.

An attempt has been made by *E. Haberstroh et al.* to simulate the filling procedure of liquid silicone rubber (LSR) to achieve the most efficient mold cavity filling.[29] A specific software, *‘2-1/2-D-simulation software based on FEM using the control volume method of Osswald’*, is used for processing simulating investigation. The filling phase is divided into two steps: 1) the first step is filling the mold to 91% of the volume; 2) the second step is called dilation phase where the cavity is filled completely by the thermal expansion of LSR. The higher filling degrees can be applied to increase processing stability. Nevertheless, the higher filling degree results in higher cavity pressure. The upper limit is 300 to 500 bar according to the mold rigidity as well as design of parting surface.[29]

After the processing, a correct washing is applied to products to remove the possible processing agent and other surface contamination. The washing can be done in industry washing device, and powered by ultrasonic.[118] Subsequently, products are dried under suitable time, pressure and temperature.

In conclusion, the DOE procedure is an evaluation of production feasibility and an improvement of technical details. Figure 11 covers, but are not limited to, considerable parameters.

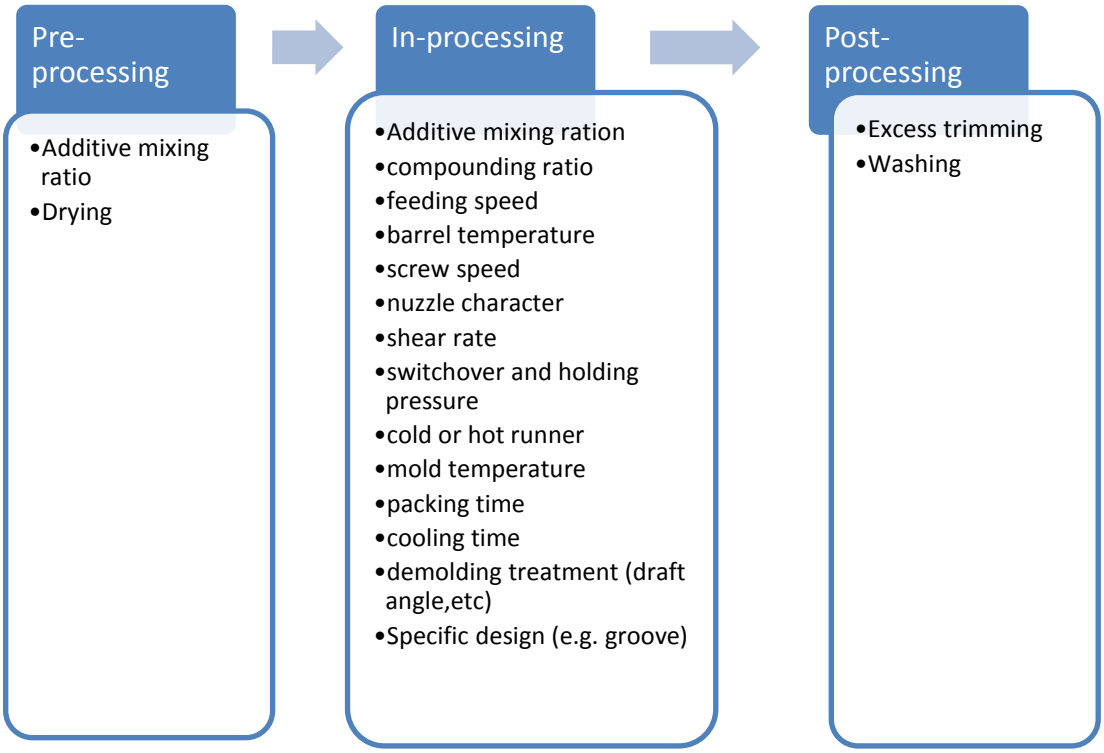


Figure 11: Parameters of polymeric medical device production

2.3 Packaging and labelling

The packaging design and material selection are part of the whole production analysis. Depending on the product dimension, statement (gas, liquid or solid), sensitivity, sterilization method, shelf life and transportation way, that according to *ISO 11607: packaging for terminally sterilized medical devices*, the design of packaging is varying all the time. A packaging design e.g. for contact lenses is completely different than a scalpel handle. When the product is required to be terminally sterilized, it always means the product should be presented aseptically within packaging system for the end-user.[30]

Due to the specific nature of medical device, the choosing appropriate materials for terminally sterilized medical device packaging systems is influenced by the interrelationships that are illustrated in Figure 12.

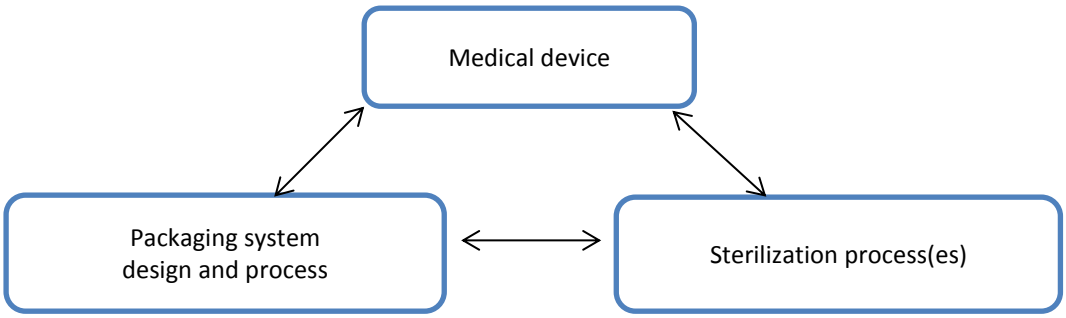


Figure 12: Interrelationships influencing the choice of appropriate materials for terminally sterilized medical packaging system[30]

If the device is intended to be terminal sterilized by EtO or steam, the sterile barrier system has a permeable component to allow the sterilizing gases to enter, kill the microorganisms, and escape without significant residual concentrations.[30] If the device is to be terminal sterilized by irradiation, a permeable component may not be required and the sterile barrier system can be made entirely of impermeable materials.[30] In addition, *Lecon Woo, et al*. have reported that the e-beam is, generally, less harmful to polymer than that of gamma radiation because of shorter processing time.[31]

There are many types and variations of sterile barrier systems used to package sterile medical devices, such as pre-formed rigid tray and a die-lid, flexible peel pouch, sterilization bag, header bag, form/fill/seal (FFS) process, and four-side-sealing (4SS) process.[30] The ultimate goal of a sterile barrier system is providing microbial barrier properties, and sufficient protection under certain storage and transportation within shelf life, subsequently, ensuring a aseptic and valid presentation of device for end user.[30]

The requirements on materials referenced shall apply to those used in pre-formed sterile barrier systems, as well as sterile barrier systems.[30] According to *ISO 11607*, the packaging material selection is similar to material selection mentioned in this study in previous chapter.[30] It is noticeable that the packaging and labelling material and component, e.g. coatings, ink, or chemical indicators, shall not adversely affect the medical device by reaction, contamination and/or transfer before, during or after the defined sterilization process.[30] Beside the design requirements listed in *ISO 11607*, another aspect is the reinforcing attachment where the highly durable environment required device is packaged, a rigid plastic tray may be used.[32]

The testing of packing is given in ISO 11607 as follow,

"Integrity of sterile barrier system shall be demonstrated after sterilization and subsequent performance testing. Physical tests, along with microbial barrier testing of porous packaging materials, can be used to establish the capability of the sterile barrier system to maintain sterility. Standardized test methods for evaluating the integrity of the sterile barrier system are preferred. However, in the absence of applicable validated sterile barrier system integrity tests, microbial barrier performance characteristics can be established by testing the microbial barrier properties of materials and the integrity of the seals and closures."[30]

The following, but not limited to, are some practical tests:[33]

- Internal pressure
- Dye penetration
- Gas sensing
- Vacuum leak
- Seal strength
- Transportation simulation
- Accelerated aging
- Microbial barrier

Meanwhile, a stability testing, which is a different entity form performance testing, shall be launched to demonstrate the sterile barrier system integrity maintenance over time.[30]

Figure 13 shows a commercialized packaging product by *Merrill's Packaging, USA*. It is custom designed with snap features to protect delicate components. This thermoformed PETG heat sealable tray is paired with a Tyvek lid for EtO sterilization.[34]

Figure 13: Packaging of medical procedure tray kit[34]

The labelling of medical device is regulated by Global Harmonization Task Force and FDA, which include format, content; and the used symbols are defined in *ISO 15223*.[35][36] An example of labelling which is valid in EU and the USA is illustrated in Figure 14. The label contains information about the product name, expire date, reference and lot numbers, manufacturer information, bar code, details about the item, and an illustration of the item. The meaning of symbols can be found in *ISO 15223: Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*.[36]

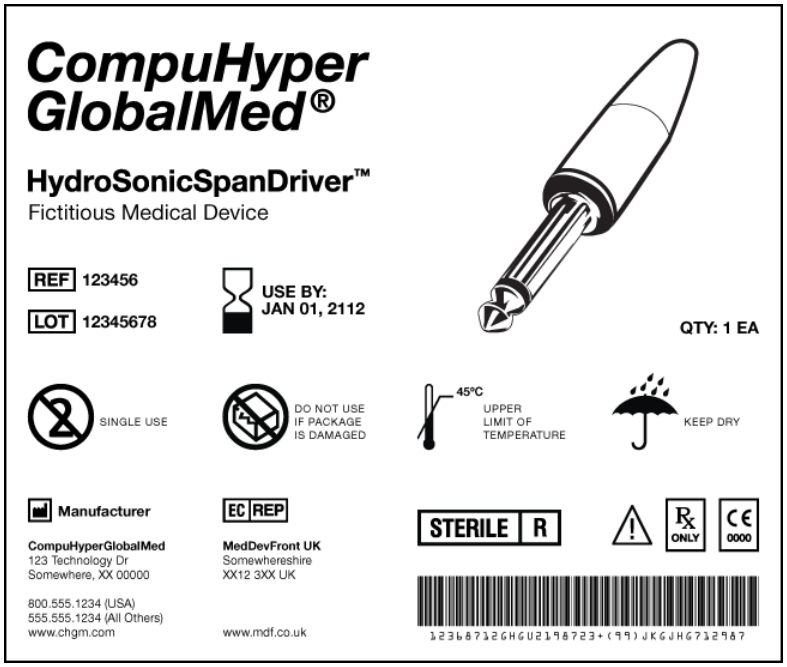


Figure 14: Example of what a unique device identification (UDI) could look like on a medical device label[37]

2.4 Regulatory issues

In order to achieve valid production of medical device, the processing and quality control should be under the consulting which related to regulatory issues. *ISO 10993* is a series of standards that detail all characterization and biocompatibility tests needed for medical grade materials and medical devices before clinical studies.[38] This standard is recognized in both Europe and the United States (FDA version) as well as in China. The details all relevant biological tests needed for the material/device evaluation protocols are given in *ISO 10993-1*; and the subsequent standards are more specific to the type of biocompatibility or toxicity tests. The characterization tests needed for plastics of medical purpose are given in *ISO 10993-18*.[38] The necessity of biocompatibility tests of material/device can be decided by the decision tree shown in Figure 15. Biocompatibility tests of medical device are required according to contacted condition with the human body. The type and degree of testing will differ depending upon the extent and location of contact. Generally, the tests are decided by consultant and out sourced by a qualified institution. Existing data might be sufficient for submission if they are scientifically valid.[38] In a nutshell, no biocompatibility test needs to be applied when both material and device (includes packaging and sterilization) are exactly as same as existed commercialized product. Otherwise it is necessary to assess whether and what test protocol should be followed.

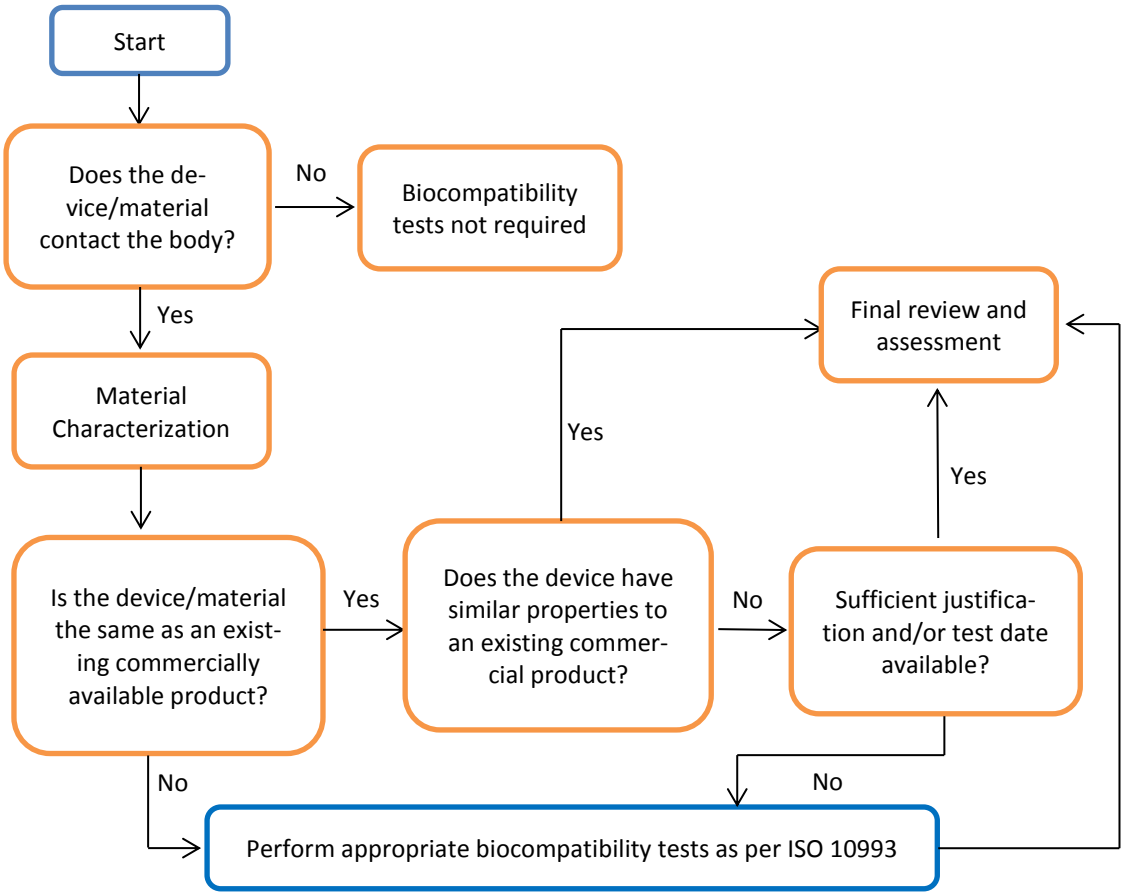


Figure 15: *ISO 10993* Biocompatibility evaluation decision tree for material/device[38]

The term *biocompatibility* is the interaction occurring by a material/device contacting with skin, tissues, or biological fluids for defined or extended periods of time. The materials which have no effect on the composition, function or safety of the biological systems in the patient are required to achieve good biocompatibility. The biocompatibility of a medical device depends upon its nature and composition of material, the design of the device, the contact nature with patient, the duration time of contact and the temperature during contact.[38]

Table 5: ISO/FDA/MHLW test chart[39]

Device categories			**Initial evaluation**								**Supplemental evaluation**	
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Acute systemic toxicity / Pyrogenicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity
Surface device	Skin	A B C	• • •	• • •	• • •							
	Mucosal membrane	A B C	• • •	• • •	• • •	 0 0	 0 •	 •	 0 0		 0	
	Breached/ compromised surface	A B C	• • •	• • •	• • •	0 0 0	 0 •	 •	 0 0		 0	
External communicating device	Blood path indirect	A B C	• • •	• • •	• • 0	• • •	 0 •	 •	 0	• • •	 •	 •
	Tissue/bone dentin communicating	A B C	• • •	• • •	• # #	0 # #	 # #	 • •	 • •		 #	 #
	Circulating blood	A B C	• • •	• • •	• • •	• • •	 # •	0 • •	 # #	• • •	 •	 •
Implant device	Bone/tissue	A B C	• • •	• • •	• # #	0 # #	 # #	 • •	 • •		 •	 •
	Blood	A B C	• • •	• • •	• • •	• • •	^ # •	 • •	• • •	• • •	 •	 •
Test time-consuming (weeks)			2~3	4~9	4~8	3~4	21~ 23	4~ 12		2~6	34~ 36	

A = Limited exposure (≤ 24 hours) B= Prolonged exposure (24 hours – 30 days) C= Permanent contact (> 30 days) • = FDA, ISO and MHLW evaluation tests # = Additional tests for FDA and ISO 0 = Additional tests for FDA ^ = Additional test for ISO

Biological effects include: cytotoxicity; sensitization; irritation/intracutaneous; systemic toxicity; subchronic toxicity; genotoxicity; implantation, and hemocompatibility. These factors are indicators for biocompatibility tests as well. The coverage of these factors is lying on the intended purpose of device, accordingly.[119]

A summary of different biocompatibility tests that should be applied is shown in Table 5, which the different requirements are given as well according to the regulations of ISO, FDA and Japanese Ministry of Health, Labour and Welfare (MHLW).

3. CLASSIFICATION OF MEDICAL DEVICES

A classification of medical devices is necessary to sort the products into certain groups systematically to order to identify the according regulation, processing file, and tests efficiently. In this study, the classification is based on the material, reuse or disposable nature, and application.

3.1 Biomaterials

The first definition of the term biomaterials was committed in 1987 by European Society for Biomaterials and some consistency was achieved.[40] However, the ever evolution of material science and health technology has raised confusion and disarray within new area, such as drug and gene delivery systems, tissue engineering and cell therapies, organ printing and cell patterning, nanotechnology based imaging and diagnostic systems and microelectronic devices, by the old definition. In result, a refined definition is present:

"A biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine."[40]

In this study, the metal, ceramic and glass, synthetic polymer and composite used as biomaterials are discussed, respectively.

3.1.1 Ceramic and glass

Although ceramics and glass had been regarded as brittle materials whose range of applications were constrained by their relatively poor mechanical properties historically, advances in processing technology and a deeper understanding of structure and properties of ceramic and glass have led to the expansion of their capability into a whole host of different areas. The high melting point of ceramic and glass is advantage in engines and turbines at elevated temperatures. With improved toughness, they have been introduced into body armor design as a consequence.[41]

With excellent wear resistance, high compressive strength properties, pleasing aesthetic appearance and proven biocompatibility, ceramic and glass are attractive candidates for biomedical application. Known as bioceramics, they are now used extensively in many different areas of medicine to augment or replace parts of the body. For example, alumina and zirconia are used to fabricate components of hip joint replacements;

hydroxyapatite (HA) and glass ceramics are used as coatings on prosthetic stems.[41] The successful applications are countless and still expanding.

3.1.2 Metallic material

The favorable properties such as toughness, good fracture resistance, electrical conductivity and formability as well as the well-established and widely available manufacturing techniques (e.g. casting, forging, machining), have promoted metal use in medical area. Besides the common medical instruments, metal and alloys are extensively used in the fields of orthopedics and dentistry primarily. The applications of metal and alloy have been expanded to cardiovascular devices (e.g. artificial heart valves, blood conduits and other components of heart assist devices, vascular stents), and neurovascular implants (aneurysm clips). In addition, the good electrical conductivity of metals favors their use for neuromuscular stimulation devices, the most common example being cardiac pacemakers.[42]

3.1.3 Polymeric material

Polymers have been employed in every aspect of medical device industry for many years.[43] Biopolymers based on medical applications can be categorized into three groups, namely inert, bioactive and biodegradable polymers. Each category of this classification comprises natural and synthetic polymers. The inert polymers suit very well with some applications that are aimed to last for a lifetime, such as breast implant polymer, or extracorporeal material. While, if the purposed functionalization time of the product is just for a certain period of time, e.g. one year or so, the biodegradable polymers are considerable choices.

3.1.4 Composite material

Bone, wood, dentin, cartilage and skin, which often exhibit hierarchical structures in which particulate, porous, and fibrous structural features are seen on different microscales, are natural composites. In general, composite materials are solids which contain two or more distinct constituent materials or phases, on a scale larger than the atomic. Composite materials offer a variety of advantages in performance, which highly depending on the structure, comparing with homogeneous materials. There is the potential for stiff, strong, lightweight materials as well as for highly resilient and compliant materials.[44]

In biomaterials, it is important that each component of the composite is biocompatible. Moreover, the interface between components should not be degraded by the body environment via contacting with patient for certain level and time. Dental filling composites; reinforced methyl methacrylate bone cement, and ultra-high molecular weight polyethylene; and orthopedic implants with porous surfaces are good examples of composites for medical applications.[44] In addition, coating is sometimes regarded as composite as well.

3.2 Disposable versus reusable

There are two distinctive different medical devices: disposable ones and reusable ones. The disposable devices are designed to be discarded after use; while the others are being cleaned and reused on the same patient or on different patients. The common concern for both of them is the cleanliness and sterility of the device and the subsequent safety to the patient till the first contact. There are two more basic safety concerns with reusing medical devices over disposable ones. First is the effecting of cleaning, disinfection, and sterilization on the chemical, physical, and mechanical integrity of the device.[45] Usually, the disposable devices are terminally sterilized with packaging by irradiation method; while the autoclave is commonly applied on reusable devices in hospital as well as washing and disinfection.[28] Apparently, this issue should be taken into consideration in material selection. The second concern is providing safety for the personnel who are responsible for cleaning, disinfecting, or re-sterilizing the device.[45] In other words, the personnel should be well informed about the potential risk of reusing these devices. For example, a container which may trap some body fluid such as blood inside, the incorrect opening and contacting of this container would lead to an infection threat to the personnel. Meanwhile, the design of reusable devices should ease the reprocessing procedure.

3.3 Classification by applications

According to *Directive 93/42/EEC*, the classification of medical devices is essential for the purpose of the conformity assessment procedures. The four products classes, *Class I*, *IIa*, *IIb* and *III*, are based on the vulnerability of the human body taking account of the potential risks associated with the technical design and manufacture of the devices.[46] In *Directive 93/42/EEC*, the classification of invasive time of devices is one factor to define. The term *Transient* refers to continuous use for less than 60 minutes; *Short-term* refers to continuous use for not more than 30 days; *Long-term* refers to continuous use for more than 30 days.[47]

The classification of devices is depending on the inventor, whose power is to decide the purpose of a device. For the manufacturer, the concern is of the requirements that each class relates. The *Class I* have low level of vulnerability associated with these product; whereas, for *Class IIa* devices, the intervention of a notified body is compulsory at the production stage; for devices falling within *Classes IIb* and *III* which constitute a high risk potential, inspection by a notified body is required with regard to the design and manufacture of the devices; while *Class III* is set aside for the most critical devices for which explicit prior authorization with regard to conformity is required for them to be placed on the market.[46]

In the area where the FDA guidelines are applied, the classification of medical devices is falling into Class I, II, and III with different definitions. In general, Class I devices present minimal potential harm to the user with simple design, manufacture and a history of safe use. Class II are devices where general controls are not sufficient to as-

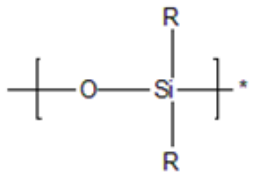
sure safety and effectiveness and existing methods/standards/guidance documents are available to provide assurances of safety and effectiveness. Class III medical devices have the most stringent regulatory controls, which usually support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to the patient.[48]

4. POLYMERIC MATERIALS IN MEDICAL FIELD

The superior design flexibility of polymeric material, comparing to metal, ceramic and glass, makes it an excellent candidate for medical application. They can be processed into myriad shapes, sizes, thicknesses, and colors, and their properties can be tailored to meet a wide range of physical, mechanical, chemical, and biocompatibility requirements. In addition, the additives and fillers can be used to render plastics flexible or rigid, insulating or conductive, hydrophilic or hydrophobic, transparent or opaque, and chemically resistant and sterilization resistant. Meanwhile, the processing methods can vary to meet the production requirements. The lightweight, balanced of strength, stiffness, toughness, ductility, and impact resistance of polymeric material give the designer a broad range of options for both performance and cost efficiency orientation.[43]

4.1 Silicone rubber

As shown in Figure 16, silicone is a group of polymer that backbone is composed by –O–Si–, and the substituent group R can be methyl, ethyl, phenyl, etc.



Silicone, R:Methyl,
Ethyl, Phenyl, etc.

Figure 16: Backbone of silicone rubber[3]

Polydimethylsiloxane (PDMS), which R is methyl, based elastomers have been used in a wide range of biomedical application in the past three decades, as a result of their physiological inertness, good hemocompatibility, low toxicity, good thermal and oxidative stability, low modulus and anti-adhesive properties.[49] When R is ethyl, polydiethylsiloxane (PDES) is tasteless, odorless, and essentially non-toxic, non-irritating, and non-sensitizing; meanwhile offers improved compatibility with better surface lubrication property, pigment wetting, skin feel over PDMS.[50] While the R is phenyl, polydiphenylsiloxane (PDPS) has higher thermal and thermo-oxidative stability than PDMS and PDES. However, the difficult processing is caused by the high isotropic molten temperature which is around 560 ℃ that much higher than decomposition temperature.

To solve this problem, a PDPS-PDMS-PDPS triblock copolymer is introduced.[51] The raw silicone rubber can be either liquid state or solid state, and the liquid silicone rubber, LSR, is the main object in this study. Among different batches of LSR, RTV refers room temperature vulcanized category while high temperature vulcanized ones are HTV.

4.1.1 Properties of liquid silicone rubber

There are many commercialized LSR suppliers, and the properties are varying to meet different requirements. The data in this study is obtained from Wacker, a worldwide silicone solution provider in Germany. And all the material batches are FDA approved. Most of the LSR raw materials are served in two components form, A and B, which B is containing curing agent. While, there is one component ready-to-use batch such as Silpuran® 4200.[52] It is an adhesive which cures at room temperature under the influence of atmospheric moisture.

The mixing of component A and B should be thoroughly by specific accessory on processing machine. The mixing timing is well instructed by supplier especially for RTV. The mixing ratio of A and B is normally 1:1 for LSR, while for the HTV batches, the ratio usually 100:1.5 or higher. Curing temperature of silicone rubbers depends on the type, for LSR the most common condition is around 150 ℃ in minutes (5 to 15) under pressure and with or without post-curing for hours subsequently. Whereas in the case of RTV, the room temperature is sufficient for curing as name implied which takes usually within 1 hour. Moreover, the higher temperature may accelerate the curing procedure of RTV. 150 to 200 ℃ is applied on HTV to cure under pressure and the post-curing is optional as well.

4.1.1.1 Mechanical property of liquid silicone rubber

The first impression of LSR is flexible, but in fact the hardness is varying from batch. From hardness Shore A 5 to 80, a broad range can be chosen. Along with the increasing hardness, the tensile strength is increasing as well, from 0.5 MPa to 11.0 MPa. However, the elongation at break is fluctuating, some batches keep both good strength and ductility. For example, the Silpuran® 6700 series have a medium Shore A hardness of 40 to 60, and the tensile strength is 8.5 MPa; meanwhile the elongation rate are keeping in 500% and higher. This strength is similar than that of low density polyethylene (LDPE), nylon 4,6 and thermoplastic elastomer, and natural material such as ligaments in young human body[53].

Wide serving temperature window is an advantage of LSR in both cold and hot ambient. LSR can be used at 150 ℃ with almost no change in properties, and can withstand 200 ℃ for 10,000 hours or more. Some product batches are even tolerated more than 350 ℃ which the most plastic and elastomer cannot bear. In cold environment, typical organic rubbers become brittle when it is less than -20 to -30 ℃, while compared to -60 to -70 ℃ for LSR. Some batches are still serving at extreme low temperature of less

than -100 ℃.[54] These properties give LSR unique advantage not only in high temperature sterilization, but also in storage and operation application. For example, the cord blood stem cells are stored under -80 ℃, therefore the liquid silicone rubber is a candidate for container of these cells.[55]

Tear strength is the most important physical property for maxillofacial prosthetic material clinically, and the most common used material is PDMS.[56] Thin margins of prosthesis is usually glued with medical adhesive to patient face and is peeled away at night or for cleaning. Therefore it is important that a material with a high resistance to tearing is used to construct theses prostheses to avoid the peeling damage. More generally, the tear strength of thin wall structure is critical when peeling or some sort of tearing is applied on it potentially.[56] The LSR offers high tear strength up to 41 N/mm, comparing to commercialized soft denture lining material which is around 10 N/mm.[57]

4.1.1.2 Surface property of liquid silicone rubber

LSR is hydrophobic material, and the low surface tension gives good release and repellent properties. Moreover, LSR is capable to wet most surfaces which include itself.[3] For medical application, preventing microorganism contamination is a challenge for devices; even the sterilization is applied, the contamination can happen during operation or other activities. With the hydrophobic nature of LSR, the surface microorganism absorption is greatly reduced by slightly treatment.[58] *C. Price et al.* found that after argon plasma treatment for 5 minutes and then immersed for 15 minutes in four separate silane solutions, the candida adhesion is greatly reduced.[58] *Zhenyu Li et al.* have reported that ambient temperature slightly influences on the hydrophobicity in the region ranges from 0 ℃ to 100 ℃; while the surface energy clearly decreases with the increases of temperature beyond 100 ℃. And there is a trend that the higher temperature, the greater hydrophobicity of LSR.[59] It is common that medical devices are exposing to saline for long time, and it might cause changes of material.[60] *J. J. Kennan et al.* exposed LSR to saline under 37 ℃ and 100 ℃ for 45 hours, and they concluded that there is no indication of significant degradation and hydrolysis occurring as well as surface tension under aging conditions.[60]

However, the high surface hydrophobicity of silicone rubber results in the adsorption of significant amounts of protein which constrains their use in biomedical applications. Especially in blood contacting applications, the mediate subsequent thrombotic and immunogenic effects with potentially catastrophic results are caused by non-specific adsorption of plasma protein to an artificial surface.[61] Therefore, it is necessary to adjust the surface properties of LSR in order to enhance its biocompatibility.

D. R. Bennett et al. claimed an invention that relates to a silicone substrate having heparin grafted to its surface. Heparin is a heterogeneous extended polymer that among the most frequently used therapeutic agents for thrombin regulation. The powder form heparin was introduced to the LSR surface before or after the ionizing radiation which

induces free radicals on the surface for grafting. The result of this invention shows a success reduction of non-specific protein absorption on LSR surface.[62] The problem of this invention is to achieve a good graft outcome, it is recommended to dust the heparin powder into uncured or partially cured LSR then cure the product completely. Nevertheless, heparin might dysfunction after the heat vulcanization.

Surface absorption feature of LSR can be modified via gas plasma treatment. The different gases are used in gas plasma treatment and the results are varying. *R.L. Williams et al.* have reported that hemocompatibility of LSR was dramatically affected by plasma treatment, both N_2 and NH_3 treatments causing a highly significant reduction in factor XII activation caused by incubation with the surfaces, that of NH_3 to a level almost indistinguishable from non-contacted platelet poor plasma (PPP).[63] Treatment of LSR with both Ar and O_2 induced a decrease in hemocompatibility, leading to shorter clotting times.[63] The problem of this method is the high costs of plasma device.

The other approach is achieved by simply introducing additive. *Stadi et al.* have reported that incorporation of tungsten metal in powder form in LSR compositions in amounts as small as 0.5% by weight of the total composition inhibits blood clot formation. There was neither deleterious effect of the tungsten in its environment in the bloodstream nor substantial degradation of the properties of the LSR as long as the amount of tungsten incorporation remains below about 33% by weight. An added advantage of the tungsten is X-ray opacity making the invasive device visible to X-rays.[64] This invention is applicable to any invasive device which can be formed from silicone rubber and to extracorporeal device designed for use in handling blood and parts of such devices which can be made from silicone rubber.[64]

4.1.1.3 Biocompatibility of liquid silicone rubber

P.V. Mohanan et al. have done a comprehensive biocompatibility tests as per the international protocol. This was no significant signs of toxicity shown in acute systemic studies throughout the period. No erythema and edema was observed at the intracutaneous injection sites of test sample at the end of study. The hemolysis induced by the LSR was well below the range. Histopathological evaluation of intramuscular implanted LSR showed an excellent biocompatibility. None of the animals have shown a rise of temperature in pyrogen test. The safety and sterility tests resulted in satisfactory outcome as well.[65] In conclusion, the biocompatibility of medical grade LSR is highly reliable.[3]

Although LSR can be chemically degraded by substances capable of acting as depolymerization catalysts, their hydrophobic nature limits the extent of their contact with many aqueous solutions. Typically, the biologic milieu does not present a particularly hostile chemical environment for LSR.[3]

4.1.1.4 Sterilization resistance of liquid silicone rubber

Due to high thermal stability and hydrophobicity of LSR, the autoclave and dry heat can be applied. The EtO and irradiation methods are investigated by *Emilie Gautriaud et al.*[66], and three typical liquid silicone rubbers were examined. Peroxide cure high consistency rubber (HCR) were hardened after both gamma and e-beam treatment; meanwhile, deterioration in mechanical properties (tensile strength, elongation, tear strength, etc.) were detected in all tested samples after irradiation sterilization and more pronounced in the case of peroxide cure HCR. Therefore, it is not recommended the use peroxide cured liquid silicone rubber in any part or component that may be subjected to irradiation-based sterilization procedures.

In contrast, EtO sterilization did not have a significant negative effect on the properties of commercialized liquid silicone rubbers; and it is even enhancing the tensile strength and tensile elongation of platinum catalyst LSR. For this reason, EtO is considered as the treatment to be the preferred method of sterilization for LSR-based medical components.[66]

4.1.1.5 Chemical resistance of liquid silicone rubber

The chemical resistance of LSR is varying from different batches and suppliers. In general, LSR resists water, isopropyl alcohol, some acids, oxidizing chemicals, and ammonia and can meet chemical resistance requirements in elevated temperatures and all methyl silicones resist ozone. The concentrated acids, alkaline, and solvents should be avoided contacting with LSR. LSR can be formulated to enhance its chemical resistance to a given chemical solution. Flourosilicone rubbers (FSR) resist solvents and fuels, and are generally the best silicone rubbers to use in corrosive settings.[67]

4.1.2 Processing of liquid silicone rubber

The most commonly used methods of molding LSR are injection and compression molding. By the nature of liquid state of raw LSR and different thermal behavior, the LSR is processed with similar production rate of thermoplastics via utilizing slightly modified thermoplastics molding equipment.[68] Thermoplastic resin is heated in the barrel and injected into a cold mold, while in contrast, LSR molding requires the liquid rubber to be kept cool in the barrel and injected into a heated mold. The tolerance, venting, and part ejection are aspects of tooling design that differ silicone from thermoplastic. The processing optimizing control is achieved by a similar way than thermoplastic, which temperature, pressure and time are essential adjustable parameters.[67]

As suggested in surface property of LSR that wetting ability to other surfaces, parts fabricated from LSR can be easily bonded to metal, glass, ceramics, silicone-glass laminates, or to LSR per se. Therefore, the coating procedure of LSR is simple without additional preparation and coating process.[67]

4.1.2.1 Injection molding of liquid silicone rubber

Though similar to thermoplastic molding in many ways, LSR molding processing can be quite different. Figure 17 shows the molding cycle breakdown of LSR, cooling of thermoplastic is replaced by heated curing and the ejection of products are taking more time over that of thermoplastic molding.[68]

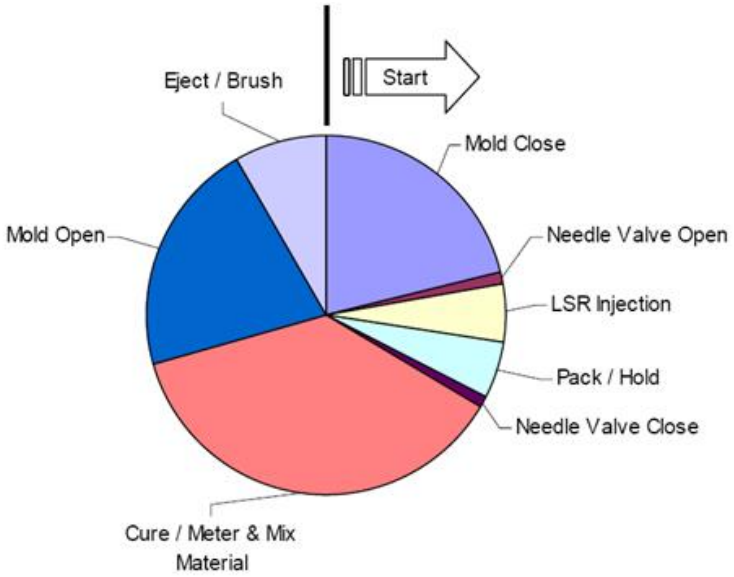


Figure 17: Liquid silicone rubber molding cycle breakdown[68]

The raw material components A and B, in most cases, are pumped from the origin container by pneumatic power. Then the two components are mixed under certain ratio, and colorant can be added at this stage. Before entering nuzzle, the LSR is screened to remove any gels, contaminations, or prematurely cured material that can develop in mixing device. Screen packs, consisting of several different mesh sizes, are retained in a steel housing with inlet and outlet ports. Like the barrel, nozzles are water cooled as well to prevent premature crosslinking during injection and dosing. The cooling channels are arranged so that they ensure the fluid path and cool nearer the nozzle tip, where LSR curing is most likely to occur. After cured in hot mold, demolding is particularly challenging due to the LSR's relatively low viscosity. Ejector pin clearances may flash, thereof, demolding is often accomplished with other means such as brushes or ejector plates.[68]

4.1.2.2 Liquid silicone rubber used as coating material

A superior combination of bond and physical properties that LSR offers is an advantage that most organic rubbers cannot match. LSR can be bonded to any porous or non-porous materials; the bond formed is highly durable and will readily withstand flex movement at high and low temperatures.[67]

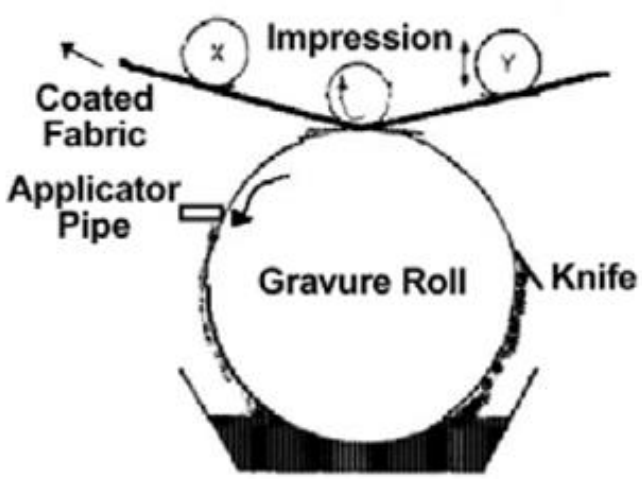


Figure 18: Rotogravure coating[69]

Typical methods for the application of LSR coating to substrate include: knife coating; dip/immersion coating; rotogravure coating (Figure 18); extrusion; spraying. With knife-coating methods, the outcome is influenced by blade type and angle as well as substrate; while rotogravure process ensures that the topcoat is delivered at a constant application rate and is not affected by substrate variability where facilitates higher line speeds.[69]

4.2 Thermoplastics

Thermoplastics are processed by applying elevated temperature, and the procedure is reversible. Therefore the recycle is an advantage of them compared to the thermosets. Based on performance, thermoplastics are categorized into commodity, engineering and high performance groups. The commodity plastics account for about 80% of plastics used for medical devices in applications like labware, tubing, containers, fixtures, and molded connectors.[70] This classification is not the only one, yet there are many other different ways.[43] Figure 19 shows the three groups in ascending fashion which the higher performance ones are in high hierarchies.

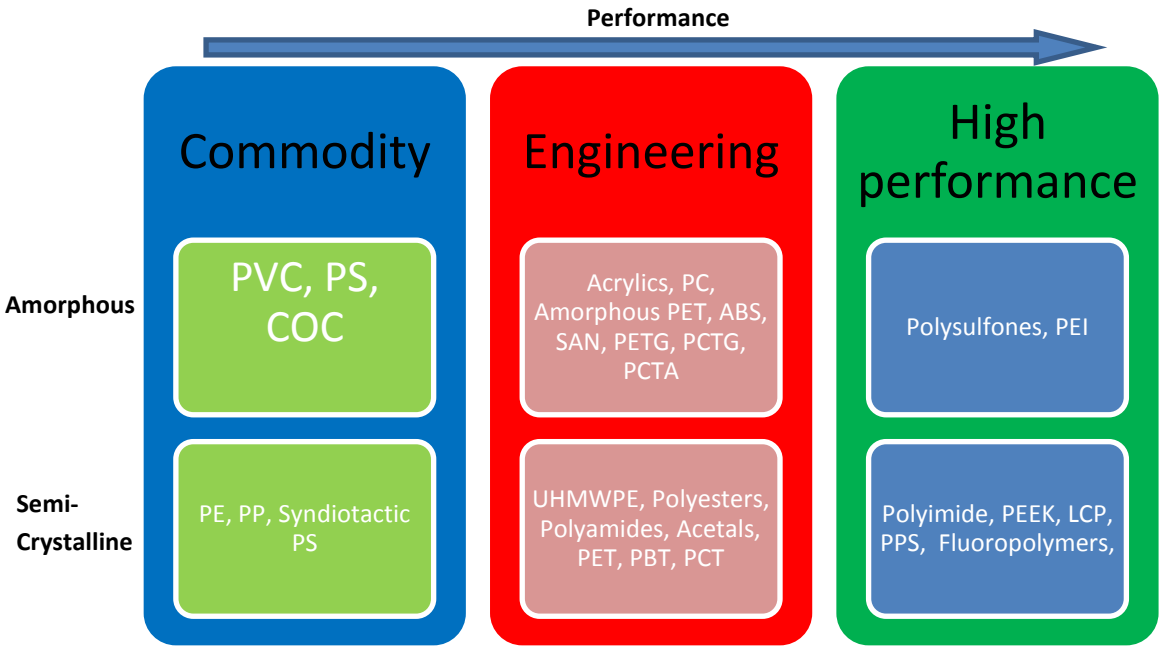


Figure 19: Classification of thermoplastics[70][120][121][122][123]

It is noticeable that there are differences between amorphous and semi-crystalline plastics. Table 6 is a general comparison of them, and it is admitted that the high technology material can break the classification barrier. Amorphous plastics usually are more isotropic in mechanical properties than semi-crystalline ones which are affected by lattice orientation. In contrast, the chemical, thermal, and wear resistance of semi-crystalline polymers are better. In addition, the transparency is highly depended on degree of crystallinity.[70]

Table 6: Amorphous and crystalline polymers comparison table[70]

Property	Amorphous	Crystalline
Optical	Typically transparent, clear	Typically translucent, opaque
Melt viscosity	High	Low
Melting point	Broad softening point	Sharp melting point
Shrinkage	Low	High anisotropic, differential shrinkage
Dimensional stability	Good; consistent predictable shrinkage	Fair
Mold shrinkage	Lower mold shrink; no post mold shrink	Higher mold shrink; can have high post mold shrink
Wear resistance	Poor	Good
Chemical resistance	Fair to poor	Good
Weld-ability	Good	Fair
Heat resistance	Lower	Higher

4.2.1 Property of thermoplastics

Same as liquid silicone rubber and even more complicated, the properties of thermoplastics are varying by types, batches and suppliers. In this study, the properties discussed are based on the commercialized raw materials. Admittedly, the ever changing

technology will make the boundary of commodity, engineering and high performance plastic more and more blurred. In addition, the properties of thermoplastics are greatly influenced by additives and fillers; in this study, the discussion is based on commercialized pure polymers and ready-to-use compounded ones, such plasticized PVC.

4.2.1.1 Mechanical property of thermoplastics

The mechanical strength of commodity plastics is lower than engineering and high performance thermoplastics. The ultra-high molecular weight polyethylene (UHMWPE) has the highest impact strength with good balance of tensile strength and elongation in polyethylene (PE) family. Among commodity plastics, cyclic olefin copolymer (COC) offers the highest rigidity and high light transmission rate. With similar light transmittance of polymethyl methacrylate (PMMA), 92%, COC has much better heat resistance and only tenth of its moisture absorption.[71]

Because of the structure and property diversity, polyurethanes (PU) are considered one of the most bio- and blood-compatible materials known today.[72] However, based on the rubber or hard plastic behavior in working temperature, PU are divided into plastic-like PU and elastomer-like TPU.[72] In this chapter, the plastic-like PU is discussed, while TPU is shown in next chapter. Properties like durability, fatigue resistance in tensile/compression/shear, elastomer character propensity became attainable via utilization of diversified PUs.[72]

Another important engineering plastic family is polyester, which includes homopolymers: polyethylene terephthalate (PET), polybutylene terephthalate (PBT), polycyclohexylenedimethylene terephthalate (PCT); polytrimethylene terephthalate (PTT) and copolymers: polyethylene terephthalate glycol (PETG), polycyclohexylenedimethylene terephthalate glycol (PCTG), polycyclohexylenedimethylene terephthalate acid (PCTA).[73] PET is high stiffness plastic, whereas PBT is better in wrap resistance than PET and PCT has higher heat resistance than other polyester. PTT has good dimensional stability and excellent surface properties. The aim of polyester copolymers is to reduce the degree of crystallinity of polyester homopolymers. PETG is high stiffness plastic with glass-like clarity; PCTG is clear and high impact resistance; and besides clarity, PCTA has higher thermal resistance and elongation than PETG.[73]

Polyamide is an old family of thermoplastics used for medical application; the commercialized materials are nylon 6, nylon 66, nylon 6/12, nylon 12 and nylon 4/6. They are light weight and robust material with balanced strength, and can be reinforced by glass fiber. However, the water absorption is a drawback of polyamide. The moisture content of polyamide can reach as high as 2.6% in nylon 6 and 2.8% in nylon 4/6. The existing of water can cause a decrease in strength and an increase in ductility. A research group in BASF has tested the mechanical deteriorating of polyamide under different temperature at the presence of moisture, the greatest change was found at 23 ℃

where 40% of its original tensile strength has lost, meanwhile, the total elongation has increased by 150%.[74]

Overall, the mechanical strength of high performance plastics is not a superior comparing to engineering plastics. The advantage of high performance plastic in common is the high continuous use temperature as shown in Figure 20. Polysulfones (PSU) and polyetherimide (PEI) are strongest ones among amorphous plastic which combine high mechanical strength and 70% to 80% light transmittance.[75] Polyether ether ketone (PEEK) is a typical stiff plastic with very high tensile strength and modulus.[75] Fluoropolymers, such as polytetrafluoroethylene (PTFE), fluorinated ethylene propylene copolymer (FEP), and perfluoro alkoxy copolymer (PFA), are more ductile mechanically weaker than most engineering and high performance plastics. Nevertheless, the other advantages make them perform well for medical application.[75]

In addition, the styrenics are polystyrene (PS) copolymers and blends with improved chemical resistance and heat resistance. And a better impact strength and toughness is achieved by introduction of rubber-like polybutadiene. The advantage of styrenics, such as styrene acrylonitrile (SAN) and methacrylate acrylonitrile butadiene styrene (MABS), is the high transparency along with high impact resistance.[76]

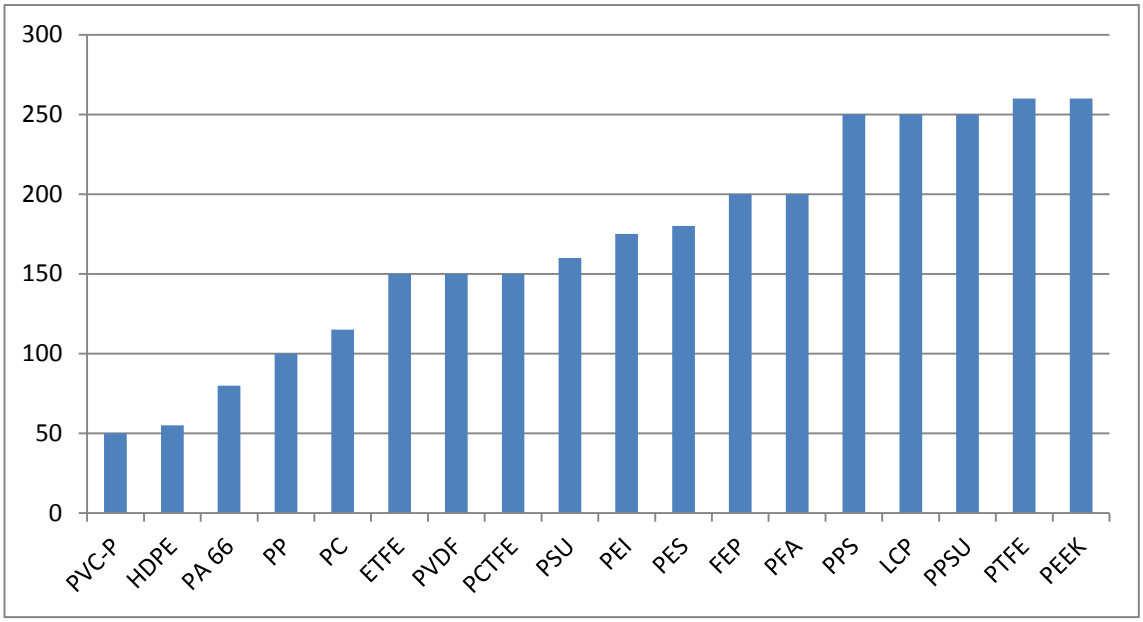


Figure 20: Continuous use temperatures of thermoplastics[75] (Y-axis is temperature in ℃)

4.2.1.2 Surface property of thermoplastics

The surface of a medical device is the place that contacting and interaction take place; therefore it is important to understand surface property of biomaterial. While the contact angle of water on a substrate is a good indicator of the relative hydrophobicity or hydrophobicity of a substrate, it is not good for the wettability of the substrate by other liquids.[77] Critical surface tension γc is associated with the wettability or release proper-

ties of a solid, which serves as a better predictor of the behavior of a solid with a range of liquids. When the surface tension is greater than 45 dynes/cm is called hydrophilic behavior, generally; hydrophobic behavior is observed with critical surface tension less than 35 dynes/cm. [77] As the surface tension decreases below 20 dynes/cm, the surface resist wetting by hydrocarbon oil and considered oleophobic as well as hydrophobic.[77] A general surface tension value for some plastics is given in Table 7, while the value is just a hint for a common view; the real value is varying with different compounding.

Table 7: Surface tension of some plastics[78][79][80][81][82]

Abbreviation	Polymer name	Surface tension (Dynes/cm)
PTFE	Polytetrafluoroethylene	18-19
FEP	Fluorinated ethylene propylene copolymer	20
	Acetal	21.2 to 44.5
UHMWPE	Ultrahigh molecular weight polyethylene	22.8 to 36.7
PDMS	Polydimethylsiloxane, silicone rubber	23
	Natural rubber	24
PVDF	Polyvinylidene fluoride	25
PVF	Polyvinyl fluoride	28
PP	Polypropylene	29 to 31
PE	Polyethylene	30 to 33
CTFE	Polychlorotrifluoroethylene	31
PBT	Polybutylene Terephthalate	32
PS	Polystyrene	34 to 37
PVC p	Plasticized polyvinyl chloride	35
	Polyacrylate (Acrylic film)	35
ABS	Acrylonitrile butadiene styrene	35
	Nylon 12	36
PVA	Polyvinyl alcohol	37
PU	Polyurethane	38
PPS	Polyphenylene sulfide	38
	Nylon 6 (polycaprolactam)	38
PVC r	Rigid PVC	39
PMMA	Polymethylmethacrylate	39 to 41
PI	Polyimide	40
SAN	Styrene acrylonitrile	40
PET	Polyethylene terephthalate	41 to 47
PEO	Polyethylene oxide	43 to 45
	Nylon 6/6	45 to 46
PC	Polycarbonate	46
PES	Polyether sulfone	46
PPO	Polyphenylene oxide	47
	Styrene butadiene rubber	48
The value of each material is just one typical value among the whole material category which the name may present; the value is for reference only.		

It is notable that the water contact angle is not always increasing along with decreasing of surface tension; and some fluctuation may happen in water contact results.[78] The surface property of plastics is depending on other factors as well, such as porosity, functional groups, surface weakness, and mold release agent residual after demolding.[79] The surface property of plastics can be changed or modified into desired manner by

proper surface treatment. For instance, the surface adhesion can be enhanced by abrasion, corona discharge, plasma treatment or flame treatment.[79]

4.2.1.3 Biocompatibility of thermoplastics

Except polystyrene (PS), most of commodity thermoplastics can be found available biocompatible or hemocompatible grade batches from supplier. Although the raw material per se is biocompatible, the additives and processing may affect the bio-performance or show threats, as described in Chapter 2.2.2.1. For example, the plasticizer of PVC, which commonly is di(2-ethyl hexyl phthalate) (DEHP), is often suspected by different authority bodies such as FDA and ISO; and the DEHP contained material is forbidden is some areas which may involve children contacting. Another example is biocompatibility of polyethylene can be influenced by radiation sterilization caused surface oxidation.[83]

Engineering and high performance plastics, including many polymer families, are medical grade available in most cases; and can be improved in bio-/hemo-compatibility by surface modification.[84] The thermoplastics are bio-stable unless it is denoted 'biodegradable'.

4.2.1.4 Sterilization and chemical resistance of thermoplastics

The most commodity plastics can withstand EtO and irradiation sterilization under certain dosage and cycles. For some plastics, such as UHMWPE, a radiation induced surface oxidation may happen; therefore, an inert gas atmosphere is required during processing and even storage.[85] The heat sterilization is not recommended to commodity plastics.[83] The resistance of solvents like tetra hydro furan (THF) and methyl ethyl ketone (MEK) is poor for most commodity plastics.[83]

Engineering plastics performs similarly in sterilization resistance than commodity ones. The polyamides are recommended to be sterilized by EtO only for reuse application. High-heat polycarbonate is withstanding all common sterilization approaches that is an advantage in some applications.[84] The chemical resistance of them is varying by different polymer families. Among these plastics, polyurethanes have the worst performance in contacting with chemicals, generally.[84]

The high performance plastics, except PTFE, can be sterilized by all sterilization methods. Moreover, they have excellent chemical resistance for most solvents and saline.[75] The Appendix 2 shows the sterilization and chemical resistance of some thermoplastics; and the level 'good' refers to long time and high dosage exposure stability, 'fair' is short and medium time period and dosage exposure stability, while 'poor' means the method/solvent cannot be used.

4.2.2 Processing of thermoplastics

Thermoplastics can be processed via conventional and new approaches into desired shape. However, the processing limits are often depended on the property of plastic itself. Such as UHWPE, PTFE, which are high viscosity polymers, are hard to be melt-processed; in industry, they are usually processed by powder sintering instead. In addition, the improvement on the processing parameters may ease the process difficulty. For example, *Shiraki et al.* have invented a general way to process UHMWPE with injection molding machine by changed parameters. The flow rate and mold cavity opening size are increased based on normal PE processing to achieve better mold filling of UHMWPE molten flow.[86] However, this invention is a challenge to mechanical property of the nuzzle and mold.

4.3 Thermoplastic elastomers

Thermoplastic elastomers are a series of synthetic polymers that combine the properties of vulcanized rubber with the processing advantages of conventional thermoplastics. In other words, they allow the production of rubber-like articles using the fast processing equipment developed by the thermoplastics industry. Most of thermoplastic elastomers are phase-separated system under working temperature. The hard phase, usually are thermoplastics, contributes strength; and the soft rubber-like phase is achieved by elastomer molecules.[87] According to *ISO 18064:2005 Thermoplastic elastomers – Nomenclature and abbreviated terms*, a nomenclature system is established for thermoplastic elastomers based on the chemical composition or polymer involved.[116] The term TPE refers generic name of thermoplastic elastomers; among TPEs, the categories such as TPU, TPS, TPV, TPO, TPA etc. are named by different composition and segments arrangement.[116]

TPU, known as one of the most intensive studied medical grade plastic[72], gives myriad performance and property combination. As mentioned in previous chapter, TPU belongs to the great family of PU with elastomeric behavior. The advantage of TPU is the adjustability of properties by same intermediates and the biocompatibility is sustained.[72] For instance, the devices, which are utilizing different hardness/stiffness materials, can be designed and implemented from TPU with same intermediates but different soft-segment and hard-segment ratio; and the biocompatibility is potentially same under this condition.[72]

Some typical commercialized medical grade thermoplastic elastomer systems are polyurethane/elastomer block copolymers TPU (*Monothane*™ from *Dow*®, *Elastollan*® from *BASF* and *Versollan*™ from *Polyone*™), polystyrene/(S-B-S+oil) blends TPS (*Dynaflex*™ from *Polyone*™, *Thermolast*® from *Kraiburg*), polypropylene/(rubber + oil) dynamic vulcanizates TPV (*Versalloy*™ from *Polyone*™), polyethylene/(polyolefin rubber) block copolymers TPO (*Dynalloy*™ from *Polyone*™, *Versify*™ from *Dow*®), polyester/elastomer block copolymers TPE (*Hytrel*® from *DuPont*®) and polyam-

ide/elastomer block copolymers TPA (*Vestamid*® from *Evonik*). Some other suppliers are keeping their formulation undisclosed, such as *Medalist*® from *Teknorapex*.

4.3.1 Properties of thermoplastic elastomers

The properties of TPEs are depended on the hard and soft phase structure and composition. Over conventional thermosets, TPEs are: 1) able to be processed more efficient and lower in cost; 2) there is little or no compounding which TPEs is supplied fully formulated and ready for fabrication; 3) the TPEs scrap can be reused as a regrind frequently producing materials have the same properties as the virgin material. However, there are some disadvantages of TPEs comparing to thermosets: 1) The number of TPEs softer than 50 Shore A is rather limited; 2) The drying prior to processing is common in manufacture of TPEs, whereas this step is almost never used for conventional thermosets.[87]

4.3.1.1 Mechanical property of thermoplastic elastomers

The mechanical property of TPEs is in between the liquid silicone rubber and engineering thermoplastics. The tensile strength of TPEs can be much higher than that of liquid silicone rubber, up to some 50 MPa, and can be as soft as less than 5 MPa depends on types.[76] Large elongation at break and low flexural modulus make them a rubber-like state. Due to molting ability of hard phase, the continuous use temperature is commonly no higher than normal plastics.[88] Due to elevated melting temperature, the TPE parts is limited serve accurately below their melting point.[87]

4.3.1.2 Surface property of thermoplastic elastomers

It is known that the best combinations of elastomer and thermoplastic for TPEs are those in which the surface energy of the two components are matched.[89] Therefore the surface energy of TPEs can be predicted by thermoplastic component which listed in previous chapter.

4.3.1.3 Biocompatibility of thermoplastic elastomers

The biocompatibility of TPEs is one highly promising advantage compare to the thermosets in medical area. Heavy metals (e.g. tin) and halogens (e.g. chlorine and bromine) that used in thermoset rubber which can leach into medications and cause disposal problems, are undesirable according to safety concerns. TPEs alter the situation by providing rubber-like behavior and simple compounding simultaneously.[90] In bio-inertness and low level of extractables and leachables property of medical grade TPEs are keeping

increasing in medical plastic market.[90] The TPEs are bio-stable unless it is denoted 'biodegradable'.

4.3.1.4 Sterilization and chemical resistance of thermoplastic elastomers

Due to thermal characteristic of TPEs, EtO and irradiation are recommended. Generally, THF, MEK, and dichloromethane, these solvents are harmful to TPEs.[76] The sterilization resistances of specific commercialized TPEs, which are used for medical application, are shown in Table 8. However, the actual part to the intended sterilization regime as factors such as wall thickness, dosage, number of cycles, can affect the results.[92]

Table 8: Sterilization resistance for some TPEs batches.[91][92][93][94][95]

Material category	Trade name	EtO	Autoclave	Dry heat	Gamma	E-beam
Polyurethane/elastomer block copolymers	*Elastollan®*	Good	Poor	Poor	Fair	-
Polyester/elastomer block copolymers	*Hytrel®*	Good	Fair	Fair	Good	Good
-	*Medalist®*	-	Fair	Fair	Good	-
Polystyrene/(S-B-S+oil) blends	*Thermolast®*	Good	Poor to Fair	-	Good	-
	Dynaflex™	Good	Poor	-	Good	Good
Polyamide/elastomer block copolymers	*Vestamid®*	-	Fair	-	-	-
-	*Versaflex®*	Good	Poor to Fair	-	Good	Good
Poor: Not suitable for most applications Fair: Suitable for some applications Good: Suitable for most applications						

4.3.2 Processing of thermoplastic elastomers

Because of the large number of types of TPEs, specific processing methods and conditions used for individual TPEs are provided by suppliers. It is noticeable that if the material is moved form a relatively cool store to a warm and humid environment in the processing plant, the drying needs to be applied.[96] Some TPEs tend to absorb moisture and these, of course, require thorough drying.[96] The TPEs are processed via normal thermoplastic fabrication method, and the production rate is similar by same approach, such as injection and extrusion.[96]

5. MEDICAL APPLICATIONS

The polymeric material based devices exist in every aspect of medical area, from simple container to sophisticated NMR coil hosing, and from extracorporeal assistance application to invasive implants. This ever changing field makes a great opportunity and challenge for the manufacturers who want to step into medical device industry. The possible applications of medical grade polymeric material are depended on the mechanical property, biocompatibility and cost efficiency. According to *Chapter 2.4: Regulatory issues*, the medical devices can be categorized by *ISO 10993*, as shown in Table 9.

However, most of the examples listed in Table 9, are integrated systems which assembled by various functional components. In order to simplify the production issues of complex configuration, the medical devices/components are discussed in this study by following three application groups: extracorporeal storage application; extracorporeal non-storage application; overmolding (a technical application).

Table 9: ISO 10993 device categories[92]

Device categories	Body contact	Examples
Surface Device	Skin	• Electrodes • External prostheses • Fixation tapes • Compression bandages • Monitors of various types
	Mucous Membrane	• Contact lenses, urinary catheters • Intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes) • Endotracheal tubes • Bronchoscopes • Dental prostheses • Orthodontic devices • Intrauterine device (IUDs)
	Breached or Compromised Surfaces	• Ulcer, burn and granulation tissue dressings or healing devices • Occlusive patches
External Communication Devices	Blood Path Indirect	• Solution administration sets • Extension sets • Transfer sets • Blood administration sets
	Tissue/Bone/Dentin Communicating	• Laparoscopes • Arthroscopes • Draining systems • Dental cements • Dental filling materials • Skin staples
	Circulation	• Intravascular catheters, • Temporary pacemaker electrodes • Oxygenators • Extracorporeal oxygenator tubing and accessories • Dialysers, dialysis tubing and accessories • Hemoadsorbents and immunoadsorbents
Implant Devices	Tissue/Bone Implant Devices	• Orthopedic pins, plates • Replacement joints • Bone prostheses, cement and intraosseous devices • Pacemakers • Drug supply devices • Neuromuscular sensors and simulators • Replacement tendons • Breast implants • Artificial larynxes • Subperiosteal implants • Ligation clipS
	Blood	• Pacemaker electrodes • Artificial arteriovenous fistulae • Heart valves • Vascular grafts • Internal drug delivery catheters • Ventricular assist devices

5.1 Extracorporeal storage application

The extracorporeal storage application refers to the devices which storing, channeling, or mixing of liquid or gas.[46] The liquid can be water, saline, solvent, blood, lymph, etc. according to intended use of device; and the gas is air, CO_2, inert gases, etc. As per classification, these devices are normally *Class I* or *Class IIa*.[46]

5.1.1 Liquid or gas channeling devices

The liquid or gas channeling devices have structures that let liquid or gas go through by certain direction and controlled speed, and sometimes split or mix the liquid or gas. Requirements for these devices are drawn from the functioning environment and type of liquid or gas whom contact with.[46]

Tubing is the most common channeling structure, along with several accessories such as tube fittings, Y-sites, connectors, stoppers and closures, valves, filters, etc. Figure 21 is an example of liquid infusion set which includes tubing, fitting, stopper, flow control unit and clip, and drip chamber. It is clear that different parts of this set are made separately and assembled. The material selection for this example is depend on each part requirements. In general, the tubing material should meet:

1) Clarity
2) Colorability
3) Flexibility
4) Kink resistance
5) Wall thickness variety
6) Chemical resistance
7) Low surface absorption
8) Sterilization and re-sterilization resistance (reused)
9) Lubricity

And the fitting, filter and drip chamber should have good dimensional stability in addition. While the flow control unit and clip are not contacting the fluid or gas directly, therefore the surface property is not crucial. The mechanical toughness which allows repeated operation is needed instead. According to these requirements, the material selection can be done by optimizing the performance and cost.[75][76][83][84]

Figure 21: Liquid infusion set[97]

Among different medical tubing, ranging from diameters and properties, multi-lumen tubing is a special category which may have a promised future potential. The purpose of a multi-lumen tube is miniaturize different function sections within smallest diameter, and originally, in order to promote less invasive procedures.[98] It is used in catheter design firstly, and expanded to fluid management, air lines, cooling lines, etc.[99] Due to the complex structure, the tolerance is a key factor for material selection and fabrication. Multi-lumen tubing can be fabricated via two approaches: extrusion and assembling, examples are given in Figure 22. The 'building up' of multi-lumen structure shown in Figure 22 (b) incorporates diverse materials that not chemical compatible, such as braid/coil reinforcement, PTFE liners, etc.[98]

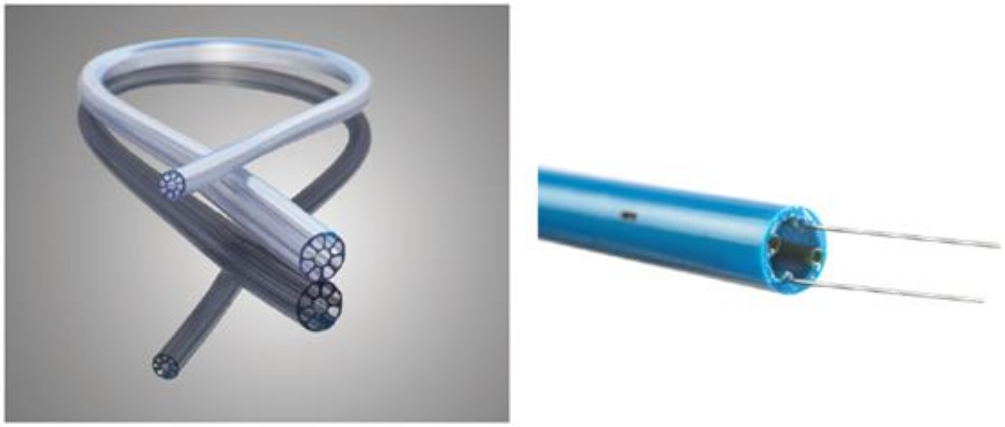


Figure 22: Left (a), 9 lumen co-extruded bump tubing; Right (b), Complex catheter assembly[98]

When the channeled liquid is body fluid and the full function of this liquid should be preserved, the device-liquid interface interaction is highly forbidden. The undesired composition change of channeled fluid is not allowed; therefore the surface property dominates material selection for such applications.[46]

5.1.2 Liquid or gas storing devices

Liquid or gas storing devices act as barrier between contained liquid or gas and storing environment. The seal-ability is sometimes needed or can be complemented by a lid. The aim of such devices is keeping the functionality of stored substrate under a certain time. The requirements for material selection are as following, in general:

1) High clarity
2) Shatter resistance
3) Low extractable and leachable
4) Low surface absorption
5) Water vapor barrier
6) Chemical and (re-) sterilization resistance
7) Dimensional stability
8) Light weight[75][76][83][84]

One example of function container is suction jar, which is usually made from polysulfone or polycarbonate. As shown in Figure 23, a flexible bag, where the fluids are collected, is a separate part adapted to the vessel of the suction jar; and the vacuum is applied between the jar and flexible bag. The idea of this invention is to drain fluids from a cavity, particularly in surgery. After operation, the flexible bag is discarded and the jar is sterilized.[100] In this kind of device, the parts are assembled, and seal-ability is key factor affecting the performance.

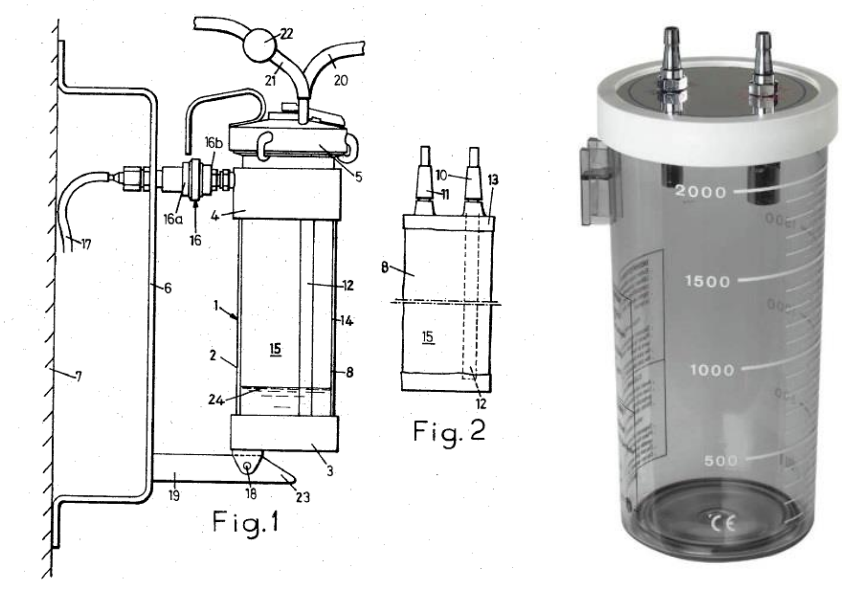


Figure 23: Suction jar[100]

Cuvettes, which are used for spectrophotometric, are a good example of high precision container. The high material purity, critical tolerance, high light transmittance are required. Cuvettes are usually made from PMMA, while in the case that heating is ap-

plied, COC is a good candidate.[71] The design of cuvettes should be fitted into commercial photometers without need for adapters[101], example is given in figure 24.

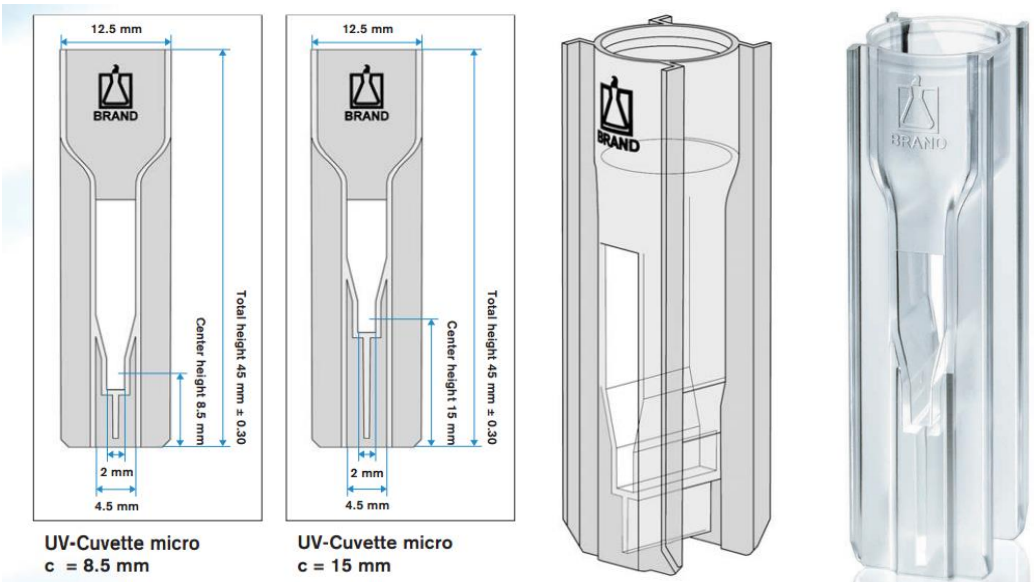


Figure 24: Cuvettes[101]

The plastic liquid/gas storing devices are sometimes designed to be disposable. Therefore, the packaged products should be sterilized by irradiation and ready-to-use.[28]

5.1.3 Liquid or gas administrating devices

This group of devices can transfer, modify the liquid or gas flow into certain targeted place, the typical examples are syringe and inhaler. The requirements for these devices are:

1) Clarity (not necessary for inhalers)
2) Impact resistance and toughness
3) Shatter resistance
4) Dimensional stability
5) Chemical and (re-) sterilization resistance
6) Low extractable and leachable
7) Burst strength[75][76][83][84]

In addition, the parts precision, abrasion, wear resistance and low coefficient are demanded for inhaler material.[102] In Europe, dry powder inhalers (DPIs) are a widely accepted inhaled delivery dosage forms by a large number of patients for the delivery of medications to treat asthma and chronic obstructive pulmonary diseases.[102] As a highly efficient system for pulmonary drug delivery, DPIs are also complicated systems which rely on design, powder formulation, and airflow generated by the patient.[102] An commercial example is Diskus®, a multi-dose device. It contains 60 doses in a foul-foil aluminum strip that is indexed, and the does blister is only opened just prior to patient in-

spiration, as shown in Figure 25.[102] Admittedly, the part design and manufacture require high precision level.

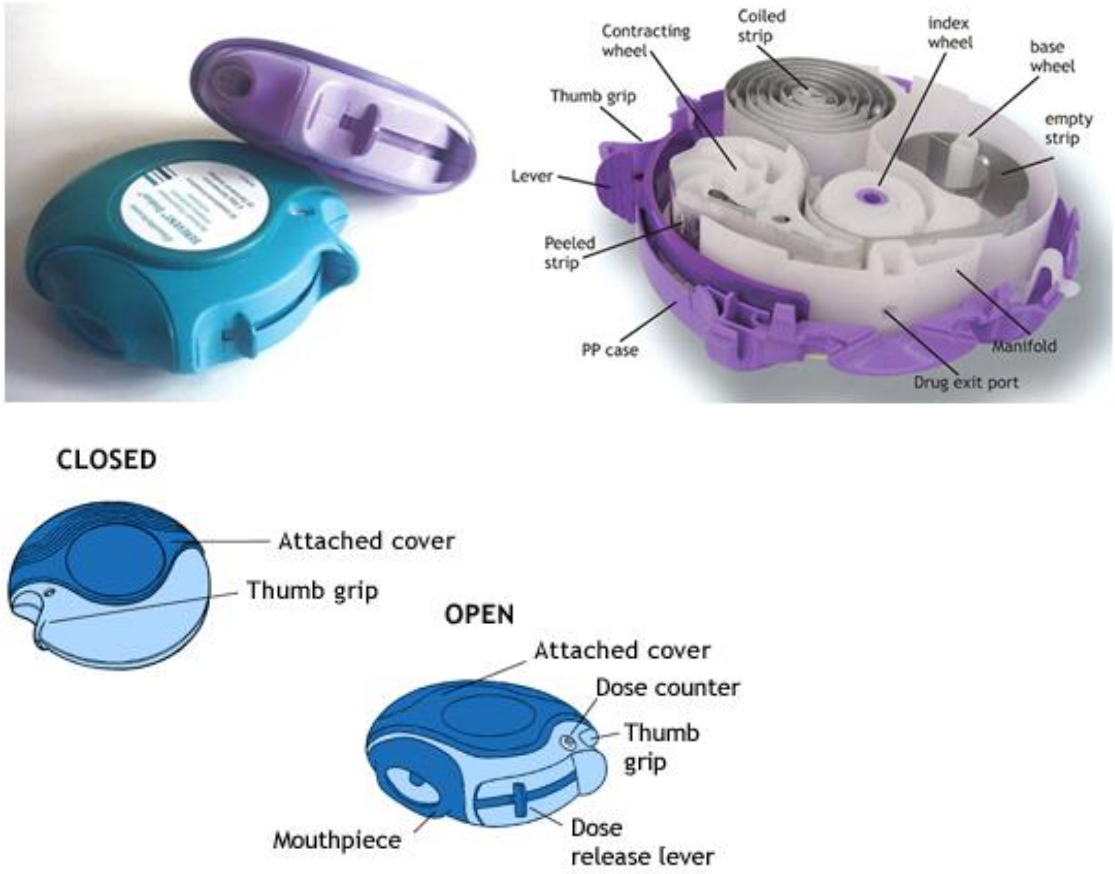


Figure 25: Diskus® dry powder inhaler[103]

Syringe is a drug and vaccine administrative tool used for over 100 years, and is still improving. Today, prefilled syringes provide excellent convenience for emergency and self-administrated medication because of their ease of use and immediate availability.[104] For this purpose, the syringe is functioning for both storing and administrating; therefore, the material selection should take these issues into consideration. For the sake of convenience, color-code is applied as shown in Figure 26.

Figure 26: UltraSafe® syringe color-coded needle guards (left); the UltraSafe® Passive Delivery System (right)[104]

5.2 Extracorporeal non-storage application

This group refers to the application that functioning as operation tool, protector, structure, etc., rather than channeling, storing, administrating liquid or gas. As per classification, these devices are normally *Class I* and *Class IIa*.[46]

5.2.1 Surgical instrument

The low cost, light weight, colorable, clear, and disposable of plastic are driven force of it to replace metal made surgical instruments, such as scalpel handle, tweezers, clamps, dental tools, trays, forceps, etc. As shown in Figure 27, an ankle clamp designed by *John Grecco* of *Stryker Orthopaedics* which was used to be metal made in the right side. Now the yoke and flippers are made from polysulfone which is capable with multiple steam autoclaves and tough enough during operation.[28]

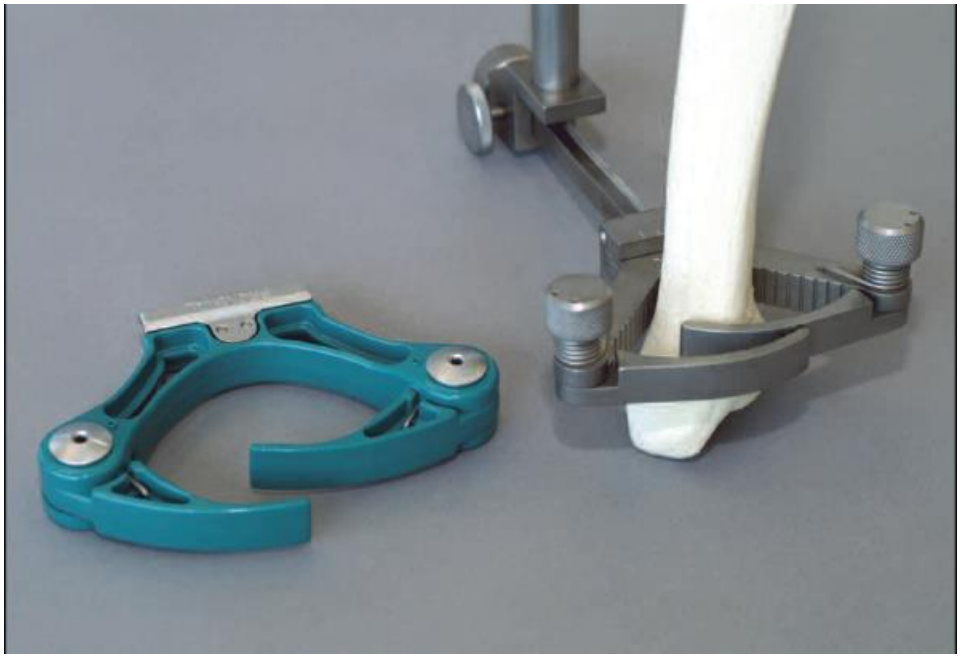


Figure 27: Plastic ankle clamp: a replacement of metal component[28]

5.2.2 Protective devices

The medical protective device is used for keeping harmful particles, vapor, and microorganism away from operating personnel and patients. Respirator is a common protective device used in many industries to avoid respiration system contamination. The design of respirator is flexible to meet different barrier levels and reusable or disposable. A typical respirator design is shown in Figure 28, which contains soft and hard molded parts. And a diaphragm attachment is shown in Figure 29 that is functioning as filter accessory to the mask in Figure 28.

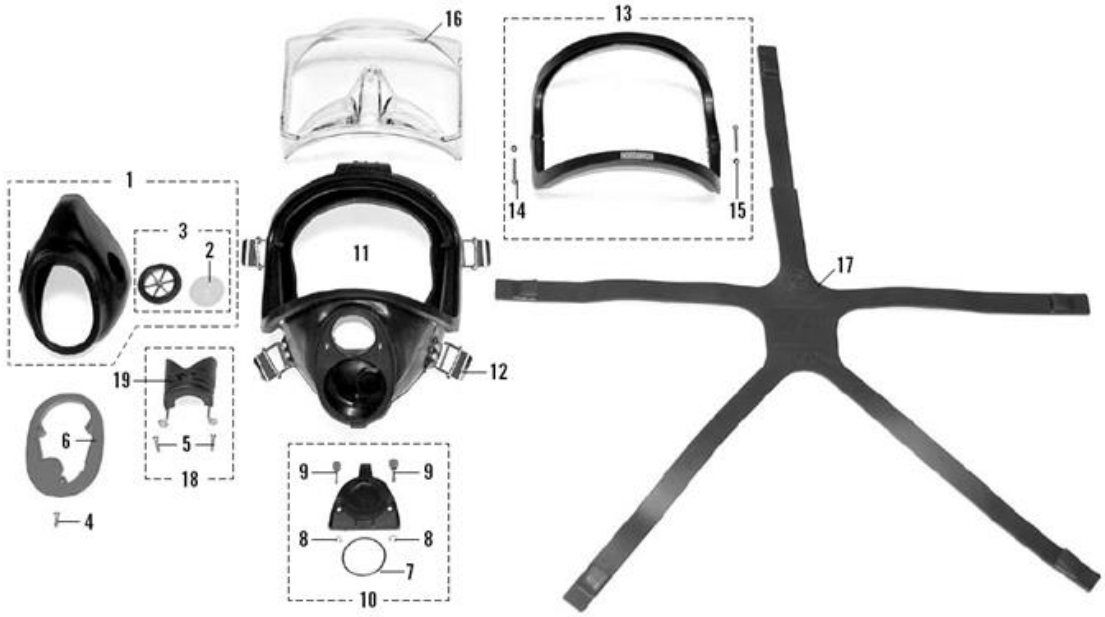


Figure 28: Respirator: face mask[105]

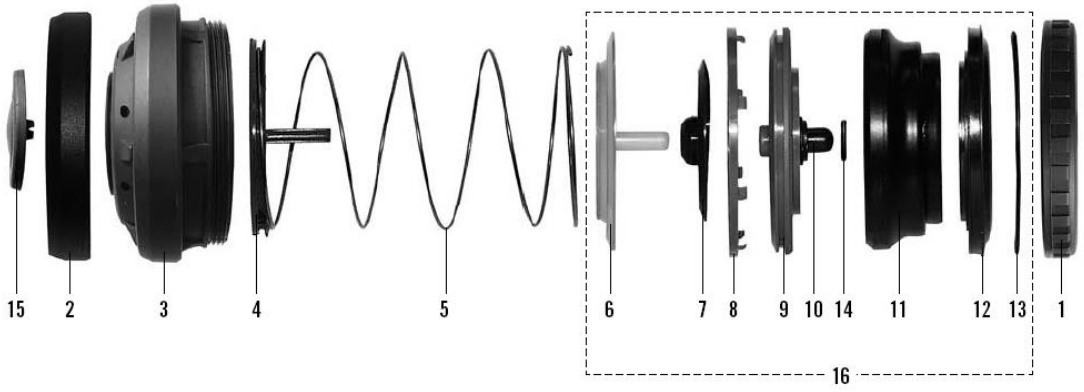


Figure 29: Respirator: diaphragm, a breakdown drawing[105]

The wearing conformability and seal-ability are key issues to be considered of respirator design and material selection. *Grace Lu-Yao et al.* have reported that a large percentage of participants in their test were unwilling to wear the respirator ensembles for the entire 8-hour work shift, even with interposed break periods[106]; therefore, there is still space to improve on this object.

5.2.3 Medical instrumentation component

As shown in Figure 30, variety of medical instrumentation parts can be made from plastic, due to the light weight and other advantages over metal and ceramic.

Figure 30: Plastic medical instrument parts

In some advanced applications, the electrical insulation, radiation opaqueness or transmittance, thermal stability, surface absorption, and chemical resistance are required. The flexibility and modifiability of plastics have offered a broad range for designer and manufacturer.[43] An example is given in Figure 31, which is MRI receiver coil configuration from *Siemens*. The mechanical stability, easy to clean, electrical insulation and radiation transmittance, and chemical resistance are key factors to design and select material for this device.

Figure 31: 32-channel head coil for MRI, Siemens.[107]

The *Emerge*^{TM} *PC/PET9500CR* advanced resin from *Styron, Berwyn, PA*, is a plastic material designed to provide chemical and ignition resistance, durability, processing characteristics, and aesthetic appeal. It also offers resistance to aggressive chemicals, including surface disinfectants and cleaners commonly used in medical environments, which can attack plastic surfaces and cause crazing, cracking, or product failure.[108] It is particular one among the commercialized plastics that meet the requirement for medical instrumentation and ready-to-process for manufacturer without extra compounding.

5.3 Overmolding

Overmolding, an injection process also known as two shot molding, has drastically changed the aesthetics, design, and functionality of consumer products over the last decade. Its potential benefits for medical application is raised by the requirements of user friendly texture, ergonomics, multi-color aesthetics, brand identification, and property modification. Plastics are used in overmolding to offer functionality addition such as noise and vibration dampening, waterproofing, and shock absorption in order to increase products' value. Co-injection, two shot, and sandwich molding are typical methods applied for overmolding technique.[110]

The basic premise of overmolding is to take economical advantage of two or more materials with uniquely different properties by incorporating them into a single molded component. A success overmolding is achieved by stable material bonding. There are three basic bonding fundamental, and they can work either individually or in a combination: 1) molecular adhesion; 2) mechanical design techniques; 3) mechanical interlocks. The molecular adhesion is determined by overmolding material surface wetting and reaction, or favored by bonding agents. Liquid silicone rubber can wet a broad range of metal, thermoplastic, or itself; however, the curing condition of silicone rubber, which usually over 100 ℃, can cause heat distortion to thermoplastic. The thermoplastic and thermoplastic elastomer usually wet the substrate with similar surface tension. The material bonding instruction is sometimes provided by supplier, for instance, the *GLS* group suggests their thermoplastic elastomer *Versaflex*® and *Versollan*^{TM} are able to bond to PC, ABS, nylon, coployester, PS, acetal and (all above) their alloys or blends.[109] Nevertheless, it is not capable for some material suppliers.

The mechanical design techniques are achieved by geometric conjunction which varies among different products. The most common way to get solid bonding physically is mechanical interlock. Via this approach, shown in Figure 32, the sophisticated material selection procedure or surface integrative design might be eased.

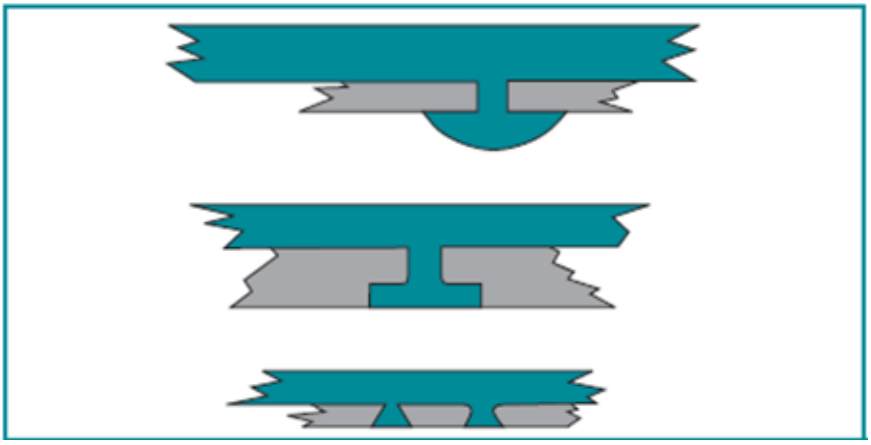


Figure 32: Three types of successful mechanical interlocks[109]

An advantage to use plastic overmold to metal is ergonomic pursuit and cost efficiency. In some cases, a part with complex geometry to fit the contours of the human body is easier to process by molding plastic than metal machining. Moreover, the soft touch of plastic may increase the ergonomic concern. An example is shown in Figure 33, these surgical instrument handles were overmolded by thermoplastic elastomer with soft touch and non-slippery texture.[110]

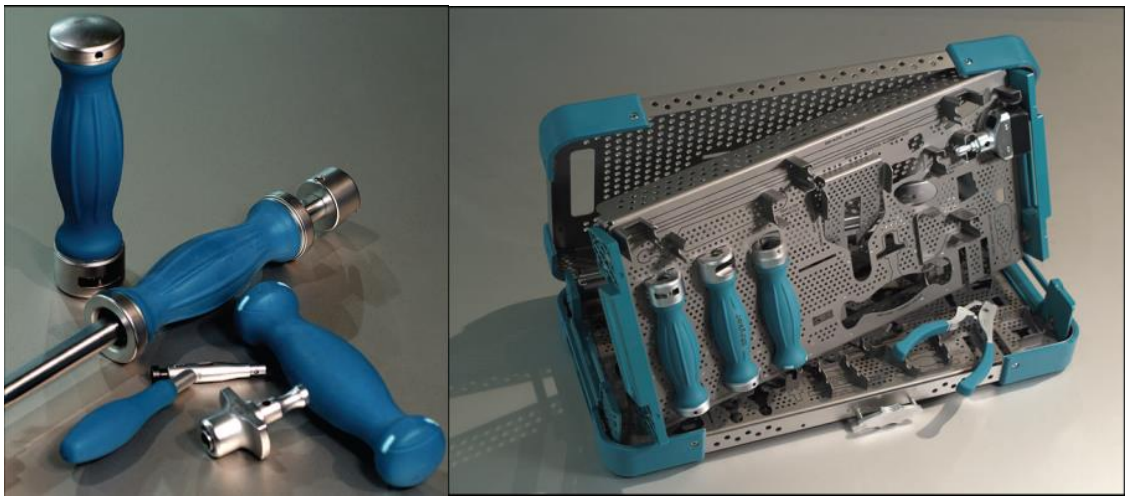


Figure 33: Overmolding surgical instruments handle set[110]

Depending on application, the biocompatibility, chemical and sterilization resistance should be taken into consideration as well. The other requirements, which are important for fragile devices, are shock absorption, and waterproofing to ensure the devices work well in emergency and harsh situation. Automated external defibrillator (AED) unit in Figure 34 is overmolded around the frame and corner. The test protocol for this unit included passing a 1.5-m drop test, a cyclic loading test, and a water ingress test. The results has shown an optimal performance-property profile for this overmolded AED unit.[110]

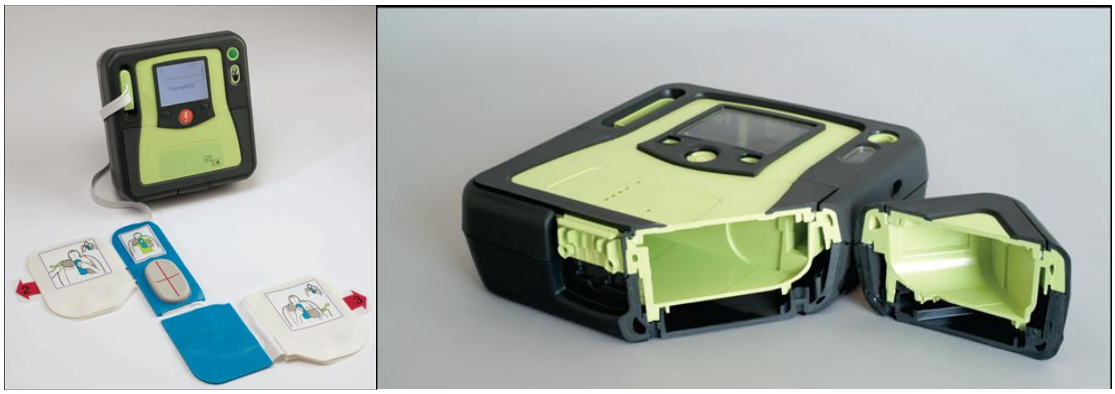


Figure 34: Overmolded AED unit[110]

In addition, this is a good example of plastic-on-plastic overmolding as well. The black material is thermoplastic elastomer with soft touch, good seal-ability; and the green substrate is rigid, impact resistant resin. The combination of these two plastic resulted in excellent engineering performance.

5.4 Case study

As mentioned previously, some medical devices are multi-component assembled configurations. The functionality is achieved by exquisitely designed elements. Table 10 shows some commercialized plastic materials and their possible applications in order to illustrate the broad range of options in this industry. The sequencing is based on approximate hardness of each plastic family; the representation of each hardness level in real life is given in Figure 35. Subsequently, two cases are given to make a direct impression of real practice.

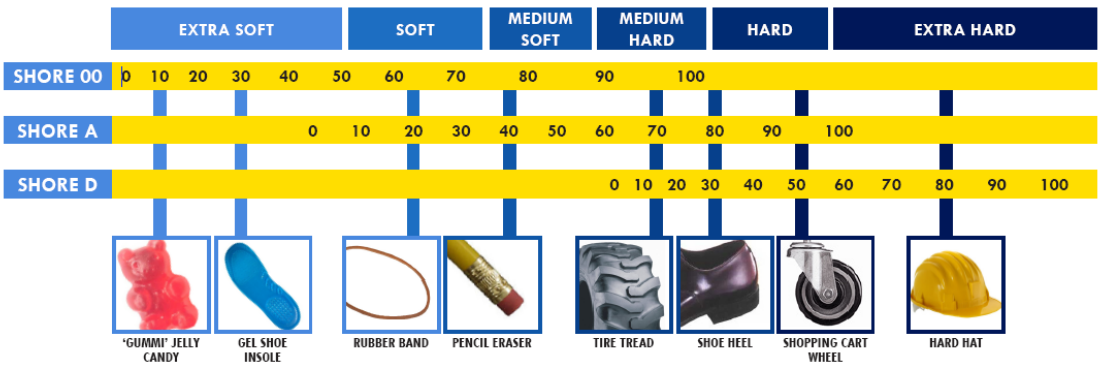


Figure 35: Shore hardness scale[111]

Table 10: Commercialized medical grade plastic material and application (Ascending order of hardness) [75][76][83][84]

Material category	Trade name and supplier	Hardness	Possible application
Silicone rubber	• Silpuran® and Elastosil® (Wacker, Germany), • Silastic® (Dow Corning, USA)	Shore 00 15 to Shore A 70	• Medical tubing and catheters • Gaskets • Membrane • Seals • Valves • Balloons • Mammary prosthesis • Orthopedics
Thermoplastic elastomers	See chapter 4.3	Shore A 5 to shore D 75	• Medical tubing and catheters • Heat shrinkage tubing • Stoppers and closures • Fluid delivery connectors and clips • Films • Collecting bags • Eye and nasal drop bottles • Gloves • Gel filled bladder, neck pack • Overmoding
PVC	Hy-Vin® and Evicom™ (INEOS, France)	Shore A 50 to 91	• Medical tubing • Catheters • Bottles • Drip chambers • Packaging • Gloves • Masks • Blood contacting containers
COC	TOPAS® (TOPAS, Germany)	Shore A 89	• Packaging • Lab-on-a-chip disc • Prefilled syringes and containers • Labware • Cuvettes
UHMWPE	HI-ZEX MILLION® (Mitsui Chemicals, Japan)	Shore D 30 to 50	• Artificial limb material • Acetabular joint • Sutures • Heart valves
LDPE	• Eletx®LDPE (INEOS, France) • Riblene® (Eni Versalis, Italy)	Shore D 55	• Medical tubing • Caps for luers and bottles • Packaging • IV fluid bottles • Single does ampoules
PS	• Styrolution® PS (Stryrolution, Germany)	Shore D 58	• Labware • Sterilization trays • IV fluid bottles • Single does ampoules
PP	Eletx®PP (INEOS, France)	Shore D 55 to 65	• Drape and gowns • Packaging • Pouch • Syringes
HDPE	• Eletx® HDPE (INEOS, France) • Eraclene® (Eni Versalis,	Shore D 68	• Slide clamp • Filters

	Italy)		
PMMA	Plexiglas® and Altuglas® Luctor™ Medical grade (Plexiglas, Germany)	Rockwell M 21 to 84	• Labware • Cuvettes
PC	• WONDERLITE®PC (CHIMEI, Taiwan) • Durolon®PC (Unigel, Brazil)	Rockwell M 75 to 90	• Intravenous IV components • Needle-free injection system • Heart valves • Ventricular assist devices • Connectors • Dialyzer components • Device housing
PU	Texin® and Desmopan® (Bayer, Germany)	Shore A 85 to D 70	• Thin-walled flexible tubing • Catheters • Connectors, luers and stopcocks • Films and fabric coatings • Component housings • Soft-touch grips • Ventricular assist devices • Pacemaker leads
PTFE	Teflon® (Dupont, USA)	Shore D 50 to 59	• Multi-lumen tubing • Heat shrinkable tubing • Guiding catheters • Vascular graft • Low surface tension applications
PSU	Ultrason® (BASF, Germany)	Shore D 80	• Flow control devices • Dialysis membrane • Surgical instruments • Suction jars
PPS	Ryton® (Chevron Phillips, USA)	Shore D 85	• Surgical instruments • Valves • Filters
PBT	Crastin® (Dupont, USA)	Shore D 85	• Miniature scalpel blade holders • Syringe pump component
PEEK	Victrex® (Victrex, UK)	Shore D 87	• Heat shrinkable tubing • Valves • Tri-leaflet heart valve • Spinal cages • Pins, screws and plates • Dental implants
PET	Rynite® (Dupont, USA)	Shore D 95	• Heat shrinkable tubing • Labware • Packaging • Blood separation cassette • Angiographic syringe
ABS	Teluran® (BASF, Germany)	Shore D 100	• Surgical instruments • Device components • Device housing • Inhaler components • Intravenous IV components
PA	Zytel® PA (Dupont, USA)	Rockwell R 70 to 121	• Medical tubing • Catheters • Sutures • Stopcocks • Device housing • Packaging

5.4.1 Case I: Housing design for a new RF breast coil concept for use in MRI applications[112]

Based on new *Aghogho Obi*'s dual channel RF breast coil concept, the author has been asked to carry out a housing design witch address ergonomics, weight, size, structural and regulatory issues by *InsightMRI* (an American MRI corporation). According to its application, it is a *Class I* device.

- Ergonomic: The patient should be comfortable during the entire screening process where MRI scans take longer time than other mechanical imaging methods. The patient's movement caused artifacts and distortions should be eliminated.
- Weight and size: Due to the handle of device, lightweight is preferred. Meanwhile, the size should keep as low profile as possible to increase the amount of free space on the magnet's bore.
- Structure integrity: This device is bearing different loading.
- Regulations: This device is able to perform within the dictated by both regulatory agencies (FDA, ISO, etc.) and the vendors (such as MRI system supplier: Siemens, Philips or GE). The regulations can be for extremely minute details (wall thickness around heat producing electrical elements) or for more general criteria (melting point of the material used).

The final design is shown in Figure 36.

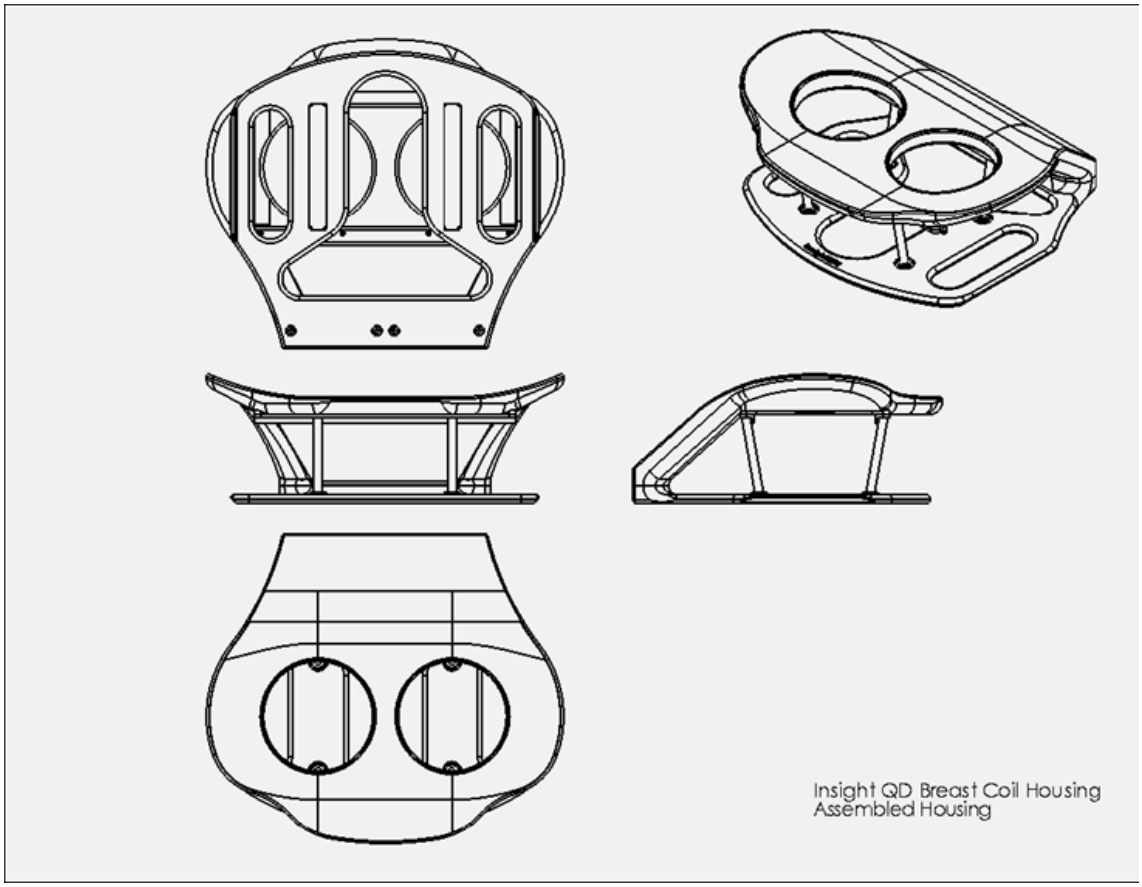


Figure 36: Breast MRI coil housing design[112]

Table 11: List of materials[112]

Part	Material	Description
Main Housing Parts		*Ultem™ 2300*: 30% glass-reinforced polyimide thermoplastic flame retardant resin *Garolite G-10*: Reinforced glass-cloth flame retardant composite epoxy resin *RapidCast®* RC-79D: Flame retardant polyurethane
Leg (Outer)	Ultem 2300	
Leg (Inner)	G-10	
Housing (Top Half)	RC-79D	
Housing (Bottom Half)	RC-79D	
Covers		
Top Half-Top Cover	RC-79D	
Top Half-Bottom Cover	Nylon	
Bottom Half-Bottom Cover	Nylon	
Rail Mount	Ultem 2300	
Fastening Features	Brass or Nylon	

The materials used in this design are shown in Table 11. For the aesthetic purpose, an off-white pigment is incorporated into the material or painted after molding. Any of the externally exposed surfaces of machined parts are also painted.

5.4.2 Case II: *CentriMag®* Right ventricular assist system component: blood pump[113]

The *CentriMag®* blood pump, shown in Figure 37, is an extracorporeal circulatory support device providing hemodynamic stabilization in patients in need of cardiopulmonary support. It is designed by *Thoratec® Corporation, USA*, and made from medical grade polycarbonate.[113] *CentriMag®* is CE-Marked in Europe for use up to 30 days to provide hemodynamic support for patients as a bridge to recovery, transplant, or a short-term ventricular assist device (VAD). *CentriMag®* is also CE-Marked in Europe for use up to 30 days as a component of an extracorporeal membrane oxygenation (ECMO) circuit to provide support to patients in need of cardiac and/or respiratory assist. According to its application, it is a Class *IIa* device.

Figure 37: *CentriMag®* blood pump[113]

The quality and functionality of *CentriMag®* is approved according to FDA and ISO standards which cover the biocompatibility, sterilization validation, hemolysis testing, shelf life studies, and shipping/transportation tests. The biocompatibility tests included:

cytotoxicity, sensitization, intracutaneous irritation, systemic toxicity, genotoxicity, hemocompatibility and sub-chronic toxicity. The recommended sterilization approach is EtO method. In addition, the packaging integrity of this device ensures the functionality under certain shelf time and transportation.[114] *F.D. Robertis et al.* have revealed the efficiency of *CentriMag*® as well as a low-cost device based on clinical test.[115]

6. CONCLUSION

In order to provide a comprehensive production procedure of polymeric medical devices, thorough discussion of technical details is made in this study. Furthermore, the requirements of regulatory issues are emphasized at each processing stage. It is clear that a valid medical device production is achieved when not only the technical aspect is fulfilled, but also the regulatory demand is complied. Therefore a feasible analysis is necessarily carried out prior to real production. Following the production synopsis given in this study, a project analysis can be made via a logical approach.

Inspired by the sponsor of this study, the polymeric materials (liquid silicone rubber, thermoplastics, and thermoplastic elastomers) are widely discussed and compared based on mechanical property, biocompatibility, surface property, sterilization and chemical resistance, etc. Subsequently, possible applications of these materials are given in a material-application manner. Such information can ease the initial selection procedure of a manufacturer. Finally, two case studies are given to illustrate the real practice of previous discussion.

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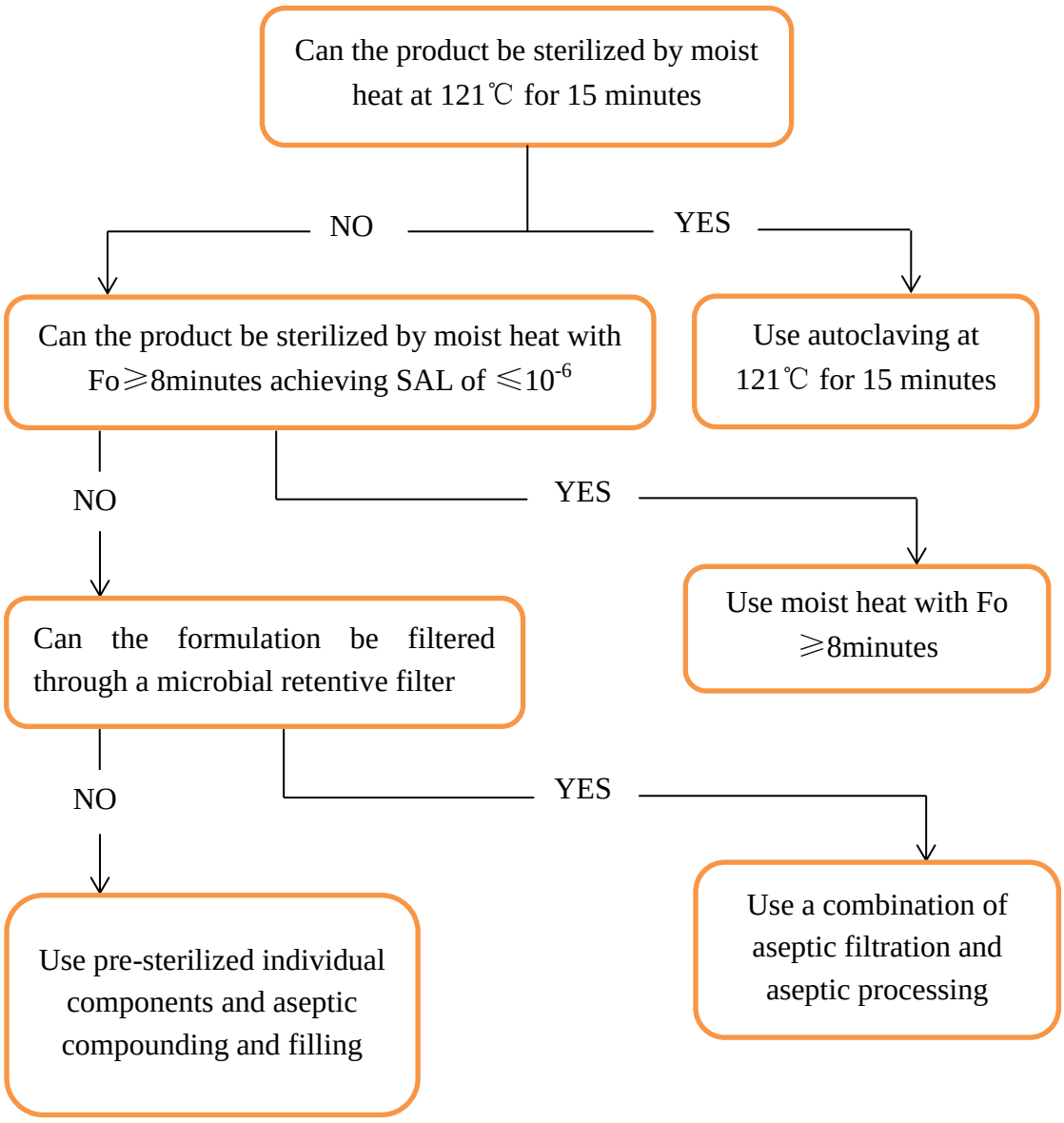
APPENDIX 1

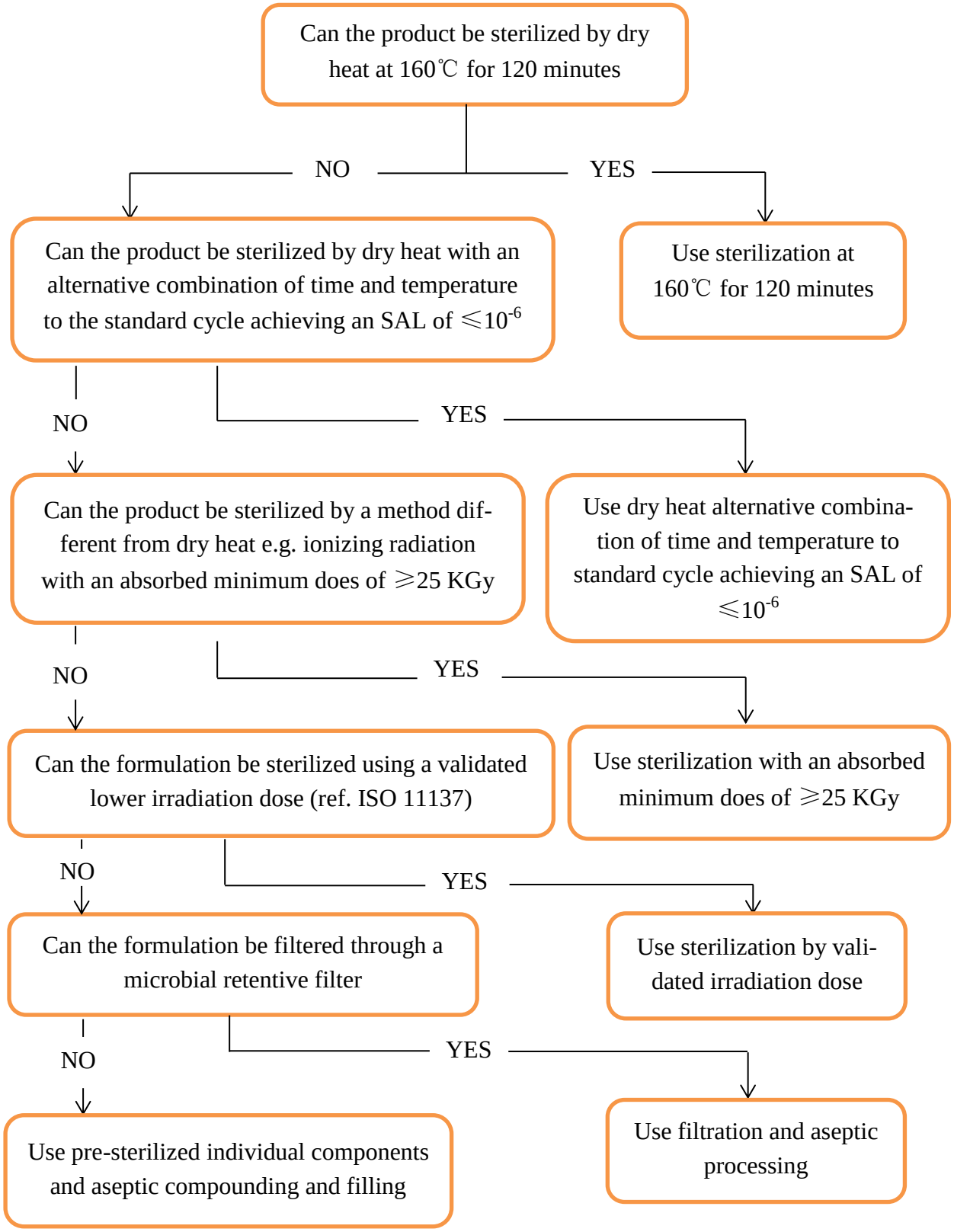
Appendix 1.1

Decision tree for sterilization choices for aqueous products[18]



Appendix 1.2

Decision tree for sterilization choices for non-aqueous liquid, semi-solid or dry solid or dry powder products[18]



APPENDIX 2

Appendix 2.1

Sterilization resistance of some thermoplastics[75][76][83][84]

	Steam	Dry heat	Ethylene oxide	E-Beam	Gamma radiation	Gamma tolerance level (KGy)
PVC-U	Poor	Poor	Good	Fair	Fair	100
PVC-P	Fair	Fair	Good	Good	Good	-
LLDPE	Poor	Poor	Good	Good	Good	1000
LDPE	Poor	Poor	Good	Good	Good	1000
HDPE	Poor	Poor	Good	Good	Good	1000
UHMWPE	Poor	Poor	Good	Good	Good	1000
PP	Good	Fair	Good	Fair	Fair	25-60
COC	Fair	Fair	Good	Good	Good	-
PS	Poor	Poor	Good	Good	Good	10000
PMMA	Poor	Poor	Good	Good	Good	100
PC	Fair	Fair	Good	Good	Good	1000
PU	Poor	Poor	Good	Good	Good	10000
Acetal	Good	Good	Good	Poor	Poor	5
PET	Poor	Poor	Good	Good	Good	1000
PBT	Fair	Fair	Good	Good	Good	-
PCT	Poor	Poor	Good	Good	Good	-
PETG	Poor	Poor	Good	Good	Good	1000
PCTG	Poor	Poor	Good	Good	Good	-
PCTA	Poor	Poor	Good	Good	Good	-
PA 6	Fair	Fair	Good	Fair	Fair	50
PA 66	Fair	Fair	Good	Fair	Fair	-
PA 6, 12	Fair	Fair	Good	Fair	Fair	-
PA 12	Fair	Fair	Good	Fair	Fair	-
Nylon 4,6	Fair	Fair	Good	Fair	Fair	-
PSU	Good	Good	Good	Good	Good	10000
PES	Good	Good	Good	Good	Good	-
PPSU	Good	Good	Good	Good	Good	-

PEI	Fair	Fair	Good	Good	Good	-
PAI	Fair	Fair	Good	Good	Good	10000
PPS	Good	Good	Good	Good	Good	1000
PEEK	Good	Good	Good	Good	Good	-
PEKK	Good	Good	Good	Good	Good	-
PEKEKK	Good	Good	Good	Good	Good	-
LCP 1	Good	Good	Good	Good	Good	-
LCP 2	Good	Good	Good	Good	Good	-
PTFE	Fair	Fair	Good	Poor	Poor	5
PFA	Good	Good	Good	Good	Good	-
FEP	Good	Good	Good	Fair	Fair	50
PVDF	Good	Good	Good	Good	Good	1000
PCTFE	Good	Good	Good	Good	Good	-
ETFE	Good	Good	Good	Good	Good	1000
ECTFE	Good	Good	Good	Good	Good	200
ABS	Poor	Poor	Good	Good	Good	1000
SAN	Poor	Poor	Good	Good	Good	1000
ASA	Poor	Poor	Good	Good	Good	-
MABS	Poor	Poor	Good	Good	Good	100
SBC	Poor	Poor	Good	Good	Good	-
TPU	Poor	Fair	Good	Good	Good	-
TPC	Poor	Good	Good	Good	Good	-
TPA	Poor	Poor	Good	Good	Good	-
TPS	Poor	Poor	Good	Good	Good	-
TPO	Poor	Fair	Good	Good	Good	-

Appendix 2.2

Chemical resistance of some thermoplastics[75][76][83][84]

	PVC-U	PVC-P	LLDPE	LDPE	HDPE	UHMWPE	PP	COC	PS
Dilute Acids	Faire	Good	Good	Good	Good	Good	Good	Good	Fair
Dilute Bases	Good	Good	Good	Good	Good	Good	Good	Good	Fair
THF	Poor	Poor	Poor	Poor	Poor	Fair	Fair	Poor	Poor
MEK	Poor	Poor	Fair	Fair	Good	Good	Good	Good	Poor
MeCl2	Poor	Poor	Poor	Poor	Poor	Fair	Fair	Poor	Poor
Acetone	Poor	Poor	Good	Good	Good	Good	Good	Good	Poor
IPA	Good	Poor	Good	Good	Good	Good	Good	Good	Good
Ethylene Oxide	Fair	Poor	Fair	Fair	Good	Good	Fair	Good	Good
Oils/ greases	Good	Fair	Fair	Fair	Good	Good	Good	Poor	Fair
Silicones	Good	Good	Good	Good	Good	Good	Good	Good	Fair
Saline water	Good	Good	Good	Good	Good	Good	Good	Good	Good
Bleaches	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hydrogen per-oxide	Good	Good	Good	Good	Good	Good	Good	Good	Good
Disinfectants	Good	Good	Good	Good	Good	Good	Good	Good	Good
Soaps/ Deter-gents	Good	Good	Good	Good	Good	Good	Good	Good	Good
Lipids	Good	Fair	Fair	Fair	Good	Good	Fair	Good	Good
Betadine	Poor	Poor	Good	Good	Good	Good	Good	Good	Fair

PA 66	PA 6	PCTA	PCTG	PETG	PCT	PBT	PET	Acetal	PU	PC	PMMA
Poor	Poor	Poor	Poor	Poor	Poor	Good	Fair	Poor	Poor	Good	Fair
Poor	Poor	Poor	Poor	Poor	Poor	Good	Fair	Fair	Poor	Poor	Fair
Good	Good	Fair	Fair	Fair	Fair	Good	Fair	Good	Poor	Poor	Poor
Good	Good	Poor	Poor	Poor	Poor	Good	Fair	Good	Poor	Poor	Poor
Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Fair	Poor	Poor	Poor
Good	Good	Poor	Poor	Poor	Poor	Fair	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Good	Good	Good	Fair	Good	Fair	Good	Poor
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Fair	Poor
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good	Fair
Poor	Poor	Fair	Fair	Fair	Fair	Good	Good	Poor	Poor	Fair	Good
Poor	Poor	Good	Good	Good	Good	Good	Good	Fair	Fair	Good	Good
Poor	Poor	Good	Good	Good	Good	Good	Good	Fair	Fair	Good	Good
Fair	Fair	Fair	Fair	Fair	Fair	Good	Fair	Good	Fair	Fair	Fair
Fair	Fair	Good	Good	Good	Good	Good	Good	Fair	Fair	Good	Good
Poor	Poor	Fair	Fair	Fair	Fair	Good	Good	Good	Fair	Fair	Fair

PEKEKK	PEKK	PEEK	PPS	PAI	PEI	PPSU	PES	PSU	Nylon 4,6	PA 12	PA 6, 12
Good	Good	Good	Fair	Good	Fair	Good	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Fair	Poor	Good	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Good	Good	Fair	Fair	Fair	Good	Poor	Poor
Good	Good	Good	Good	Good	Poor	Poor	Poor	Poor	Good	Poor	Poor
Good	Good	Good	Good	Good	Poor	Poor	Poor	Poor	Poor	Poor	Poor
Good	Good	Good	Good	Good	Poor	Poor	Poor	Poor	Good	Poor	Poor
Good	Good	Good	Good	Good	Good	Fair	Fair	Fair	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Fair	Good	Fair	Good	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Good	Fair	Good	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Good	Fair	Good	Good	Good	Poor	Poor	Poor
Good	Good	Good	Good	Good	Fair	Good	Good	Good	Fair	Fair	Fair
Good	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Fair	Fair
Good	Good	Good	Good	Good	Fair	Good	Good	Good	Poor	Poor	Poor

ASA	SAN	ABS	ECTFE	ETFE	PCTFE	PVDF	FEP	PFA	PTFE	LCP 2	LCP 1
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Poor	Poor	Poor	Fair	Fair	Fair	Good	Good	Good	Good	Good	Good
Poor	Poor	Poor	Fair	Fair	Fair	Fair	Good	Good	Good	Good	Good
Poor	Poor	Poor	Fair	Fair	Fair	Good	Good	Good	Good	Good	Good
Poor	Poor	Poor	Fair	Fair	Fair	Fair	Good	Good	Good	Good	Good
Good	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Fair	Fair
Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Good	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
Fair	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good

MABS	SBC
Good	Good
Good	Good
Poor	Poor
Poor	Poor
Poor	Poor
Poor	Poor
Good	Fair
Good	Good
Good	Good
Good	Good
Good	Good
Good	Good
Fair	Good
Good	Good
Good	Good
Good	Good
Fair	Fair