UNIVERSITÀ DI PISA

Dipartimento di Oncologia, dei Trapianti e
delle Nuove Tecnologie in Medicina

Corso di Dottorato in Tecnologie per la Salute:

Valutazione e Gestione delle Innovazioni nel Settore Biomedicale

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Ph.D Thesis

METHODOLOGY FOR RESEARCH AND DEVELOPMENT OF NOVEL MEDICAL DEVICES FOR MINIMALLY INVASIVE INTERVENTIONS

Elena Troia

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METHODOLOGY FOR RESEARCH AND DEVELOPMENT OF NOVEL MEDICAL DEVICES FOR MINIMALLY INVASIVE INTERVENTIONS

Elena Troia

Submitted to the University of Pisa in partial fulfilment

of the requirements for the degree of Doctor of Philosophy

Tutor:

Prof. Andrea Pietrabissa:

Dr. Bernardo Magnani

Prof. Arianna Menciassi

Prof. Paolo Dario

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1 Abstract

The design of innovative medical device requires extensive and hard efforts to reach good results in terms of safety, efficacy and cost effectiveness. First of all the idea has to be set and a wide search of state of the art, both technological and academic, has to be developed. Then the materials, manufacturing processes and design constraints have to be understood. In this work three examples of innovative surgical devices for minimally invasive surgery and assistance have been presented.

The Muneretto Beam catheter is a new device for atrial defibrillation. Starting from a catheter produced by Estech[1] company for the treatment of atrial fibrillation by ablating cardiac tissue during surgery, a system for the magnetic guidance of the same has been implemented. Thanks to finite element analysis of various configurations of magnets and to several in vitro tests, a final configuration which allows a good balance between the sliding of the catheter on the tissues and the magnetic interaction and adhesion to tissues has been found. Further attention has been taken to the development of the cover and the right configuration and method of use of the device.

The VideoDrain system is a new catheter for the monitoring of post-operative wound. After critical surgical procedures it is necessary to monitor the status of the surgical wound for avoiding second look surgical interventions. Therefore a new balloon catheter for allowing the vision of the abdominal cavity has been produced. Several in vitro and in vivo trials have been conducted and the device is at the pre-industrial stage.

The FloSeal GI cath. is a new device for the gastrointestinal release of an haemostatic substance of the Baxter[2] company: the Floseal thrombin matrix. It consists in a balloon catheter suited for the use in the lower and upper gastrointestinal tract in the occurrence of bleedings during endoscopic procedures. This device has been CE labelled and is now on the market.

All the devices described in this work come from ideas of surgeons leader in innovation in the field of minimally invasive interventions. Their collaboration has been fundamental for the several phases of design and tests of the devices.

This Ph.D. thesis is divided into five chapters. In the Introduction chapter the process of research and development of innovative MDs for minimally invasive surgery has been illustrated. The second chapter shows the efforts done to find a working configuration for the Muneretto Beam catheter and the subsequent first prototypes developed. The progress in the design of VideoDrain has been explained in the third chapter; the whole process goes from the idea to the animal test on prototypes and a preliminary risk analysis. The development of the Floseal GI Catheter is depicted in the fourth chapter; all the details of the materials used and tests done to ensure a CE mark have been reported. Finally, in the Conclusion chapter I have reported some lessons learned from the work in the field of MDs, as a student, researcher and engineer at close contact with the world of surgery and minimally invasive technologies. Some papers about a preliminary research activity in the field of minimally invasive surgery and robotic interventions have been also enclosed. These works have been very useful to start the understanding of the complex and amazing world of MIS.

[1] http://www.estech.com/
[2] http://www.baxteritalia.it/

Alla mia cara famiglia

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2 Table of contents

1 Abstract 3

Acknowledgements 5

2 Table of contents 6

3 Research and Development of medical devices 10

3.1 Design for Minimally Invasive Surgery 10

3.2 Methodologies for design and development of innovative devices 12

3.3 Design of medical components 15

3.3.1 Microtubes 15

3.3.2 Materials 16

3.3.3 Design for manufacturability 19

3.3.4 Assembly Techniques 22

3.3.5 Component Outsourcing 22

3.3.6 Sterilization Methods 23

3.4 Regulation 23

3.4.1 Certification aspects: definitions and classification 24

3.5 Quality system 26

3.6 Risk Management 27

3.6.1 The methodology of ISO 14971 29

4 Muneretto Beam Navigation device 30

4.1 Analysis of the medical background 30

4.1.1 Clinical evaluation in patients with AF 31

4.2 Surgical treatments for atrial fibrillation 31

4.2.1 The Maze Procedure 31

4.2.2 Circumferential pulmonary vein ablation (CPVA) 32

4.2.3 Radiofrequency ablation endoscopic procedures 33

4.2.4 Left atrial appendage (LAA) excision 34

4.2.5 Robotically Assisted AF surgery 34

4.3 Technological state of the art 35

4.3.1 Magnetically guided systems 35

4.3.2 Robots for atrial fibrillation 36

4.4 Analysis and search of materials 37

4.4.1 Permanent magnets 37

4.4.2 The B-H Curve 39

4.5 Design History 39

4.5.1 Muneretto approach 40

4.5.2 Analysis of potential configurations 41

4.5.3 Finite Element Analysis 44

4.5.4 Model validation 48

4.5.5 Main FEA results 49

4.6 Prototypes and Tests 52

5 Video drain 55

5.1 Analysis of the medical background: Anatomy and Complications of abdominal surgical wounds 55

5.1.1 Anatomical district 55

5.1.2 Ethiology and Pathophysiology 56
5.2 Market Analysis 58
5.3 State of the art: Commercial systems 58
5.3.1 Abdominal drainage tubes 59
5.3.2 Endoscopic covers 60
5.3.3 Trocar for extraperitoneal dissection (Balloon dissectors) 60
5.3.4 Balloon systems for diagnosis and intervention without insufflation 60
5.3.5 Abdominal ultrasound 61
5.3.6 Diagnostic Laparotomy 61
5.3.7 Abdominal radiography and computer tomography scan 62
5.3.8 Analisys of competitors features 62
5.4 Patent Search 64
5.5 Design of the device 66
5.5.1 Analysis of potential configuration and Computer assisted design 67
5.5.2 Analysis of materials 69
5.5.3 Final configuration and prototype 73
5.5.4 Accessories 75
5.6 Tests 76
5.6.1 Mechanical tests 76
5.6.2 Animal trials 78
5.7 Risk Managment 82
5.7.1 VideoDrain intended use 82
5.7.2 Classification 82
5.7.3 Functional Analysis 83
6 Floseal GI (Gastro Intestinal) catheter 86
6.1 Analysis of the medical background: bleedings in upper and lower gastrointestinal tract 86
6.1.1 GI Endoscopy 86
6.1.2 Ethiology and Pathophysiology 86
6.2 Market Analysis 88
6.3 State of the art: Commercial systems and therapies 89
6.3.1 Endoscopic injection needles 89
6.3.2 Thermo coagulation 90
6.3.3 Mechanical Devices 91
6.3.4 Combined Therapy 92
6.3.5 Hemostyptic sprays 92
6.3.6 Analysis of competitors features 92
6.4 Intellectual property 94
6.4.1 Accessory device: Floseal Matrix 95
6.5 Design History 96
6.5.1 Initial Specification 96
6.5.2 Underlined problems 97
6.5.3 Connections 105
6.5.4 Analysis of materials 105
6.5.5 Final configuration and prototype 109
6.5.6 Manufacturing process 110
6.6 Test sessions 114
6.6.1 In vitro tests 114
6.6.2 Ex-vivo tests 115
6.6.3 Control tests 117

6.7 Risk Management 118
6.7.1 Risk assessment 118
6.7.2 Risk evaluation and control 123
6.7.3 Sterilisation method 124
6.7.4 Instruction for Use – IFU 125
6.7.5 Packaging 127
7 Conclusions ***129***
8 List of publications ***131***
9 Bibliography ***132***
10 Annex I ***137***
Classification of Medical devices 137
11 Annex II ***140***
Biocompatible materials properties 140
12 Annex III ***142***
Flow Chart – Risk Management Activities in Design and Development 142
Grids for Risk and Measures Assessment 142
Risk Assessment Criteria 142
Measures Assessment Criteria 143
13 Annex IV ***144***
14 Annex V ***145***
Results of FE model validation 145
Comparison with datasheets 145
(magn_perm) d22_d22 axially 145
(magn_perm) d24_d24 axially 146
(t.l.v.) d24_d24 diametrically 146
Comparison with tests 146
Validation tests with hkcm magnets 148
Magnet-Cylinder Z02x02ND-48H with iron plate 148
15 Annex VI ***149***
Tests results-September 2010 149
Configuration 1 149
Configuration 2 149
Configuration 3 149
Configuration 4 150
Configuration 5 150
Configuration 6 150
October 2010 150
Configuration 1 150
Configuration2 151
Configuration3 151
Configuration 4 151
Configuration 5 152
Configuration 6 152
16 Annex VII ***153***

Drawings VideoDrain 153

17 Annex VIII ***156***

FloSeal GI cath. prototypes 156

18 Annex IX ***158***

Floseal GI cath tests 158

19 Annex X ***166***

ETO Sterization process parameters 166

3 Research and Development of medical devices

3.1 Design for Minimally Invasive Surgery

The medical practice is constantly being qualified through technological advances brought about by new Medical device (MD). Bringing a MD to the marketplace can be a long and hard road. In this Ph.D. thesis, a strategy to develop innovative MDs for various applications in minimally invasive surgery will be analyzed and implemented in few case studies.

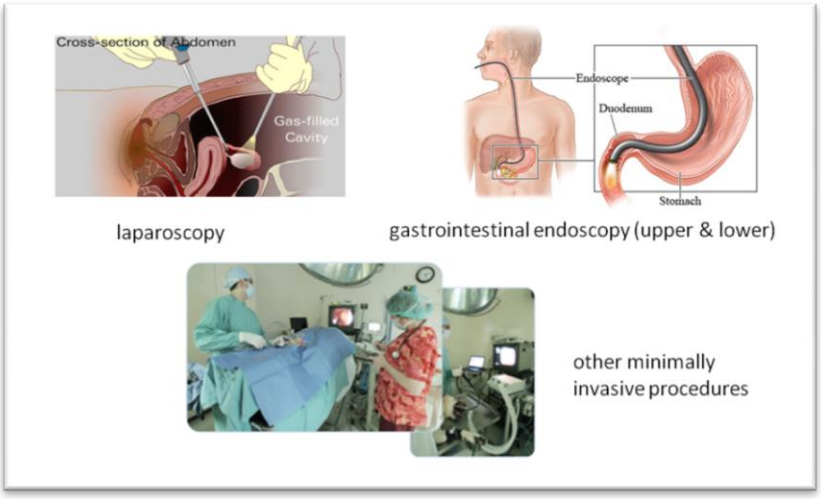


Figure 1 Minimally invasive surgery (MIS) procedures

Using laparoscopic techniques, specialized equipment and at times robotic assistance, the expert surgeons are able to make tiny, precise movements through very small incisions. These innovative techniques cause minimal trauma to the body. Minimally invasive surgery can offer the following advantages to the patients:

- Smaller incision, which reduces pain and shortens recovery time, as well as resulting in less post-operative scarring
- Reduced hemorrhaging, which reduces the chance of needing a blood transfusion.
- Less pain, leading to less pain medication needed
- Although procedure times are usually slightly longer, hospital stay is less, and often with a same day discharge which leads to a faster return to everyday living
- Reduced exposure of internal organs to possible external contaminants thereby reduced risk of acquiring infections.

The various step (see Figure 2) through a valid development of MD starts from the specification of an *idea,* born from a real *need* of improvement of patients' quality of life. Anatomical and physiological knowledge and a full medical literature research are necessary to implement that idea. Many of these devices are invented by the physicians who foresaw the potential benefits the new device would have on their own practice and that of their colleagues. After a specific market analysis and a feasibility study a first prototype is made in order to assure some initial critical aspects. Thanks to the close cooperation with surgeons and observation of clinical practice, a phase of co-invention starts. Engineers and surgeons cope to find a common language and define strict specification for a prototype which become a "proof of concept". Around this tangible idea active business and feasibility plans are compiled. The device must respect some fundamental issues in order to be acceptable for production. First of all the marketability and effectiveness. They must assure a reduced

recovery and hospitalization time. With the use of the new device the abilities of the surgeon should be increased and the procedures simplified. Ergonomics and usability must be pursued in the design.

Figure 2 The rules of safe and effective Innovation

Protecting and licensing commercial rights for a new MD could mean the difference between success or failure. A patent protects against the unauthorized use of an idea and the inventor of a MD should take advantage of the available intellectual property rights to protect and defend against the unlawful infringement or theft of valuable intellectual property associated with a new MD.

In conjunction with protecting the idea, it is necessary to develop a strategic *business plan*. It has several purposes. First, it will help to identify a "roadmap" for how the MD can be successfully marketed and define benchmark objectives and realistic dates to achieve those goals. Second, the strategic business plan is imperative if the company will need to raise equity or borrow money to fund the business venture.

The cost and the safety are key issues for a MD. The material, the technologies and the processes used must be compliant with regulations. The device must be approved, certified and classified with existing legislation depending from the country of deployment of the device.

The life of a MD can be divided in seven phases (1) from conception and development to disposal. The systems and devices described in this PhD work are enclosed in the first pre-market phase through various level of examination (Figure 3).

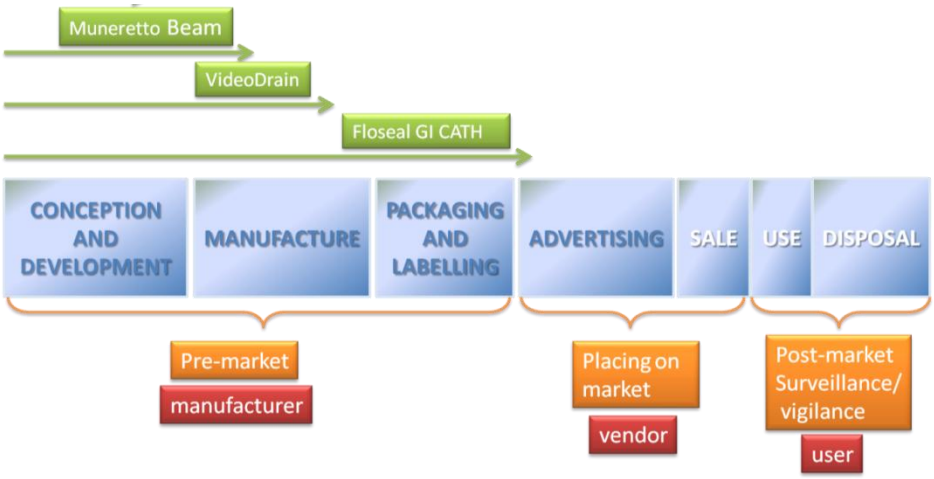


Figure 3 Medical Device life span and subjects involved in each phase

3.2 Methodologies for design and development of innovative devices

TRIZ is a method and a set of tools developed in Russia in 1946; starting from the examination of a very large number of patents, it deducts the general laws underlying the evolution of technical systems and propose a system to develop innovative solutions. The search of solutions is methodical and is obtained overcoming the technical and physical contradiction which comes with the search of improvement. In Figure 4 [3]it is represented the process of development of new innovative products. All the main activities (violet) are surrounded by sub-activities (green) which contribute to clarify and analyze the work in a systematic way.

[3] JOC- Job Outcomes and Constraints
CAM-Computer Aided Manufacturing
CAE- Computer Aided Engineering
CIM-Computer Integrated Manufacturing
FEM-Finite Element method
MRP-Material Requirements Planning
MKTG-Marketing

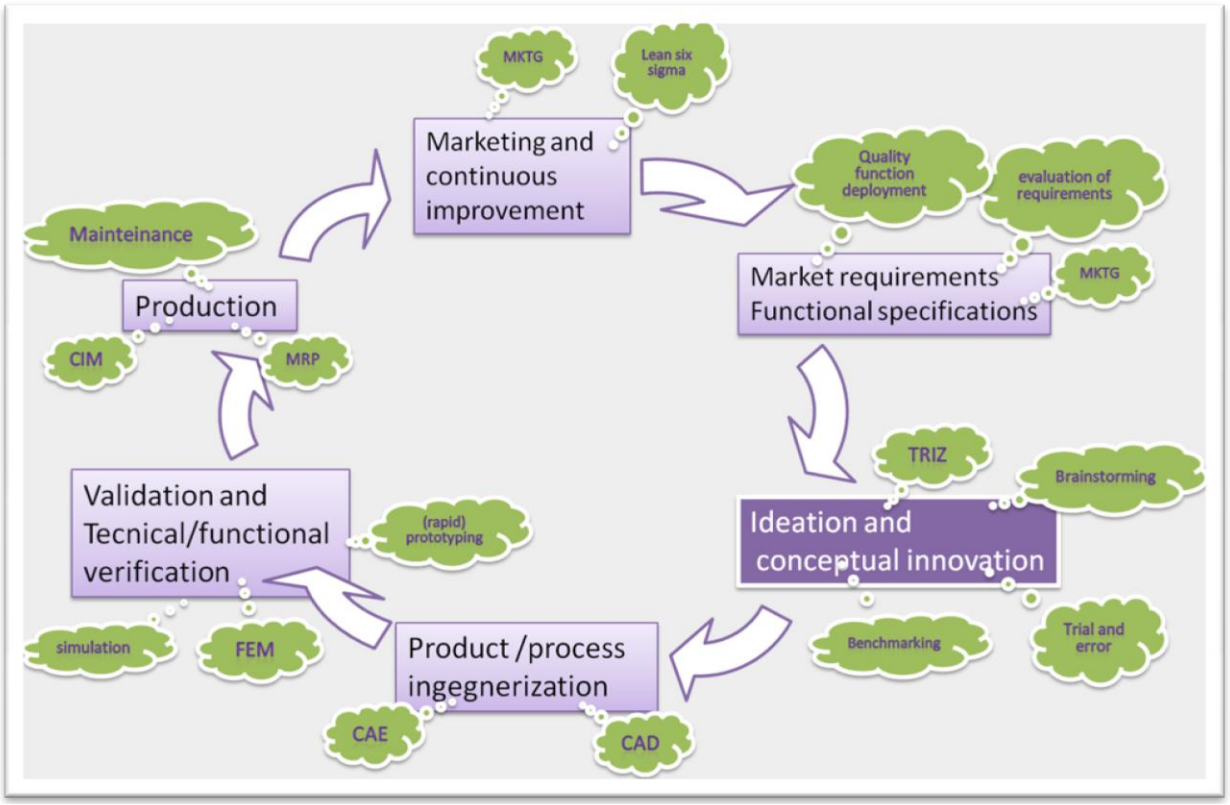


Figure 4 Development of new products

The design process followed in this work represents an implementation of the above scheme and it can be summarized in the following phases:

- Clear Identification of the intended use
- Analysis of the medical background
- Market analysis
- State of the art and patent search
- Analysis of potential configurations and associated CAD[4]
- Analysis and search of materials, components
- Realization of Prototypes
- Preliminary tests and FEM
- Choice of final configuration
- Deployment of the device
- Mechanical strength tests
- In vivo tests
- Study and editing of technical file and Instruction of Use
- CE mark, labelling, packaging
- Post market surveillance.

Some characteristics (2) in healthcare device design can be identified and Each of them is briefly described below:

[4] CAD Computer Assisted Drawing

- *Functionalism* refers to the belief that the intended function of something should determine its design, construction, and choice of materials. It is also seen as a philosophy which emphasizes on practical and utilitarian concerns
- *Ergonomics* is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data, and methods to design in order to optimize human well-being and overall system performance. In medical design, the domain of ergonomics mainly refers to physical ergonomics, which deals with the human body's responses to physical and physiological loads
- *Technology* can refer to the development and application of techniques for manufacturing and productive processes; a method of applying technical knowledge, and a sum of practical knowledge with regards to material culture
- *Appearance* and *Aesthetics* refers to product qualities such as smoothness, shininess/reflectivity, texture, pattern, curviness, color, simplicity, usability, velocity, symmetry, naturalness, and modernism
- *Universal Design* is related to "inclusive design" and "design for all," is an approach to the design of products, services and environments to be usable by as many people as possible regardless of age, ability or situation
- *User experience and Emotional Design* is about improving people psychologically to feel that they are recuperating better overtime.

During the design phase the principles of Human Factor Engineering has been followed; its application to system design improves ease of use, system performance and reliability, and user satisfaction, while reducing operational errors, operator stress, training requirements, user fatigue, and product liability. In Medical device design it is very important not to forget that the beneficiary of the invention and its user are the patient and the medical professional, so all the efforts of the designer must be focused on these subjects' needs.

Addressing use-related hazards should be undertaken within the context of a thorough understanding of how a device will be used. Essential components of this understanding include:

- Device users, (e.g., patient, family member, physician, nurse, professional caregiver)
- Typical and atypical device use
- Device characteristics
- Characteristics of the environments in which the device will be used
- The interaction between users, devices, and use environments.

Following a thorough understanding of device use, specific ways that devices could be used, that are likely to result in hazards, should be identified and investigated through analysis and testing. In addition to investigating known or suspected problems with device use, testing prototype devices with users can identify ways of using devices that could be hazard-related, that were not anticipated. This is important because it is extremely difficult to identify all significant device use problems in advance.

After use-related hazards are understood, the hazards are mitigated or controlled by modifying the device user interface (e.g., control or display characteristics, logic of operation,

labelling) or the abilities of users to use the device (e.g., training, limiting use to qualified users).

3.3 Design of medical components

3.3.1 Microtubes

The main sub components used for minimally invasive devices are catheters, available in different configurations and materials. Catheters are medical devices, typically in the form of a tube, that are inserted into the body to remove fluid, create an opening, or deliver a drug. All the device described in the current work rate catheters of different shapes and dimensions between their main components.

Among the main design qualities of tubings (3), the profile or form factor as well as its trackability, pushability, and torqueability can be mentioned. Trackability means the ability of a catheter to go through tortuous paths to its ultimate destination. It depends on:

- Shaft flexibility
- Friction between a catheter and its surrounding environment
- Column strength, which is the capacity of the tube to withstand axial forces without compression or stretch.

Catheter torqueability describes the behaviour of a tube when a moment of torque is placed about its longitudinal axis (Figure 5).

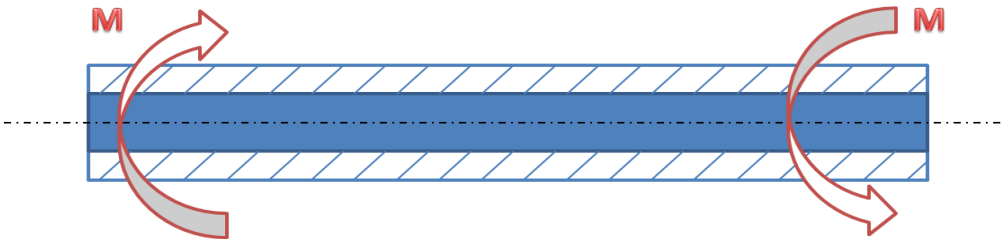


Figure 5 Torque or moment (M) applied to a tube.

For small deflections, the tube's mechanical properties approximate a spring system, in which torsional stiffness is determined such that:

$$Ktorq = GJ/L$$

where $Ktorq$ is the torsional spring constant, G is the shear modulus, J is the polar moment of inertia, and L is the length of the catheter shaft.

Tube flexibility can be modelled as a clamped beam system subject to a downward force at the beam, as shown in Figure 6.

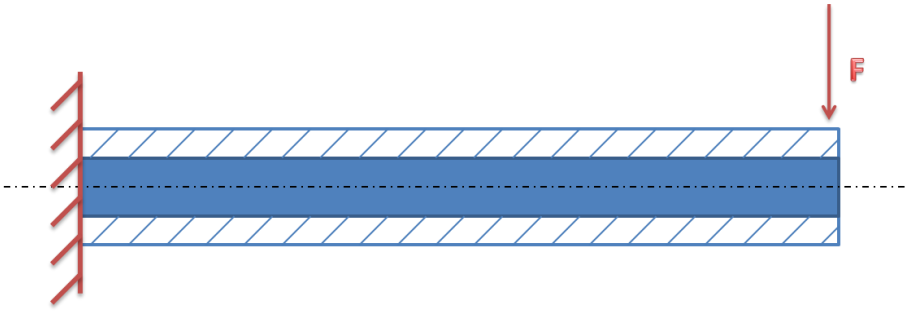


Figure 6 Flexibility (F) or bending force applied to end of tube

For small deflections, the tubing approximates a spring system, with the flexural stiffness determined by:

$$Kflex = 3EI/L^2$$

where $Kflex$ is the flexural spring constant, *E* is the modulus of elasticity, *I* is the moment of inertia, and *L* is the length of the catheter shaft. In many cases, it is desirable to minimize the flexural stiffness of the catheter (6.5.2) and it's possible by :

- Minimizing the moment of inertia
- Minimizing the modulus of elasticity by using a soft material
- Increasing the overall part length.

The pushability is the response of a tube when a longitudinal force is applied along its axis (Figure 7).

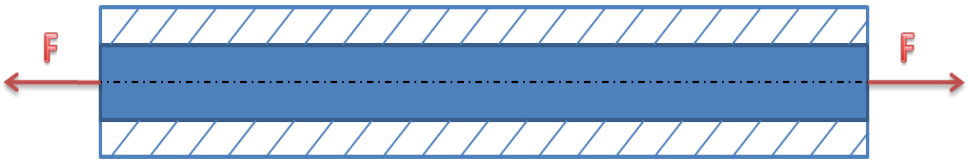


Figure 7 Force applied on the longitudinal axis of a tube

For small deflections, the tubing properties can be considered to approximate a spring system, in which the longitudinal stiffness of the spring is determined by the equation:

$$Klong = \frac{EA}{L}$$

Where $Klong$ is the longitudinal spring constant, E is the modulus of elasticity, A is the cross-sectional area, and L is the length of the catheter shaft. In order to maximize pushability, it's necessary to maximize the parameter $Klong$:

•By maximizing the cross-sectional area of the tubing

•By maximizing the modulus of elasticity using a stiffer material

•By decreasing the overall part length.

In minimally invasive surgery, often it is very important not to augment the diameter of the tubing, so there is a wide search of new materials which offer a good compromise between stiffness, flexibility and biocompatibility.

Commonly, composite tubing designs are used for catheter delivery systems. These include designs consisting of one or more plastic materials (6.5.4) as well as wire-reinforced (braid or coil) designs (VideoDrain device 5.5.1).

3.3.2 Materials

In designing a medical tube, it is important considering four basic physical properties of materials, which are critical to function (in Table 49 some properties of the most common materials for medical use):

- durometer (the hardness of the resin)
- flex modulus (the flexibility of the resin)
- ultimate tensile (the force it takes to break the tube)
- elongation (how much the material will stretch before breaking).

Two other important criteria are biocompatibility of the resin and postextrusion processability. The biocompatibility of catheters, as with other medical devices, can be defined as the ability of the device to perform its intended function without eliciting undesirable side effects. Their biocompatibility is related not only to the basic polymers, but also to the various additives used.

It is also important to understand if the materials, once processed, can be used without hazards. Infact accidental release of particles of materials can occure for several purposes: friction, temperature, wrong conditions of use, intrinsic features of the material.

Polyvinylchloride (PVC)(4) is an inexpensive plastic material that is used in a wide variety of industrial and domestic applications. PVC is used in some situations with minimal additives, in which case it is a hard rigid material; most often, an additive described as a plasticizer is used, and the resulting plasticized, or soft, PVC finds extensive applications, especially in medical tubings. Many short-term catheters and drains are used in the clinic, including umbilical vessel catheters, wound drainage tubes and osteotomy shunts.

Natural rubber latex (NRL) is a highly elastic, very-low-durometer material exhibiting high tear resistance and high elongation. It has long (5) been used to manufacture a wide range of healthcare products and components for medical devices. But as latex allergy has become a major occupational health problem for healthcare workers, non-allergenic alternatives to NRL are in greater demand to meet the needs of the medical device industry for latex-free materials.

Silicones, one of the most thoroughly tested and widely-used groups of biomaterials, are well known for their intrinsic biocompatibility and biodurability. These key characteristics have been attributed to the material's inherent chemical and thermal stability, low surface tension and hydrophobicity. As a result of these properties, silicones have the benefit of extensive application in catheters and other medical products. Silicones have been successfully applied in short- and long-dwelling catheters, drains, and shunts for over sixty years (6). Silicone elastomer is a thermosetting material, capable of being processed by various moulding, dipping, and extrusion methods. Like polyurethanes, silicones are excellent for low-durometer applications—strong, resilient, stretchable, and more stable than latex.

Silicone elastomers used in medical device applications normally include reinforcing filler; Incorporation of reinforcing filler into the cross-linked matrix reduces material stickiness, increases hardness, and enhances mechanical strength. Silicone catheter raw materials are more expensive than legacy materials such as latex and PVC, but when examining healthcare choices, possibility of infection should be taken into account.

TPU is a thermoplastic *Polyurethane* (see VideoDrain materials) and has gained wide acceptance as an alternative to silicone. When employed as part of an invasive device, polyurethanes soften considerably within minutes of insertion in the body, reducing patient discomfort and the risk of vascular trauma. The high strength and ease of processing of polyurethanes make them an excellent choice for soft-elastomer applications. Advances in PU

formulations have made polyurethane a suitable replacement for latex in a variety of medical device applications.

A prominent device application (5) for polyurethane and silicone is in low-pressure elastomeric balloons, as the ones used in the current work. These components are different from high-pressure medical balloons, which are made of non- or low-compliant materials such as PET and nylon and are generally used to apply force in a variety of diagnostic and therapeutic procedures, including angioplasty and other dilatation applications.

Fluoropolymers (7) exhibit very good lubricity compared with other plastics. PTFE is the most lubricious polymer available, with a coefficient of friction (COF) of 0.1, followed by fluorinated ethylene propylene (FEP), with 0.2. These two polymers represent the vast majority of all fluoropolymer tubing used in medical devices. Fluoropolymers, especially PTFE, has an excellent biocompatibility

PTFE (Teflon) is very difficult to extrude, due to its high viscosity and it needs particular material for the equipment because of its high corrosion in the molten state.

3.3.2.1 Disposal

For several years, regulations (8) for the reduction of waste and minimization or elimination of hazardous substances have been enforced in the European Union (EU). Standards such as the Waste Electrical and Electronic Equipment (WEEE); Restriction on Hazardous Substances (RoHS); Registration, Evaluation, and Authorization of Chemicals (REACH); and the Energy Using Products (EuP) regulations have significantly altered the manufacturing processes of electronics at industrial and consumer products companies.

The WEEE Directive requires the use of specific labelling, compliance with disposal restrictions, and creation of instructions for end-of-life management and recycling.

Methods such as Six Sigma and lean manufacturing promote low defect manufacturing and encourage process flexibility. Lean manufacturing specifically targets and attempts to reduce seven waste streams, namely overproduction, waiting time, transportation, processing, inventory, motion, and scrap. These concepts, while originally developed to improve efficiency and reduce production costs, also align with many of the goals of sustainable design and production.

Disposal of medical products made from PVC can be problematic. The preferred biohazard waste disposal method for hospitals is often incineration. Incineration of used PVC medical devices such as catheters and tubing generates hazardous gases including hydrochloric acid (HCl), dioxins, and polychlorinated biphenyls (PCBs). In addition to the environmental impact of such air population, the HCl shortens the life of the incinerator.

With respect to disposable medical products, choosing materials that limit environmental damage during disposal and incineration can reduce toxic air emissions and reduce waste processing costs. In addition, products that have a durable or reusable component and smaller disposable components can minimize waste without damaging the lucrative nature of the disposable device business model. The critical factor in the durable or disposable product concept is to create a simple, repeatable interface between the two component sections so as not to impair the functionality or efficacy of the product.

3.3.3 Design for manufacturability

Achieving an efficient catheter system figures among the fundamental design requirements in developing a novel medical procedure.

Most specifications for medical tubing consist of a drawing of a tube with the material, dimensions and tolerances. For single lumen tubing(9), the dimensions will usually include two of the following three dimensions; inner diameter (ID), outer diameter (OD) and the tubing wall thickness, along with their associated tolerances. In addition, the tubing length and tolerance would be included unless the tubing is to be provided in a continuous length on a spool.

One of the pressing issues for any new product(3) or process development project is the complexity of the required manufacturing process and its expected yields. Optimizing the manufacturability of the design from the beginning of the development process is a key issue for medical devices in particular. Oftentimes, the process parameters and the equipment used to extrude the tubing are as important or even more important than the actual dimensions of the tube. The tolerance requirements for metal instruments are completely different from those for plastic molded components. The device must be properly designed in order to have proper function in spite of these variations.

The following sections summarize recent trends in catheter manufacturing, including assembly techniques, component outsourcing tactics, and sterilization methods. The most important manufacturing techniques for the industry of plastic sub components (also for the device developed in this thesis) are the extrusion, the moulding and the dipping.

3.3.3.1 Extrusion process

During extrusion, the billet, heated to the proper hot-working temperature, is placed in the chamber of an extrusion press. The horizontally mounted chamber contains a die at one end and a hydraulically driven ram at the other. The face of the ram is fitted with a dummy block that is slightly smaller in diameter than the billet.

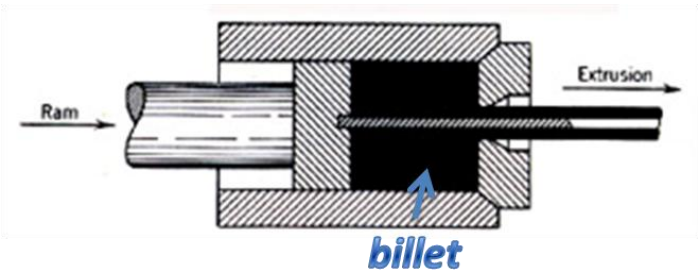


Figure 8 Extrusion of tubing from a hollow billet

An extrusion line is a combination of several pieces of equipment. The major elements of a medical extrusion line include a resin drying system, the extruder, the die, the cooling tank, a take-up device (puller) and a cutter or winder.

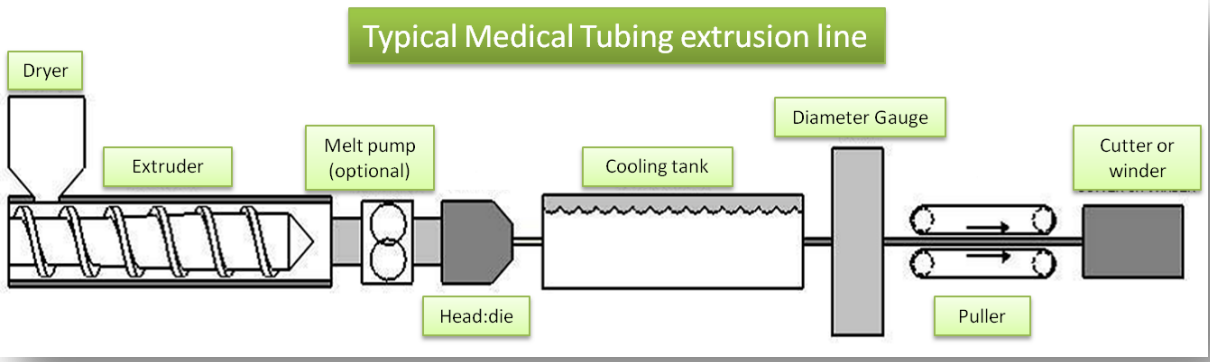


Figure 9 A typical medical tubing extrusion line.

Many polymers used in the medical device industry are "hygroscopic", i.e. they absorb moisture readily from the environment. Hygroscopic polymers must be carefully dried prior to being melt extruded or compounded. All materials are not *dried* under the same parameters. Some require high temperatures for long periods of time while other materials may require low temperatures for shorter periods of time. Residual moisture in the polymer results in hydrolysis during extrusion. Hydrolysis is a degradation process that results in significantly lower molecular weight. Over-drying is another problem that can occur; If not properly monitored, this can result in over-drying which can cause thermal degradation in some materials. Many polymers, such as nylon and polycarbonate, can be sensitive to over-drying.

The *extruder* is a melting and pumping machine. It converts solid pellets into a uniform, molten state and forces the material through the die at a constant rate. Melting is accomplished through frictional heat generated from the mechanical work of the screw and heat conduction from the heated barrel of the extruder. The design of the extrusion screw is critical in achieving uniform melting and pumping of the polymer without over-working (over-shearing) the material.

The *extrusion die* sits at the end of the extruder and is the point where the polymer exits into a cooling tank. The die forms the initial shape of the tube. A tubing die typically consists of two major components; a mandrel or tip that forms the tube ID, and a die, or ring, which forms the tube OD. The die and mandrel are typically contained inside the extrusion "head". The design of these components plays a critical role in the extrusion process and the ability of the extruder to produce precise dimensions and maintain proper physical properties of the material. The relationship between the die and mandrel dimensions and the finished tube dimensions is typically referred to as the draw down ratio.

3.3.3.2 Drawing

Drawing simply involves pulling the hollow tube through a series of hardened steel dies to reduce its diameter.

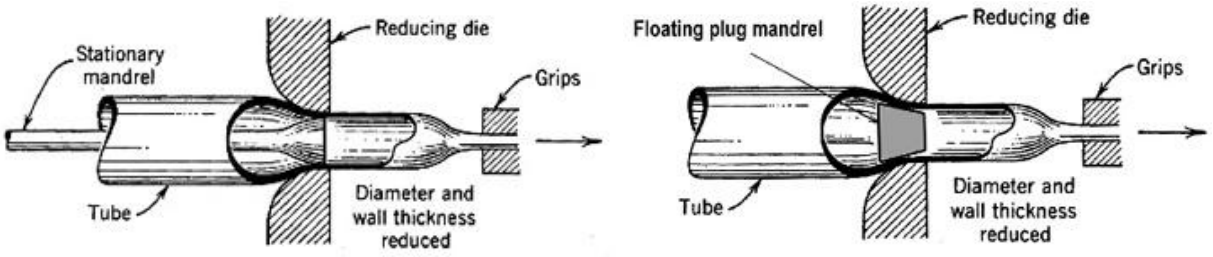


Figure 10 Tube Drawing over Fixed Mandrel (left); tube Drawing over a Floating Plug Mandrel (right)

A tapered plug mandrel, which may be either fixed or floating (Figure 10) depending on the process used, is placed inside the tube. Floating plugs are used with bull blocks. Stationary mandrels are used for relatively short lengths of tube that are drawn on linear drawbenches. As the tube is drawn onto the spinning bull block, the mandrel and die act together to reduce both the tube's outside diameter and its wall thickness. The mandrel also imparts a smooth surface to the tube's inside surface. The tube is drawn in several stages until the desired diameter and wall thickness is attained. Drawing work-hardens the copper, and the tube is now quite stiff.

3.3.3.3 Moulding

Plastic moulding is a very methodological and technical process. There are several plastic moulding process:

- Injection Moulding
- Blow Moulding
- Multimaterial molding.

In Injection Moulding, melted plastic is forced into a mold cavity. Once cooled, the mold can be removed. This plastic injection moulding process is commonly used in mass-production or prototyping of a product. Typically this process is used to produce plastic mouldings where the relatively high tooling cost can be justified by low unit costs and tolerances which cannot be achieved by other moulding processes.

The process is divided into three steps: injection, blowing and ejection. Blow moulding is like **plastic injection moulding** except that hot liquid plastic pours out of a barrel vertically in a molten tube. The mold closes on it and forces it outward to conform to the inside shape of the mold. When it is cooled, the hollow part is formed. Equipments needed in setting-up a blow moulding business are relatively higher than injection moulding.

Overmolding (10), or two-shot molding, results in parts in which it is clearly evident that more than one material is being used. In these processes, only part of a product is molded in one material, and that molded piece is manipulated so the second material can be molded around, over, under, or through it to complete the final part. This method is sometimes referred to as in-mold assembly, since the resulting part effectively acts as an assembly of two materials rather than as a layered structure.

3.3.3.4 Dipping

Dip molding of polyurethane and silicone is a relatively recent development. To dip mold a product, a mandrel in the shape of the object being molded is heated, dipped into the resin solution, then removed from the dipping tank. Mandrels can be machined from metal or formed from other materials. Metal is typically used for high-volume production. Glass

mandrels produce a very smooth surface but are challenging to use because of their fragility. The mandrel should be lowered gradually into the solution to avoid solvent gassing or bubbles in the solution, which can result in pinholes and weakness in the finished product.

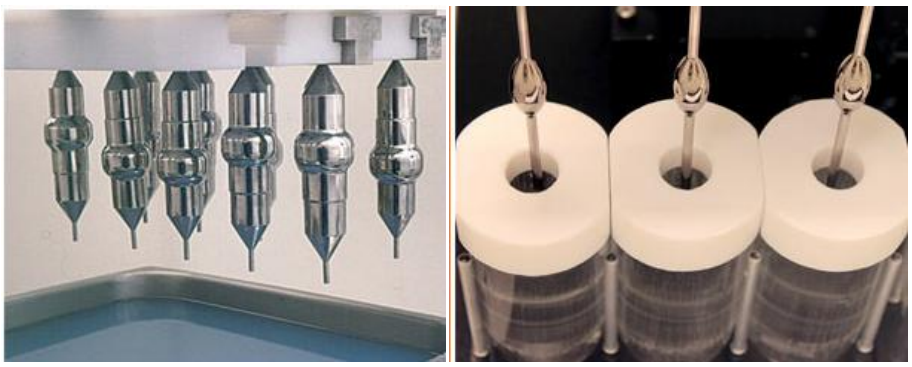


Figure 11 Dipping of medical balloons

After dipping, the thin coating of the polymer that remains on the surface of the mandrel is allowed to cure, then is stripped off as a finished product.

Dip moulding is a cost-effective process for low-volume production of thin-film products, offering consistent wall thickness and uniformity, relatively low tooling costs, and fast setup for new product development.

3.3.4 Assembly Techniques

Epoxies were commonly used in catheter assemblies thanks to their very high performance. However they require long cure cycles or elevated cure temperatures and additional facilities dedicated for thus use. As a result, the use of epoxies in catheter subassemblies has often been replaced by the next alternatives:

- Adhesives that can be cured on demand through exposure to *ultraviolet light*
- *Thermal welding* of mating parts. This is accomplished via localized heating of certain materials (for example, Pebax and urethanes), which causes them to reflow and create a integral adhesive bond for the surrounding parts
- Elimination, in some cases, of the use of adhesives altogether through *innovative processes*. For example, variable-stiffness catheter products can be manufactured as a continuous process
- *Surface modification* in the form of chemical etching is required for those non stick materials as PTFE.

3.3.5 Component Outsourcing

Many medical device manufacturers outsource more subassembly to component manufacturers. Additional operations, typically requested from component manufacturers, include:

- Cutting to exact length tolerances of non-braided tubing products.
- Cutting to length of braided components in which the tip is non-deformed and the braid wires are embedded in the tubing product (non-frayed).
- Secondary operations such as flaring, tipping, hubbing, hole drilling/punching, curve forming, and ID/OD tube tapering.
- Surface preparation of fluoropolymer materials for bonding (Teflon).

Problems with outsourcing subassembly operations can often be minimized by requiring that the component manufacturer have a good quality system in place. ISO certification of quality systems (ISO 13485) is fast becoming a requirement for medical component suppliers.

3.3.6 Sterilization Methods

The first step is deciding whether to design instruments to be reusable or whether to make them disposable. The material requirements for each instrument are quite different. Reusable instruments are most likely going to be steam sterilized. For this type of application, manufacturers should select plastic resins that can be autoclaved. It's important to note, however, that autoclavable resins are much more expensive than those that can be used for disposables.

An important issue concerns the terminal sterilization method used for the finished catheter device. Many catheter manufacturers are tending to favor the use of E-beam or gamma irradiation over ethylene oxide gas. The preference for high-energy sterilization has the result of eliminating the use of some fluoropolymer materials, such as fluorinated ethylene propylene (FEP) or polytetrafluoroethylene (PTFE) in catheter assemblies. This can compromise the finished devices' performance, since equivalent substitutes have not been found that offer all of the performance attributes of these two materials.

Once cross-linked into the desired configuration, silicone (6) catheters are thermally stable (reported operating range from -80 °C to +230 °C), remaining essentially unaffected by repeated autoclaving. They can usually be dry-heat sterilized as well.

Specific requirements for documentation and validation of processes for sterile medical devices are shown in the ISO 11137-1, 3 (Table 1). In Annex II, some tables of different materials with the associated possible sterilization methods are enclosed.

3.4 Regulation

The process of design of a MDs should work with certification proactively. The key determinant for approving a MD to be marketed is that it must be safe and effective. There are a variety of mechanisms to prove a MD is safe and effective and they will be investigated.

When placing a MD on the market the manufacturer must have demonstrated through the use of appropriate conformity assessment procedures that the device complies with the Essential Principles of Safety and Performance of MDs (Table 1). Any of the phases in Figure 3 can affect them. The scientific principles upon which a device is based are fundamental: the more complex the device, the higher the risk of user error. Soundness of concept and adequacy of design, construction, and testing (including verification, validation and clinical trials) require analysis to ensure that design parameters and performance characteristics do not impose unwarranted risks.

Good, functional medical devices are produced when the manufacturing process is adequately managed. This consideration has led to the development of good manufacturing practice (GMP) for drugs, biological products and medical devices.

In Table 1 there is a short list of the principal regulations to follow in the design of MDs. The first is the generic EMDD, the primary approach to the world of MD development.

Regulation	Directive
(EMDD) European Medical Device Directive	2007/47
***(AIMD)* Active implantable**	90/385/EEC
(IVD) In vitro diagnostic	98/79 CEE
Medical electrical equipment	IEC 60601
Application of risk management to medical devices	ISO 14971
Quality management systems - Requirements for regulatory purposes	ISO 13485-13488 ISO 14969
Fundamental aspects of safety standards for medical electrical equipment	IEC/TR 60513
Biological evaluation of medical devices	ISO 10993
Clinical evaluation of medical devices for human subjects	ISO 14155
Guidance on the selection of standards in support of recognized essential principles of safety and performance of medical devices	ISO 16142
Packaging for terminally sterilized medical devices	ISO 11607
Sterilization of medical devices	ISO 11135, 11137, 11138, 11140

Table 1 Principal regulations for MD design and development

Clinical evaluation (Table 1) is the assessment and analysis of clinical data pertaining to a MD in order to verify the clinical safety and performance of the device . It is an ongoing process conducted throughout the life cycle of a MD. The Clinical Evaluation can be based on clinical data derived from literature or based on data related to the specific device. It's mandatory to specify the criteria for the evaluation of the data (description of the methods). The clinical evaluation is required for all the classes of devices, Class I included. For active implantable devices, Class III and no active implantable devices clinical investigations are required. The absence of clinical data has to be duly justified. The clinical evaluation has to be updated on the basis of a post market surveillance plan.

3.4.1 Certification aspects: definitions and classification

MD means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring and treatment of disease or disability
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- Investigation, replacement or modification of the anatomy, or of a physiological process
- Control of conception.

In the classification and certification of a MD the manufacturer must follow the directions of Directive 2007/47.

All the considerations summarized in Directive 2007/47/EEC are mandatory steps for the manufacturer to obtain the CE mark on devices manufactured on his behalf. There are many components that contribute in parallel with the release of the CE mark as in Figure 12.

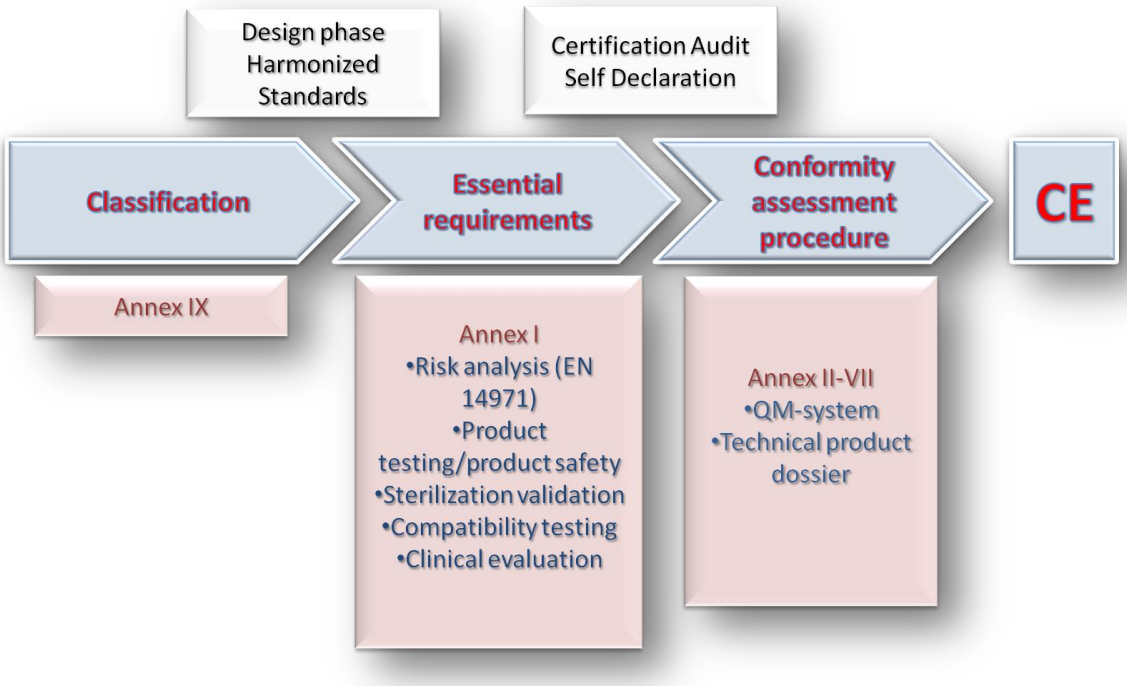


Figure 12 Steps to CE mark

A simple set of classification rules based on technical features of MDs existing now and in the future is impossible, because of the vast number and the changing nature of variables involved. The human body, however, is a relatively unchanging element of the equation. The European legislator established therefore a classification concept which is essentially based on potential hazards related to the use and possible failure of devices taking account of technology used and of health policy considerations. The classification rules (see) are based on terms related to duration of contact with the patient, degree of invasiveness and the part of the body affected by the use of the device. These terms are defined in Section I of Annex IX of the directive 2007/47.

Concepts of duration such as transient, short term and long term are defined in terms of continuous use. Continuous use must be understood as an uninterrupted actual use for the intended purpose.

Any device which, in whole or in part, penetrates inside the body, either through a natural body orifice or through the surface of the body is an invasive device. A surgically invasive device always implies that it enters through an artificially created opening. The concept “act by converting energy” includes conversion of energy in the device and/or conversion at the interface between the device and the tissues or in the tissues.

The derived classes of MDs are:

- Class I: non-invasive devices, i.e. those which do not come into contact or interact with the body;
- Class IIa: invasive short-term devices, used through natural orifices of the body and invasive surgical for temporary use;
- Class IIb: short term surgical invasive devices
- Class III: includes devices which come into contact with vital organs.

3.5 Quality system

Deming in the 1950's proposed that business processes should be analyzed and measured to identify sources of variations that cause products to deviate from customer requirements. He recommended that business processes be placed in a continuous feedback loop so that managers can identify and change the parts of the process that need improvements. This continuous process can be summarized in a diagram commonly known as the PDCA cycle for Plan, Do, Check, Act:

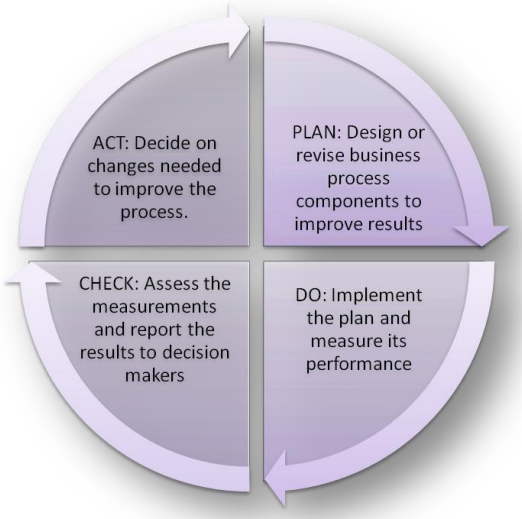


Figure 13 PDCA diagram

The law outlines general requirements for MD quality system management, covering issues such as design, production, installation, and sales. A Quality System is defined as the organizational structure, responsibilities, procedures, processes and resources needed to implement quality management. The international quality system standards for MDs are issued by the International Organization for Standardization (ISO) (ISO13485:1996 and ISO13488:1996). ISO13485:1996 includes all the elements of ISO9001:1994 plus a set of minimum supplementary requirements for MDs.

Similar to the ISO 9001:2000 standard(11), ISO 13485:2003 standard for medical device manufacturers has a strong focus on customer satisfaction and improvement, but with an added focus on safety. This explains why ISO 13485:2003, unlike ISO 9001:2000 requires medical device companies to maintain a risk management system.

MDs should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

Manufacturers of MDs have to face many challenges to enter the global medical technology market(11). Growing competition requires frequent design changes, shorter time to market, assembly of small parts with complex geometry and tight tolerances, and difficult to work with materials such as titanium and silicone, just to mention a few.

The cost of fixing a single error in a device increases exponentially with the discovery time. Thus, the earlier a problem can be identified the more money a company will save; so the design and testing phases are crucial for saving costs.

Design controls (Figure 14) are a component of a comprehensive quality system that covers the life of a device. Design control begins with development and approval of design inputs, and includes the design of a device and the associated manufacturing processes (12). A specific focus is mandatory on the controls in the work environment to ensure product safety : clean rooms, machines, including also the procedure for cleaning parts coming from external providers.

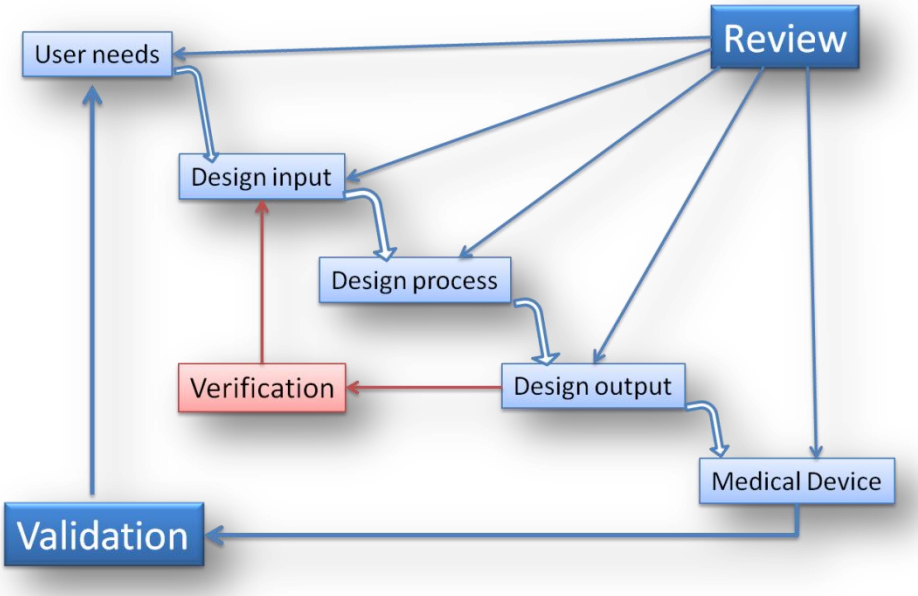


Figure 14 Application of Design Controls to Waterfall Design Process

The production of the developed devices has been prevalently outsourced but in all cases sufficient evidence has been given in the technical file about the competence of the subcontractor to undertake supply of some parts, material or service in relation to the medical device in question (as said in (13)).

3.6 Risk Management

Risk management principles should be applied throughout the life cycle of medical devices and used to identify and address safety issues. The current approach to device safety is to estimate the potential of a device becoming a hazard that could result in safety problems and harm. This estimate is often referred to as the **risk assessment**.

In general, risk management(14) can be characterized by phases of activities:

- Determination of levels of risk that would be acceptable in the device
- Risk analysis
- Risk evaluation
- Risk control and monitoring activities.

The procedures to determine risk acceptability criteria comes from an analysis of the experience with similar medical devices or research on what appears to be currently accepted

risk levels by regulators, users, or patients, given the benefits derived from diagnosis or treatment with the device.

The risk analysis starts with identifying hazards that may occur due to characteristics or properties of the device during normal use or foreseeable misuse. The ISO 14971 is an international standard for manufacturers of medical devices. It specifies a process through which the manufacturer can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of that controls.

The functional analysis is the starting point and can be carried out using the ISO 14971; questions that can be used to identify medical device characteristics that could impact on safety are presented (pg.83 and 119).

Hazards typically considered in risk analysis include:

- Chemical hazards (e.g., toxic chemicals)
- Mechanical hazards (e.g., kinetic or potential energy from a moving object)
- Thermal hazards (e.g., high temperature components)
- Electrical hazards (e.g., electrical shock, electromagnetic interference (EMI))
- Radiation hazards (e.g., ionizing and non-ionizing)
- Biological hazards (e.g., allergic reactions, bio-incompatibility, and infection)
- Use related hazards.

The comparison between estimated risks and risk acceptability criteria will determine an appropriate level of risk reduction, if necessary. The combination of risk analysis and risk evaluation is called *risk assessment*.

Risk control activities should begin as early as design input and continue through the design and development process, manufacturing, distribution, installation, servicing and throughout the medical device life cycle.

The objective of risk management is rarely to eliminate all risk, but rather to reduce risk to an acceptable level while maintaining feasibility and functionality. Risk management activities should begin as early as possible in the design and development phase, when it is easier to prevent problems rather than correcting them later.

After release of the device to market, risk management activities should be linked to quality management processes, for example, production and process controls, corrective and preventive actions, servicing and customer feedback. In Annex III a flow chart for the risk management activities in design and development has been enclosed.

The specific performance of the device must be analyzed for each conceivable failure, and ranked by probability and consequence of that failure. In order to identify the risk acceptability, existing criteria (i.e. already indentified for similar products) can be used or determined using the following methods: Failure Mode and Effect Analysis (FMEA[5]), Fault

[5] The FMEA analysis is a regulated process (ISO 13485 and 9001) detailing the failure mode, its causes, its effects, the frequency of occurrence, the severity of occurrence and the actions to mitigate the effects.

Tree Analysis (FTA), Hazard and Operability Study (HAZOP). When the risk is unacceptable, some additional methods cha be used:

1. indirect methods (i.e., design modification),
2. direct methods (i.e., in case of radiation, protections or screens)
3. description methods (i.e., device application description or prescription)
4. re-definition of the intended use.

3.6.1 The methodology of ISO 14971

The methodology for creating and updating the technological risk analysis for a general product can be summarised in the next steps, as parts in Analysis of Technological Risk:

- identification of a "risk", defined as the chance to have a negative outcome of the project or of one of its activities, related to events – "**Unwanted events UE**" - that may be foreseen. The name and a brief description of the impact related to the risk must be reported
- for the identified risk, the **probability** of occurrence must be estimated according to the probability scale of the sub-table "Risk Assessment Criteria". This value must be reported in column "**Probability - P**" (Annex III)
- the negative **"impact level – IP"** that may affect the project outcomes in case the identified risk occurs must be estimated according to the impact level scale of sub-table "Risk Assessment Criteria". This value must be reported in column "Impact Level"
- the **probability** and the **impact level** must be multiplied together in order to fill the column labelled "**Risk Estimation**"
- once the risk has been estimated, the "**Risk Estimation**" value must be compared with the numerical values of table "Measures Assessment Criteria". This will be useful in order to decide the need of proper measures for decreasing the risk. If the "**Risk Estimation (RE)**" value falls within the:
- "red" zone ("**Risk Estimation**" ≥ 18), then measures **must be** introduced to decrease the "**Risk Estimation**" down to a value that falls within the green or, at least, the yellow zones;
- "yellow" zone (5 ≤ "**Risk Estimation**" < 18), then measures **may be** introduced to decrease the "**Risk Estimation**" down to a value that falls within the green zone;
- "green" zone ("**Risk Estimation**" < 5) then no measures are required.
- according to point 5 (in cases 5.a or 5.b) measures must or may be introduced. The proper measures, once identified, must be described in the row named "Measures and contingency". This has to be placed in the column corresponding with the level of probability of occurrence(EI).
- if Measures have been introduced and applied, the new probability and impact level values named in the "Probability after Measures" respectively the Probability after Measures and the Impact Level after Measures must be multiplied together in order to fill the column , labelled "**Risk Estimation after Measures or Residual Risk - RRE**". This value must fall within the green or, at least, the yellow zones
- steps from 1 to 9 must be repeated for each risk that has been identified.

4 Muneretto[6] Beam Navigation device

A preliminary study for the development of a new device for minimally invasive intervention for the treatment of atrial fibrillation has been here reported. A proof of concept will be presented.

4.1 Analysis of the medical background

Normally with each heartbeat, the electrical impulse begins at the sinoatrial (SA or sinus) node in the right atrium. The SA node produces the electrical impulses that set the rate and rhythm of the heart beat. The electrical activity (Figure 15,left) spreads through the walls of the atria and causes them to contract. The electrical impulse then crosses the AV node and spreads down to the ventricles, causing them to contract. This generates the heart beat.

Atrial fibrillation (AF, Figure 15 right) is a supraventricular tachyarrhythmia characterized by disorganized atrial electrical activity and progressive deterioration of atrial electromechanical function. Electrocardiographic manifestations(15) of atrial fibrillation include absence of sinus P waves (atrial impulse); rapid oscillations (or fibrillatory waves) that vary in amplitude, frequency, and shape; and an irregular ventricular response. AF may occur in isolation or in association with other arrhythmias, most commonly atrial flutter or atrial tachycardia. In AF, various regions of the atrial wall pulse 400-600 times per minute and the ventricular rate is determined by the interaction between the atrial activity and the filtering function of the atrioventricular node.

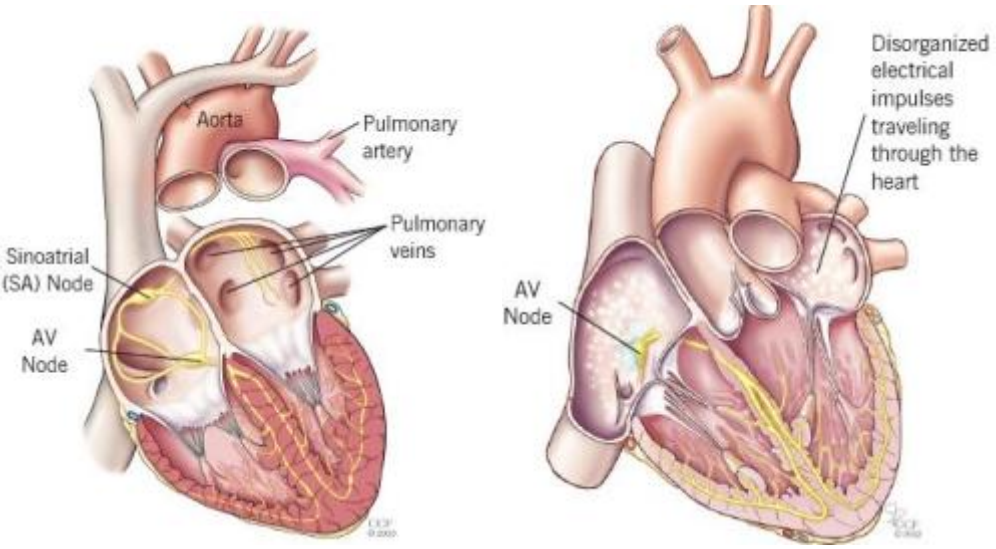


Figure 15 Electrical System of the Heart (left) Atrial Fibrillation (right)

Abnormalities in the heart's electrical impulses in patients with AF cause blood to be pumped improperly, resulting in pooling or clotting. If a blood clot moves to an artery in the brain, AF can lead to stroke. AF is also associated with increased risk of congestive heart failure and cardiomyopathy (heart muscle disease).

AF is the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. Most data regarding the epidemiology, prognosis, and quality of life in AF have been obtained in the United States and western Europe. It has been estimated that 2.2 million people in America and 4.5 million in the

[6] University of Brescia

European Union have paroxysmal or persistent AF. It is an extremely costly public health problem: the annual cost per patient is close to €3000.

4.1.1 Clinical evaluation in patients with AF

The minimum evaluation for the assessment of AF comprises:

- History and physical examination to define presence and nature of symptoms associated with AF
- Electrocardiogram to identify Rhythm (verify AF)
- Transthoracic echocardiogram, to identify valvular heart disease
- Blood tests of thyroid, renal, and hepatic function.
- Additional test can be performed to identify the type of AF (Holter monitoring or event recording), to identify left atrium thrombus or to guide cardioversion (Transesophageal echocardiography), to identify a predisposing arrhythmia such as atrial flutter (Electrophysiological study).

4.2 Surgical treatments for atrial fibrillation

The goals of treatment for atrial fibrillation include regaining a normal heart rhythm (sinus rhythm), controlling the heart rate, preventing blood clots and reducing the risk of stroke. Many options are available to treat atrial fibrillation. These include medications, lifestyle changes, procedures and surgery. Several surgical treatments for atrial fibrillation are available :

- Maze procedure
- Surgical pulmonary vein isolation (endoscopic and percutaneous)
- Left atrial appendage (LAA) excision.

The drive to make ablation procedures more acceptable to a wider group of patients, particularly those with lone atrial fibrillation who otherwise would not be having surgery, has led surgeons to develop minimally invasive methods by which these devices can be introduced into the chest and made to create lesions on the heart.

4.2.1 The Maze Procedure

The Maze III procedure is a surgical procedure that cures atrial fibrillation by interrupting the electrical impulses that cause the abnormal heart rhythm. The surgery involves the placement of incisions (Figure 16) in both atria. When the incisions heal, scar tissue forms and prevents the abnormal electrical impulses from passing through the heart. The procedure works essentially by creating blocks that the electrical impulses cannot cross. It corrects all the major problems associated with atrial fibrillation: it stops the atrial arrhythmia, it restores normal rhythm between the atria and the ventricles, and it preserves the ability of the atria to contract on its own.

Figure 16 Maze III incisions

Surgery for the treatment of atrial fibrillation in isolation has not been widely adopted, however, because the procedure remains complex, time-consuming, and requires cardiopulmonary bypass. Recently a minimal access technique, derived from Maze, has been deployed: a catheter can be inserted through a small incision outside the heart. Instead of making surgical incisions, a radiofrequency device is used to create the lesions on the atria.

Recent reported series (16) have demonstrated the feasibility of treating patients undergoing cardiac surgery for other structural heart disease with limited, left-atrial ablation lesion sets using alternative energy sources (radiofrequency, microwave, high focused ultrasound, laser).

Experimental mapping studies have suggested the importance of a primary local generator, such as a single small re-entry circuit or ectopic focus. Collectively, these recent findings challenge the long held view that all AF results from multiple-circuit re-entry and support the rationale for developing surgical procedures for the treatment of AF that focus on the left atrium and pulmonary veins

Catheter-based ablation of the left atrium is technically demanding, time consuming, and associated with a number of complications (16). However, the alternative lesion patterns used by these procedures, such as individual curcumferential and segmental pulmonary vein isolation, may serve as an important guide for modification of partial Maze procedure lesion sets.

4.2.2 Circumferential pulmonary vein ablation (CPVA)

This procedure is performed in the electrophysiology lab by a specially trained cardiologist. During the procedure, catheters are passed through the femoral veins (in the groin) and into the heart. Two catheters are inserted into the right atrium and two into the left atrium. The left atrium is accessed through a trans-septal puncture, and intracardiac echocardiography is used to visualize the atrium during the procedure. One catheter in the left atrium is used to map or locate the abnormal impulses coming from the pulmonary veins. The other catheter is used to deliver radiofrequency energy to ablate, or create lesions, outside the pulmonary veins. The procedure is repeated for all four pulmonary veins. The lesions heal and form a circular scar around the pulmonary veins within four to eight weeks. The scar tissue blocks any impulses firing from within the pulmonary veins, thereby "disconnecting" the pathway of the abnormal rhythm and curing atrial fibrillation. Catheter ablation should be considered to maintain sinus rhythm in selected patients who failed to respond to antiarrhythmic drug therapy.

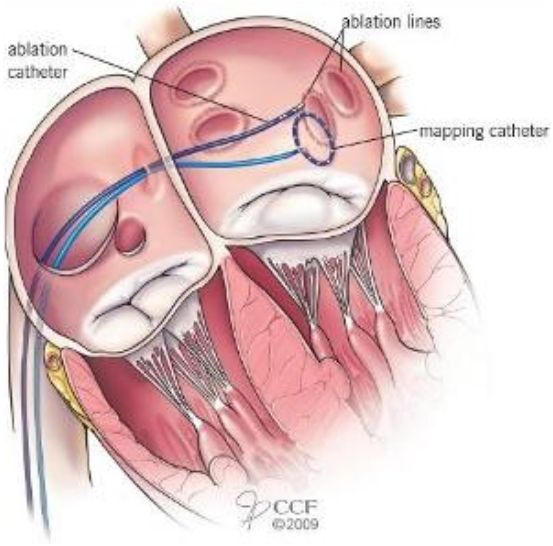


Figure 17 Pulmonary vein ablation

Ablating the openings of the pulmonary veins is technically much easier than making a series of linear ablations, and takes much less time (though it still takes up to 4 - 5 hours).

Problems remain, however. This new approach works best in patients who have "paroxysmal" atrial fibrillation - that is, relatively brief episodes. It works less well in patients with persistent atrial fibrillation. Also, while it is much quicker than the "linear" approach, it is still a lengthy procedure.

Complications(15) of catheter ablation include the adverse events associated with any cardiac catheterization procedure in addition to those specific to ablation of AF. Embolic stroke is among the most serious complications of catheter-based ablation procedures in patients with AF. Atrioesophageal fistula may be more likely to occur when extensive ablative lesions are applied to the posterior LA wall, increasing the risk of atrial perforation.

Further,(17), ablating in or near the pulmonary veins can cause partial obstruction of the veins, leading to pulmonary vein stenosis - a very serious and potentially life-threatening condition.

4.2.3 Radiofrequency ablation endoscopic procedures

Radiofrequency (16) energy uses an alternating current from 350 kHz to 1 MHz to heat tissue, resulting in thermal injury. There has been a significant experience accumulated using radiofrequency ablation to treat patients via catheter-based approaches. This success has led to the development of a number of radiofrequency energy probes that are useful for application to atrial tissue during cardiac surgery. These probes can be applied to either endocardial or epicardial (18) heart surfaces to create transmural linear lesions that block atrial conduction. Radiofrequency ablation by epicardial application holds promise for developing off-pump and minimally invasive procedures for AF.

The majority of radiofrequency ablation procedures to date have been performed with unipolar systems in which the patient is grounded by an indifferent skin electrode. In such systems, current flows from the radiofrequency probe to contacted atrial tissue, where thermal energy is released as a result of resistance to conduction.

Bipolar radiofrequency probes, show great promise to develop truly minimally invasive approaches to surgical procedures for AF.

The surgeon has the advantage of direct visualization of the left atrium and pulmonary veins, both on the endocardial side than on the epicardial and this allows to create lines of ablation on atrial side of the pulmonary veins in order to minimize the risk of complications such as stenosis of the same. By using bipolar catheters, in contrast to unipolar, the risk of esophageal injury is eliminated, since the ablation is carried out between the two jaws of the catheter and there is energy transmission, and then heat, to adjacent structures. For the same reasons, the risk of thromboembolism, resulting from excessive heating of the blood, that comes into contact with the catheter during the unipolar distribution of power, is virtually abolished by using bipolar instruments. In addition, the ability of the surgeon, to exclude the left atrial appendage, by suturing the same, virtually eliminates the risk of stroke, particularly in patients who fail to restore sinus rhythm.

4.2.4 Left atrial appendage (LAA) excision

This procedure has been proposed as a standalone treatment for chronic atrial fibrillation because it removes the most important thromboembolic source for patients with chronic AF.

The left atrial appendage is a small, ear-shaped tissue flap located in the left atrium. This tissue is a potential source of blood clots in patients with atrial fibrillation. Physicians and researchers at Cleveland Clinic [7] have developed a ligation device (Figure 18, right) for isolating and removing the left atrial appendage during heart surgery. Following its removal, the tissue is closed with a special stapling device.

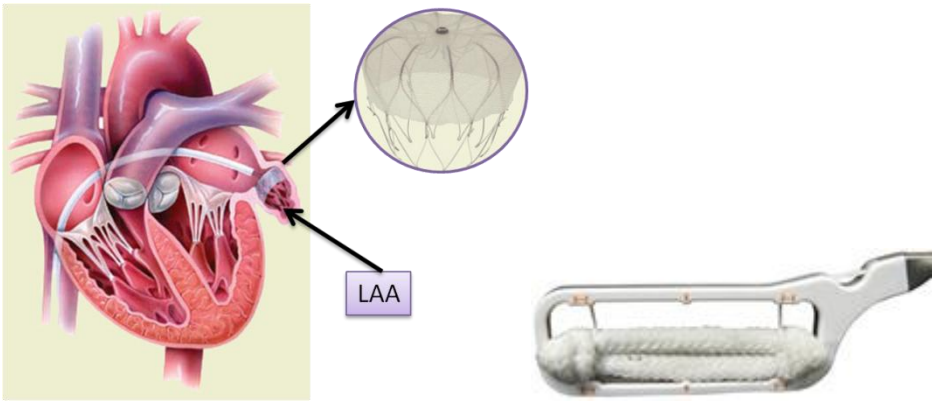


Figure 18 The Watchman® Left Atrial Appendage Filter System (left); The Gillinov-Cosgrove Clip*(right)

The Watchman Left Atrial Appendage Filter System (Figure 18, left) is under study as an alternative solution to removing the left atrial appendage. It consists of a rounded, self-expanding device that isolates the left atrial appendage and prevents clots from dislodging. It can be implanted through a catheter into the ostium of the left atrial appendage in combination with other interventional procedures such as pulmonary vein antrum isolation. Studies are under way to test the safety and effectiveness of this device.

4.2.5 Robotically Assisted AF surgery

(19) have recently developed a new technique (Niobe II, Stereotaxis, Stereotaxis, Inc., St. Louis, MO, USA) for remote ablation using a soft magnetic catheter. The operator is

[7] http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/atrial-fibrillation/

positioned in a separate control room at a distance from the X-ray beam and the patient's body. A 4mm magnetic catheter (NaviStar-RMT) is integrated with a newly developed electro-anatomical mapping system (CARTO-RMT mapping system). Additional magnets in the distal portion of the device can be deflected in any desired direction and steered by the magnetic navigation system.

Remote circumferential pulmonary vein ablation (CPVA) is usually performed with a target temperature of 65°C and a power limit of 50W. Magnetic field vectors for each navigation target are stored and, if necessary, they are reapplied at any time while the magnetic catheter is navigated automatically. Electrical disconnection even of challenging targets can be achieved remotely with relatively few ablation lesions.

At present, remote CPVA technology requires expensive equipment, and significant benefits over conventional catheters must be demonstrated to justify its purchase.

The Columbia team has developed a totally endoscopic, beating heart version of surgical atrial fibrillation ablation. In this minimally invasive, robotic operation, the ablation is performed through small puncture wounds in the chest and without stopping the heart or using the heart-lung machine.

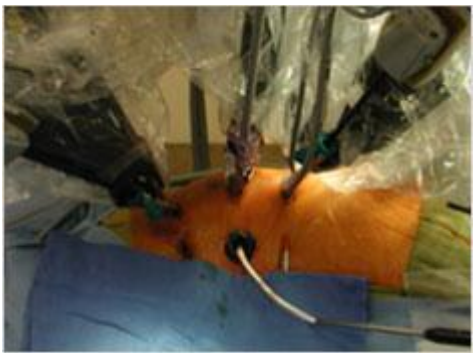


Figure 19 Totally endoscopic, beating heart atrial fibrillation ablation

4.3 Technological state of the art

4.3.1 Magnetically guided systems

A lot of groups have used magnetic force to control devices inside human body. It can be applied to control microforceps internally in assistance with EMR (20) and to control endoscopic cameras(21) and laparoscopic instruments inside the abdomen without additional scars (22).

Magnetic actuation can be used for minimally invasive control of medical devices such as robotic catheters. A device, that actuates pieces of high-permeability metal to redirect magnetic lines of flux, is used to regulate the attractive force exerted by a large controlling magnet on a smaller moving magnet(23). (24) demonstrated accurate catheter navigation using a magnetic guidance system (MGS) to create RF lesion on canine atria.

A new guidance system (25) for intramyocardial therapy utilizes magnetic fields and catheter-tip sensors to locate a position in space and reconstruct three-dimensional left ventricular electromechanical maps without using fluoroscopy.

4.3.2 Robots for atrial fibrillation

The Sensei™ Robotic Catheter System uses computed catheter technology to provide stable and predictable control of catheter movement. This innovative technology is designed to provide fine guide catheter control in three dimensions, to enhance the physician's ability to access hard to reach anatomy, repeat procedure steps, and maintain stability during interventional procedures. The safety and effectiveness of this system for use with cardiac ablation catheters in the treatment of cardiac arrhythmias, including atrial fibrillation, have not been established, but studies are under development.

Niobe robotof Sterotaxis has been used in several cases (26)(19) for the treatment of atrial fibrillation with good results.

The only drawback of these systems is the high cost so a device as Muneretto Beam catheter could be the right compromise between less invasiveness and reduction of costs.

4.3.2.1 Patent Search

A patent search for magnetically guided catheters for atrial fibrillation ablation has been conducted. The main results are two patents:

- Magnetized electrode tip (27)
- Magnetic catheter ablation device and method (28).

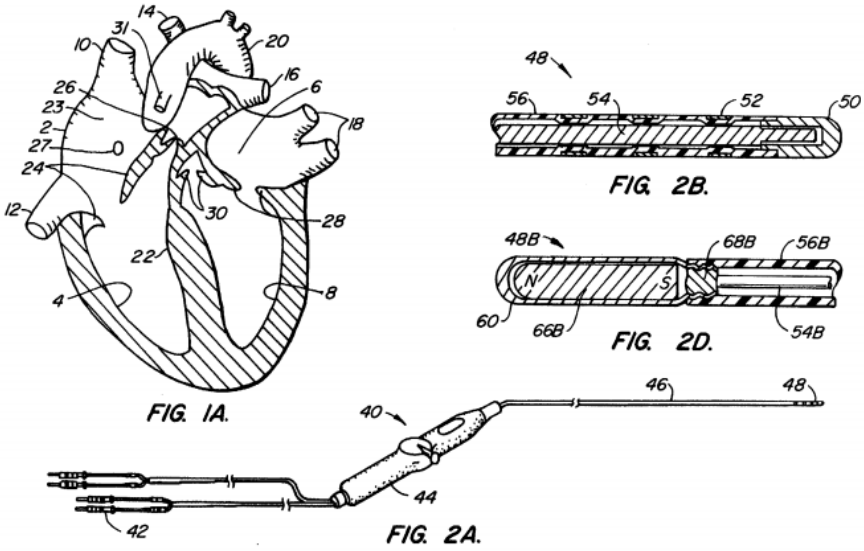


Figure 20 Magnetized electrode tip

The *first* patent resides in a method for ablating localized cardiac tissue by the use of two catheters with magnetized tips. Collectively, the catheters serve both mapping and ablating functions, permitting both a determination of the locus of an arrhythmia and the ablation of locus to correct the arrhythmia without the need to relocate the locus between these two functions. The magnetic attraction is across cardiac tissue and serves to secure the proper positioning of the ablation function.

While the mapping and ablation functions can be either on a single catheter or divided among the two catheters, the preferred arrangement is the latter, i.e., with one catheter serving as the "targeting catheter" which performs the mapping function, and the other serving as the "ablation catheter" which performs the ablation. In either arrangement, since ablation is done without removal of the targeting catheter, this invention involves a lesser use of such

procedures as x-ray exposure and fluoroscopy than conventional methods, as well as a reduction in the risks associated with these procedures. Regardless of the arrangement, both catheters have magnetized tips and are preferably positioned on opposing sides of cardiac tissue.

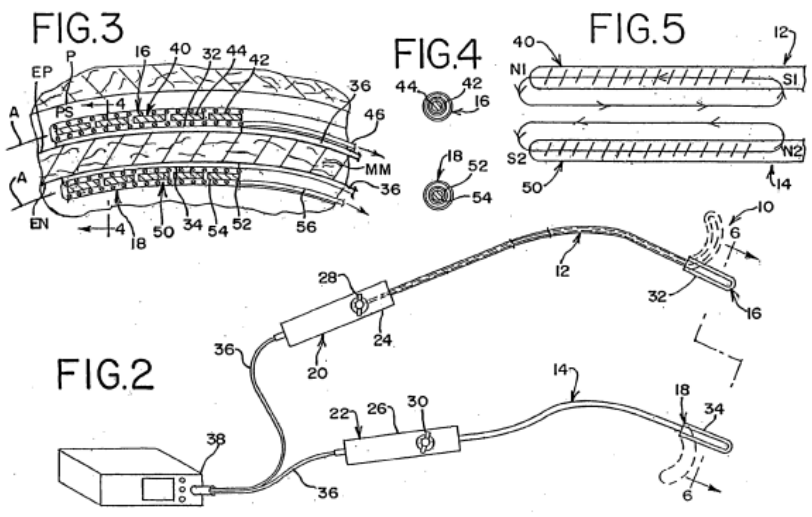


Figure 21 Magnetic catheter ablation device

In the *second* patent a method and apparatus for ablation of a layer of tissue is achieved by providing first and second bodies on opposed sides of the tissue. The first body includes a first ablation member and a source of magnetic force adjacent one side of the tissue. The second body includes a second ablation member and a magnetically attractive element responsive to the magnetic force adjacent the other side of the tissue. The magnetic attraction between the source and the attractive element is adapted to align the first and second bodies in opposed relationship on the opposed sides of the tissue. One of the first and second bodies may include at least one expendable member for controlling the magnetic attraction between the bodies.

4.4 Analysis and search of materials

4.4.1 Permanent magnets

Magnets function as transducers, transforming energy from one form to another, without any permanent loss of their own energy. General categories of permanent magnet functions are:

- Mechanical to mechanical - such as attraction and repulsion
- Mechanical to electrical - such as generators and microphones
- Electrical to mechanical - such as motors, loudspeakers, charged particle deflection
- Mechanical to heat - such as eddy current and hysteresis torque devices
- Special effects - such as magneto resistance, Hall effect devices, and magnetic resonance.

There are four classes of modern commercialized magnets, each based on their material composition. Within each class is a family of grades with their own magnetic properties. These general classes are:

- Neodymium Iron Boron

- Samarium Cobalt
- Ceramic
- Alnico.

NdFeB and SmCo are collectively known as Rare Earth magnets because they are both composed of materials from the Rare Earth group of elements. Neodymium Iron Boron (general composition $Nd_2Fe_{14}B$, often abbreviated to NdFeB) is the most recent commercial addition to the family of modern magnet materials. At room temperatures, NdFeB magnets exhibit the highest properties of all magnet materials (Table 2). Ceramic, also known as Ferrite, magnets (general composition $BaFe_2O_3$ or $SrFe_2O_3$) have been commercialized since the 1950s and continue to be extensively used today due to their low cost. A special form of Ceramic magnet is "Flexible" material, made by bonding Ceramic powder in a flexible binder. Alnico magnets (general composition Al-Ni-Co) were commercialized in the 1930s and are still extensively used today.

Characteristic	Ceramic	alnico	Bonded ND-Fe-B	Sm-Co	Nd-Fe-B
Highest energy product Bhmax(kJm-3)	32	59	79	254	382
Maximum operating temperature (°C)	300	550	150	300	150
Resistance to demagnetization	Moderate	Low	High	Very high	High
Corrosion resistance (uncoated)	Excellent	Excellent	Good	God	Poor
Mechanical toughness	Moderate	Tough	Moderate	Very brittle	Brittle
Relative cost	Very low	Moderate	High	Very high	High

Table 2 Comparison of key characteristics of commercially available magnetic materials

Nd-Fe-B is an obvious example of a ferromagnetic material. In magnetic materials, a magnetic field is produced because of the movement of electrons within the material, which produces the field around the material and a magnetization effect within it. An electrical charge moving through a conductor will also produce a magnetic field; therefore the magnetic field strength H can be measured in A.

When a material experiences a magnetic field, the individual atomic moments contribute to the overall response of that material to the field. This response is called the magnetic induction B and is an inherent property of the material; it is also known as the flux density and is measured in Tesla (T). The relationship between the applied field and the response of the material is known as the permeability of the material . In free space:

$$\mu = B/H$$

and the permeability of free space is $4\pi 10^{-7}$ $WbA^{-1}m^{-1}$. In any other medium, however, the permeability may not be a linear function of H; although B(H) may vary with the applied magnetic field, particularly in ferromagnetic materials.

4.4.2 The B-H Curve

The basis of magnet design is the B-H curve, or hysteresis loop (Figure 22), which characterizes each magnet material. This curve describes the cycling of a magnet in a closed circuit as it is brought to saturation, demagnetized, saturated in the opposite direction, and then demagnetized again under the influence of an external magnetic field.

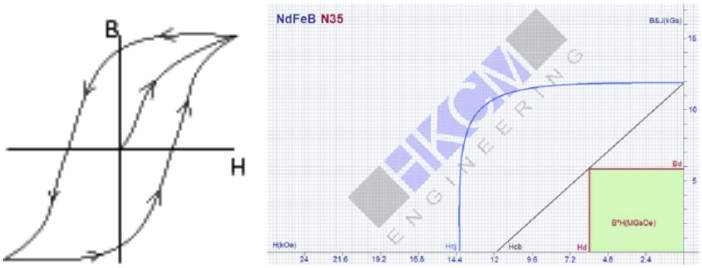


Figure 22 Hysteresis loop

The second quadrant of the B-H curve, commonly referred to as the "Demagnetization Curve", describes the conditions under which permanent magnets are used in practice. A permanent magnet will have a unique, static operating point if air-gap dimensions are fixed and if any adjacent fields are held constant. Otherwise, the operating point will move about the demagnetization curve, the manner of which must be accounted for in the design of the device.

The three most important characteristics of the B-H curve are the points at which it intersects the B and H axes (at B_r - the residual induction - and H_c - the coercive force - respectively), and the point at which the product of B and H are at a maximum (BH_{max} - the maximum energy product). B_r represents the maximum flux the magnet is able to produce under closed circuit conditions. In actual useful operation permanent magnets can only approach this point. H_c represents the point at which the magnet becomes demagnetized under the influence of an externally applied magnetic field. BH_{max} represents the point at which the product of B and H, and the energy density of the magnetic field into the air gap surrounding the magnet, is at a maximum. The higher this product, the smaller need be the volume of the magnet. Designs should also account for the variation of the B-H curve with temperature.

4.5 Design History

The ideal non pharmacological treatment for atrial fibrillation should:

- Ensure an appropriate pattern of lesions;
- Be performed in a minimally invasive manner, and therefore without cardiopulmonary bypass;
- Minimize the risk of damage to structures adjacent to the heart;
- Avoid as much as possible exposure to X-rays;
- Ensure transmural lesions;
- Allow for resection or exclusion, however, of left appendage.

The idea of a new device is property of Prof. Muneretto, who decided to develop a new magnetic guidance system for a device for the ablation of atrial fibrillation. The surgical approach can be defined linear magnetically guided endoscopic ablation.

4.5.1 Muneretto approach

The design started from the study of two devices of Estech[8] company: the COBRA® Adhere XL and the COBRA® Bipolar Surgical System.

The COBRA® Adhere XL (Adhere) (Figure 23) is a device which allows the surgeon to easily create a complete epicardial box lesion using standard open surgical technique or through minimally invasive approaches.

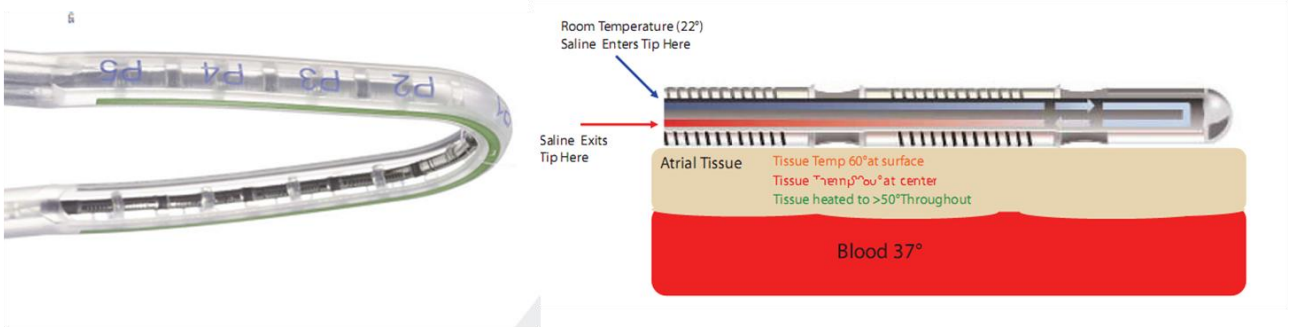


Figure 23 COBRA Adhere XL: probe(left), adhering mechanism (right)

It is comprised of two components, the Cobra Adhere XL Surgical Probe with integrated Suction Stabilizer and the Cobra Adhere XL Introducer. The stabilizer is designed to engage tissue under negative pressure such that constant contact between probe and tissue to be coagulated is maintained throughout the procedure. The Introducer is designed to facilitate introduction and advancement of the Probe/Stabilizer to the desired anatomical position.

The surgical Probe has a flexible distal section. This probe is designed to conform to the specific anatomy of the tissue area to be coagulated. The distal section of the probe can have from two to fourteen 15 mm electrodes spaced 2mm apart along the body. Any linear combination of coagulating electrodes may be used.

The COBRA® Bipolar Surgical System (Bipolar) is intended for the coagulation of soft tissue using radiofrequency energy during general surgery, creating rapid reproducible transmural lesions. The System may also be used to coagulate blood and soft tissue to produce hemostasis. It is comprised of two components (Figure 24), the COBRA Bipolar Inserts and the COBRA Bipolar Clamp. The Clamp is designed to fit over the Inserts and engage tissue such that constant contact between Inserts and tissue to be coagulated is maintained throughout the procedure. The Inserts have a flexible distal section. They are designed to conform to the specific anatomy of the tissue area to be coagulated, according to the chosen clamp. The distal section of the Inserts has two RF electrodes spaced 2mm apart and one return electrode. The Inserts fit into the groove of each clamp jaw.

[8] www.estech.com

Figure 24 Clamps (left), Bipolar inserts (right)

The initial specifications were to modify the previous Estech devices enabling a magnetic guidance of the same. The new device will have features coming from both the unipolar and bipolar instruments.

Linear or focal radiofrequency(29) ablation with the magnetic catheter is not compromised by the magnetic field. The critical (19) purpose of navigation and ablation is a stable contact of the catheter tip with the endocardium at the time of RF applications. Hence a magnetic coupling between an internal and an external catheter can be a good solution for a good RF ablation.

4.5.2 Analysis of potential configurations

In a first configuration analyzed, (config. A, Figure 25), it has been decided to use the two inserts of the Bipolar device and to obtain the alignment and the guidance of the same with some small magnets on both inserts. The idea is to introduce one insert, thanks to endoscopic guidance, on the external wall of the hearth, and the other insert internally by means of a trocar of 8 Fr (2.7mm). Once inserted the catheter would be guided by the external one thanks to the magnetic coupling.

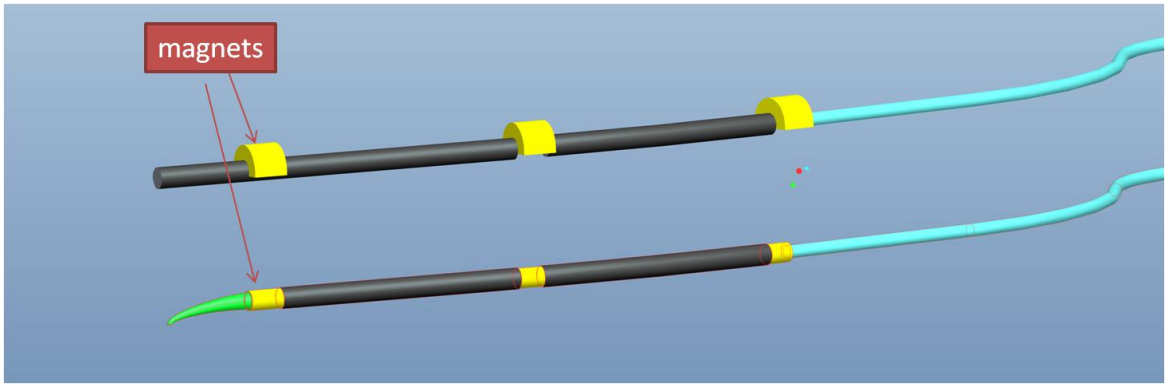


Figure 25 Configuration A

The main issue has been to understand the type of magnets to use, their position, magnetization (Annex IV) and material (4.4). A series of shapes and dimensions have been designed. Spherical, cylindrical, U-shapes (Figure 26) mainly due to the configuration of the catheter for atrial fibrillation.

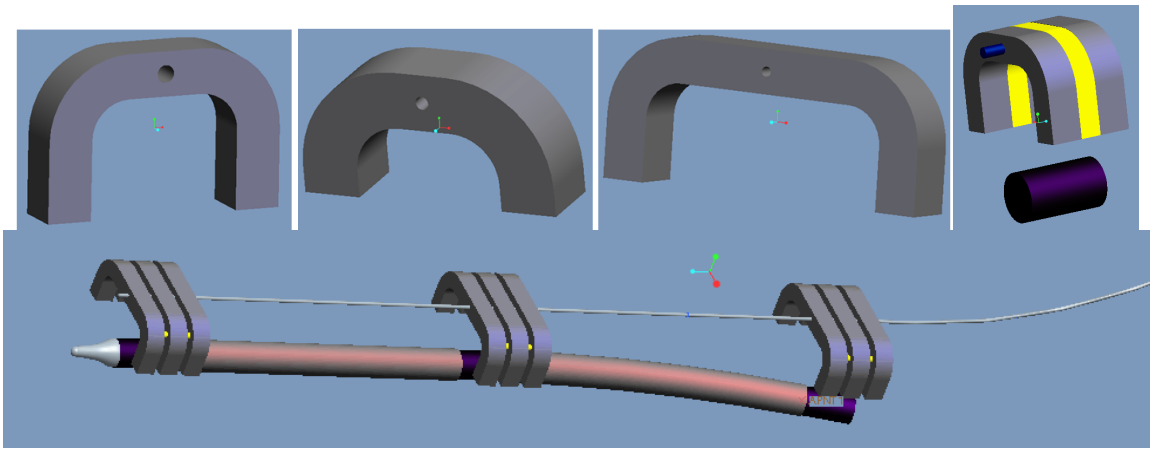


Figure 26 U- shapes

Cobra monopole silicone cover could be a good solution for the envelop of the external catheter. In Figure 27 a possible configuration for the magnets inside the cover is shown (config. B).

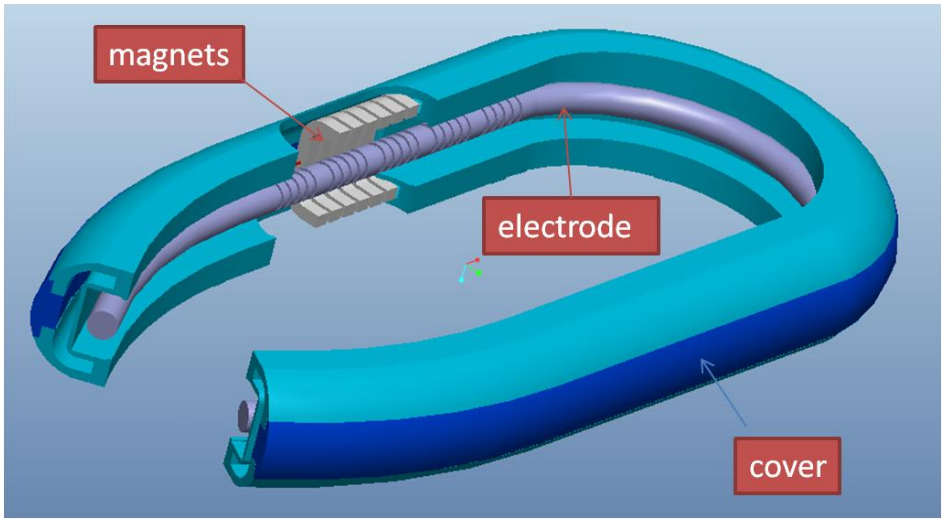


Figure 27 Cobra Monopolar cover modified

Since magnets of such shapes are difficult to reach on the market (non customized), the design has moved to a simpler form of magnets (cylinders diametrically magnetized, see also section 4.5.5).

Therefore a third configuration (config. C) has been evaluated. The external catheter would be inserted pericardially, the internal one (Ø2.7mm) intracardially by means of a 8 french trocar. Both catheters are sliding.

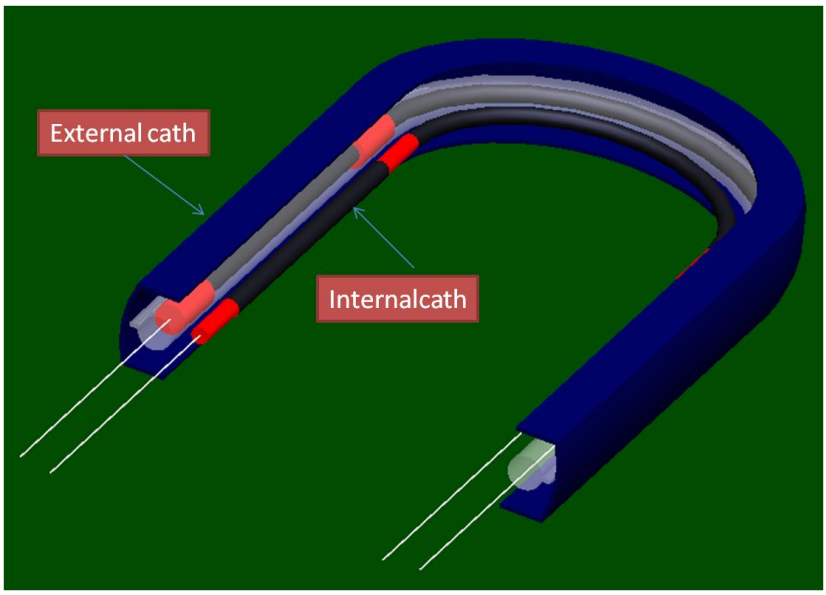


Figure 28 Configuration C

In order to guarantee the sliding of the external catheter into its silicone cover a system of inserts has been designed (Figure 29). Both magnets and platinum electrodes are embedded in a dacron cover for ensuring the thermal contact between electrodes and biological tissues.

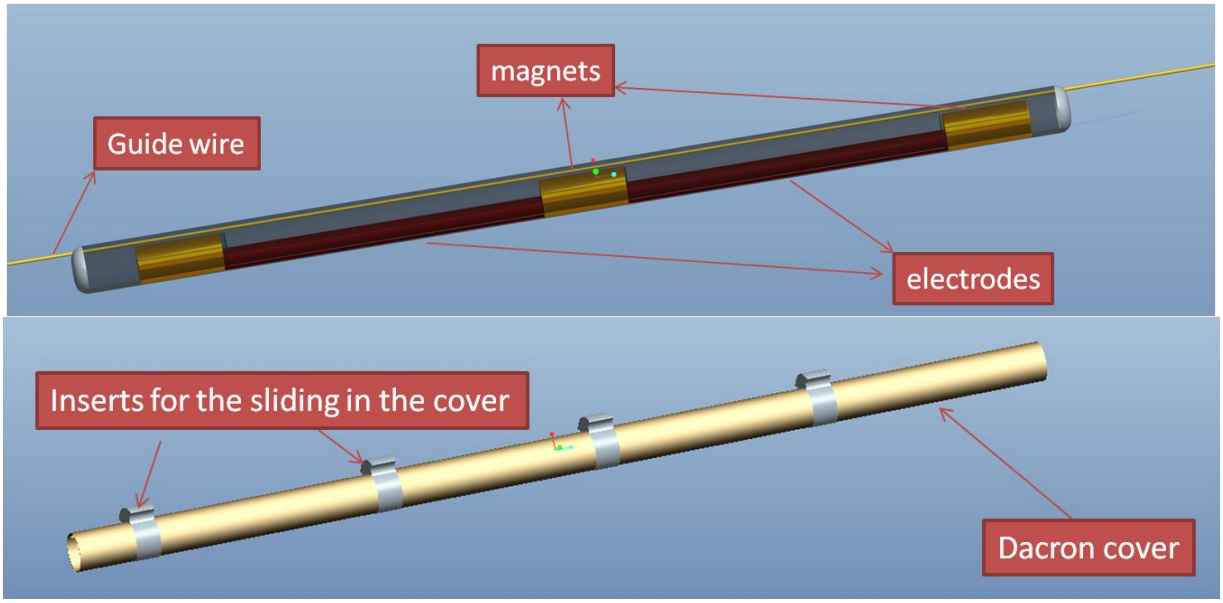


Figure 29 Config. C: External catheter(up), Dacron cover (down)

The only drawback of this configuration is the high curvature which the internal catheter is subjected. It could be reason of decoupling inside the atrium, because the curvature inside the organ are very small. Professor Muneretto provided some dimensional indications about the curvature , by means of two test benches (Figure 30).

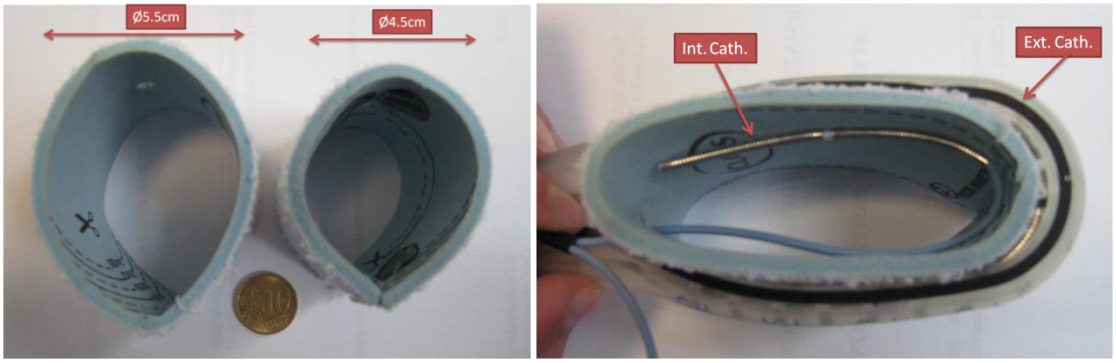


Figure 30 Test bench for catheter curvature

Clinical efficacy (30) has driven the use of larger electrodes (7F, length > or =4 mm) for radiofrequency ablation, which reduces electrogram resolution and causes variability in tissue contact depending on electrode orientation. With active cooling, ablation electrode size may be reduced. The Estech Cobra device has an internal circuit for cooling. Thus a length of 1 cm for each electrode would be enough for a good action.

Therefore a last configuration with smaller electrodes and magnets has been developed (config. D). In this configuration the catheters are fixed. The internal catheter is inserted into the atrium by means of a plastic sheath and it is bended in two parts. When the catheter is inserted, the front magnet couple with the frontal one of the external catheter and then the other two magnets are released from the oversheath.

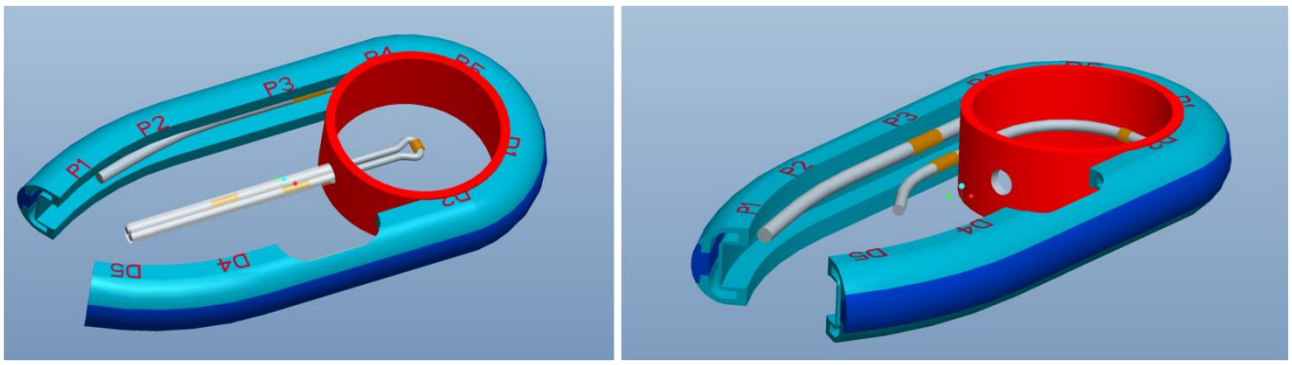


Figure 31 Final configuration (D)

The best magnetic coupling is obtained by configuration1 (October tests): magnets in neodymium with dimensions of 2 and 3.5 mm in diameter and length 10 mm. The length, both of magnets and electrodes, has been reduced due to the change in the specification for the curvature that Prof. Muneretto provided.

4.5.3 Finite Element Analysis

Basic problems of permanent magnet design revolve around estimating the distribution of magnetic flux in a magnetic circuit, which may include permanent magnets, air gaps, high permeability conduction elements, and electrical currents. Exact solutions of magnetic fields require complex analysis of many factors, although approximate solutions are possible based on certain simplifying assumptions. Obtaining an optimum magnet design often involves experience and tradeoffs.

Finite Element Analysis (FEA) modelling programs are used to analyze magnetic problems in order to arrive at more exact solutions, which can then be tested and fine tuned against a prototype of the magnet structure. Using FEA models flux densities, torques, and forces may

be calculated. Results can be output in various forms, including plots of vector magnetic potentials, flux density maps, and flux path plots.

The software used in this work in Comsol Multiphysics 3.5. Several attempts has been made in order to establish the right parameters for our purposes. First of all the definition of the problem: at first it has been decided to study only the interaction between the magnets, without the thermal and electrical effect of the ablative electrodes.

In *magnetostatic* problems, where *no currents* are present, the problem can be solved using a scalar magnetic potential. In a current free region, where

$$\nabla H \times 0 = 0$$

Equation 1

it is possible to define the scalar magnetic potential, Vm, from the relation

$$\boldsymbol{H = -\nabla Vm}$$

Equation 2

This is analogous to the definition of the electric potential for static electric fields. Using the constitutive relation between the magnetic flux density and magnetic field

$$B = \mu_0(H + M)$$

Equation 3

together with the equation:

$$\nabla B = 0$$

Equation 4

It is possible to derive an equation for Vm:

$-\nabla(\mu_0 \nabla Vm - \mu_0 M_0)$=0

Equation 5

The force on the magnet is calculated by integrating the surface stress tensor over all boundaries of the magnets. The expression for the stress tensor is,

$$\boldsymbol{n}_1 T_2 = -\frac{1\,(\boldsymbol{H}\cdot\boldsymbol{B})\boldsymbol{n}_1}{2} + (\boldsymbol{n}_1 \cdot \boldsymbol{H})B^T$$

Equation 6

where n1 is the boundary normal pointing out from the magnet and T2 the stress tensor of air. The integration gives the actual force on the magnet.

4.5.3.1 Modeling Using the Graphical User Interface

When COMSOL Multiphysics starts, the first window that appears is the Model Navigator (Figure 32) in which the main application is chosen: the Space dimension (3D and 2D) and the Application Modes (Magnetostatics, No Currents) are selected.

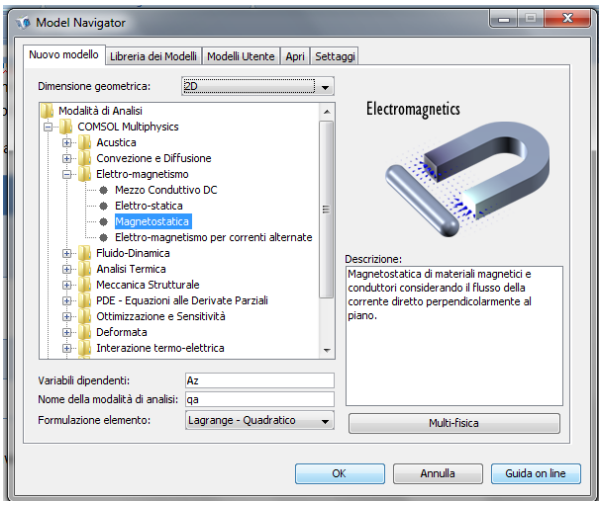


Figure 32 Comsol Model Navigator interface

Then the constants are set (Table 3) and the geometry is drawn or imported from another Cad Software (Pro-engineer 5.0).

NAME	EXPRESSION	DESCRIPTION
mur	$\mu_{tissue} \sim \mu_{air} = 1$	Relative permeability of air
Br(N/(mm*A)	0.0017	Residual magnetic flux

Table 3 example of the main constants used

4.5.3.2 PHYSICS SETTINGS - Boundary Conditions

Magnetic Insulation

Along the boundaries far away from the magnet, the magnetic field should be tangential to the boundary as the flow lines should form closed loops around the magnet. The natural boundary condition is

$$\boldsymbol{n} \cdot (\mu_0 \boldsymbol{\nabla} \boldsymbol{V_m} - \mu_0 \boldsymbol{M_0}) = \boldsymbol{n} \cdot \boldsymbol{B} = \boldsymbol{0}$$

Equation 7

Thus the magnetic field is made tangential to the boundary by a Neumann condition on the potential. The magnetic insulation boundary condition sets the normal component of the magnetic flux density to zero. This boundary condition is useful at boundaries confining a surrounding region of air.

Magnetic Potential

The magnetic potential boundary condition

$$V_m = V_{mo}$$

Equation 8

allows specifying the potential at the boundary.

Zero Potential

Along the symmetry boundary below the magnet, the magnetic field should also be tangential, and therefore the same Neumann condition can be applied there. The zero potential boundary condition

$$V_m = 0$$

Equation 9

sets the magnetic potential to zero at the boundary.

Continuity

The continuity boundary condition

$$\boldsymbol{n} \cdot (\boldsymbol{B_1} - \boldsymbol{B_2}) = \mathbf{0}$$

Equation 10

is the natural boundary condition ensuring continuity of the normal component of the magnetic flux density.

POINT CONDITION

To obtain a unique solution, the potential at (at least) one point must be provided. If the magnetic insulation boundary condition is used everywhere, the potential has to be fixed using a point condition (i.e. Equation 8 where V_{m0} is a given constant).

Hence from the Physics menu, in Boundary settings of the models studied, magnetic insulation is set on the air around the magnets and the continuity on the magnets.

4.5.3.3 PHYSICS SETTINGS - Subdomain Settings

For the various configurations analyzed the relative permeability for the magnet, the magnetization vector, and constitutive relations and force variables are set in this module.

	Constitutive relation
air	$B=\mu_o\mu_r H$
magnets	$B=\mu_o\mu_r H+B_r$

Table 4 Constitutive equations used

4.5.3.4 MESH GENERATION

To resolve the field a mesh generation is necessary. Mainly Free Mesh has been used, but in some cases, when the size of the model is too big, the mesh has been mapped. In the region of interest (i.e. area between 2 magnets) the mesh size was smaller, while in other areas it had bigger elements (thus coarse calculation).

4.5.3.5 Computing the SOLUTION and POSTPROCESSING

In the Solver Parameters dialog box, the Adaptive mesh refinement check box underneath the Solver list is sometimes selected. When modeling, it is important to select a mesh that minimizes the errors in the quantities of interest. However, it is not easy to minimize the error in a desired quantity by manually specifying a mesh. In many applications, the algorithm must resolve the solution in great detail only on small portions of the domain. Adaptive mesh generation identifies the regions that require a high resolution and produces an appropriate mesh.

In the Plot type area it is possible to choose the type of visualization and the quantities for the solution (Slice, Arrow, Contour, Surface..).

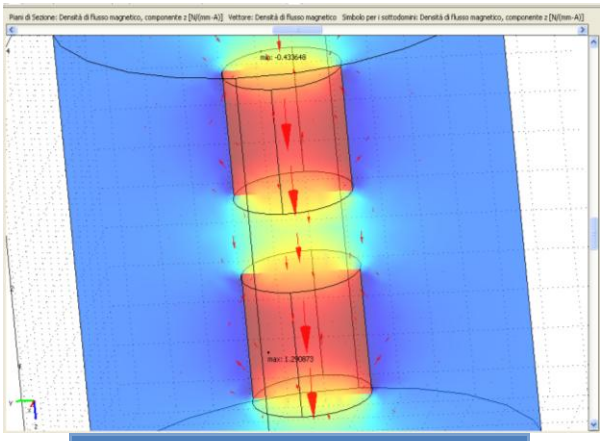
4.5.3.6 Force Calculation

To calculate the force on a magnet, the surface stress tensor has been used (see Equation 6).

The electromagnetic force variable is defined on one magnet in the Sub domain Settings dialog box; it generates the variables forcex_emnc, forcey_emnc, and forcez_emnc, which are the forces on the magnet in the x, y, and z directions, respectively.

4.5.4 Model validation

The simulation activities, especially with a program of electromagnetic simulations, must start with a validation of the mathematical model. Therefore the results of the first simulations have been compared with the datasheets of the first available magnets. In Annex V the complete comparative data are reported. From the data obtained it results that the FEA model works enough good to understand the magnitude of the forces interested by the magnetic coupling.



Δx(mm)	0.11	0.3	1	2
F(N)	4.52	3.53	1.53	0.46
Fdatasheet	3.34	2.44	1.11	0.53

Table 5 d22-d22 (axially magnetized) interaction

These simulations are then also compared with the experimental data of the interaction forces between the magnets available. In Table 6 there is a list of the features of the first magnet used for the validation of the model. Magnetic force at a distance of s for the magnets used is:

$$Fr = Fh / (1 + s\text{^}3)$$

Equation 11

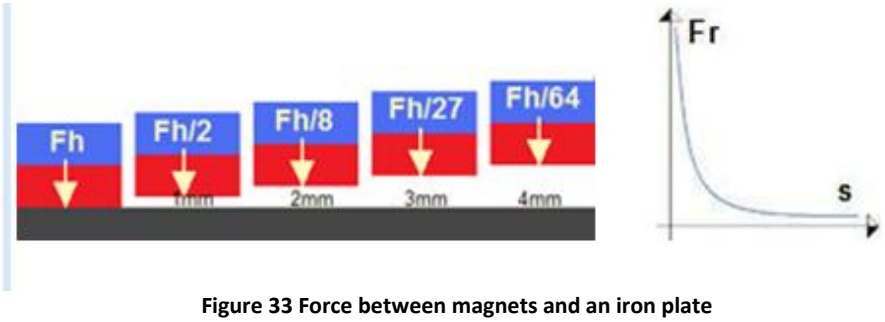


Figure 33 Force between magnets and an iron plate

The holding force F_h decreases with the distance s exponentially.

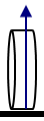
	Ø (mm)	H (mm)	M_{dir}	Grade	Br_{max}(T)
Sphere s3	4.76	-		N42	1.32
Cylinder D22	3.175	3.175		N52	1.48
Cylinder D24	3.175	6.35		N50	1.45
Disk S09	9	2.50		N52	1.45

Table 6 First magnets used: features

It is particularly necessary using a program like Comsol, extremely complicated, with lots of boundary conditions to be set correctly to understand if the used model is trustable. In this case, the final comparison was made between the SW model and mechanical tests carried out with a load cell (that determines the strength of interaction between the two magnets in various configurations choices).

Figure 34 Load cell and test bench

As of the comparisons of forces obtained from simulations and first tests, it is possible to understand that the model, excluding some exceptions (see red value in Table 60), is enough trustworthy for the purpose, even if, in some cases, a refinement in term of mesh construction is necessary.

Therefore a new comparison has been made between the model of a cylindrical magnet and a iron plate has been done and the results from the FEA compared with forces obtained from the datasheets. A good correspondence has been found (see Annex V and Table 7).

Δx(mm)	**0**	**1**
F(N)	1.3	0.59
Fdatasheet	1.26	0.63
ΔF	0.04	0.04

Table 7

4.5.5 Main FEA results

As a result of the first session of simulations and tests one of the configuration chosen is a d22-d22 diametrically magnetized, because these magnets allowed more stability without damaging tissues (the spheres and the disc perforated the tissue). This coupling could be good

for the configuration A (section 4.5.2) but the local forces are a little bit low comparing them with the results of the first tests (section 4.6).

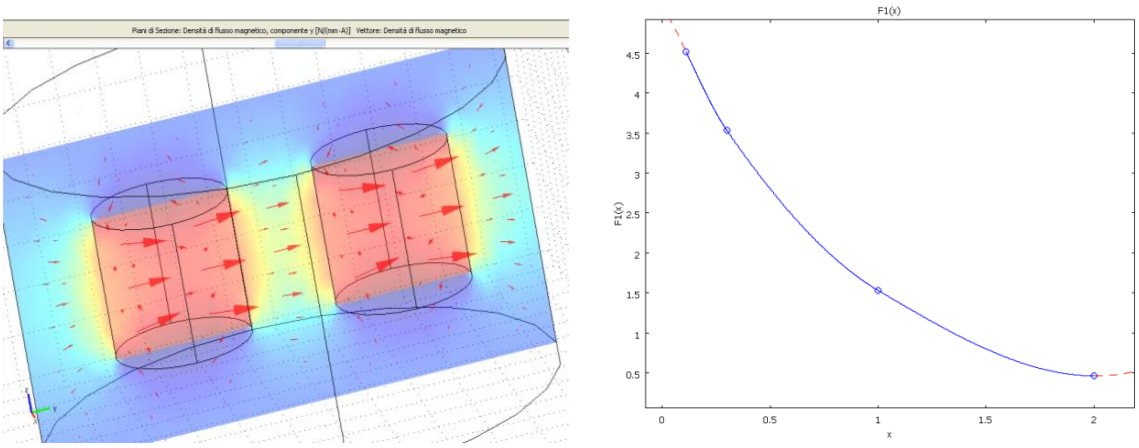


Figure 35 d22-d22 Interaction diagram; on the y axis the force in N and on the x axis the distance between magnets

Δx (mm)	0.11	0.41	1	2
F (N)	3.62	2.5	1.35	0.52

Table 8 interaction forces

These results helped in the purchase of new diametrically magnetized magnets (Validation tests with hkcm magnets)

Another useful use of the simulation has been in the evaluation of forces deriving from drilling of magnets for the embedding into the final catheter (to allow the passage of the platinum electrodes). In Figure 36, two Magnets (3.5x10mm) has been drilled to make holes of Ø2mm coaxially (2) and eccentric (3). The calculation has been done with Magnetic insulation condition on all surfaces, Vm=o in one extreme point and a standard mesh. Air volume is a cube of 40x40x40mm.

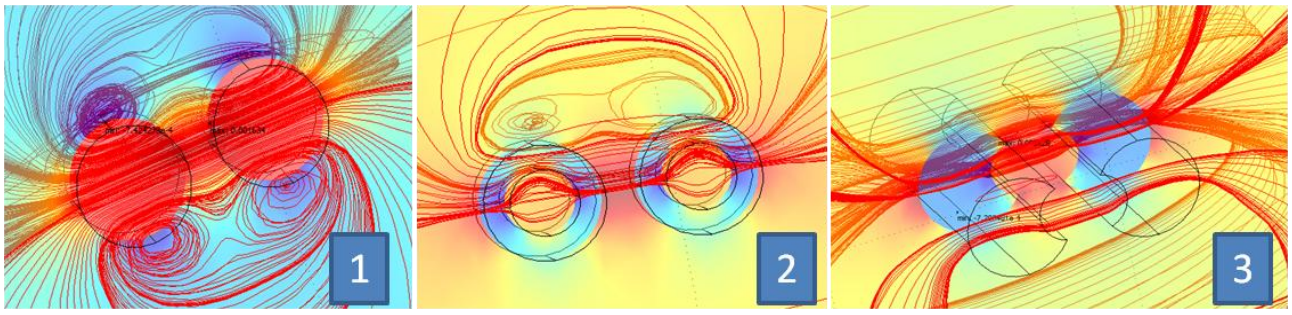


Figure 36 Comparison between cylindrical magnets and drilled ones

Δx (mm)	**F1(N)**	**F2(N)**	**F3(N**
1	7.61	3.49	2.02

Table 9 Forces comparison

From this first simulation it has been decided to reduce the holes (Table 10) and to allow only electrical wires to pass through the magnets.

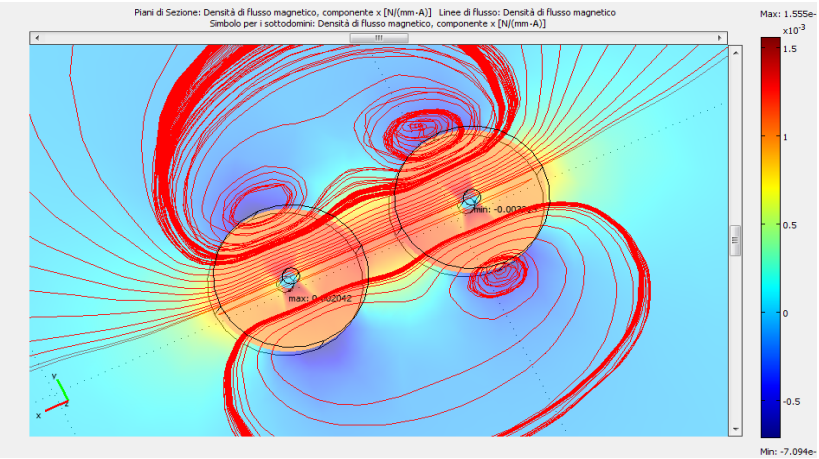


Figure 37 Magnets 3.5x10mm, smaller holes

Ø holes (mm)	1	0.4
F (N)	6.34	7.5
Δx (mm)	1	1
Volume air	40x40x40	40x40x40

Table 10 Force with smaller holes

Finally simulation of the magnets chosen from the last test (config. 1, October 2010) have been done in order to understand the acting forces on magnets and drilled one (Ø 0.4mm).

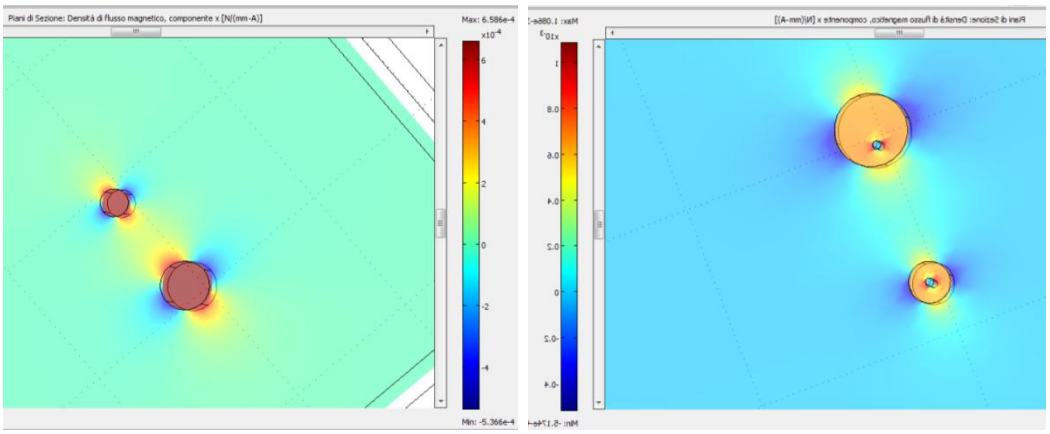


Figure 38 Magnets with diameters:2 and 3.5 mm

No holes	F on z3.5 (N)	0.096	0.18	0.27	0.70	1.58	3.9
	F on z2 (N)	-0.16	-0.26	-0.39	-0.76	-1.56	-4.10
Distance	Δx (mm)	5	4	3	2	1	0
With holes	F on z3.5 (N)	0.0666	0.19	0.38	0.68	1.50	3.92
	F on z2 (N)	-0.16	-0.24	-0.37	-0.7	-1.54	-3.92

Table 11 Results of FEA on the final configuration (with and without holes)

As from Table 11 holes of such diameter don't influence magnetic force in a wide way. Therefore a decision about the design can be taken and in the last configuration D electrical wires can be passed through the magnets without reducing the force value.

4.6 Prototypes and Tests

Several tests have been conducted:

1. To validate the FEA model (1 session) (see 4.5.4)
2. To understand the forces required for the magnetic coupling (4 sessions).

A preliminary in vitro test with the magnets in Table 6 on a pig atrium have been made on the 24/02/2010 in order to have a preliminary idea about the feasibility of Prof. Muneretto design.

As in Figure 39 it has been shown that a certain coupling and sliding with magnets could be achieved. Therefore a consequent work could be done.

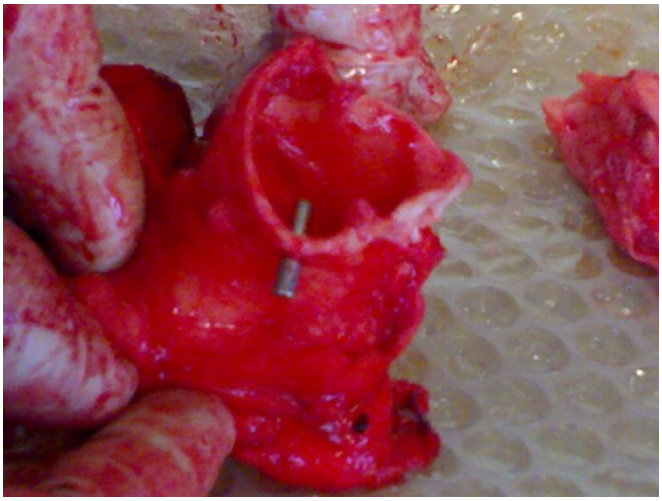


Figure 39 Test session 24/02/10

The first session of in vitro trials with a pig hearth has been conducted in Pontedera (14/03/2010) with the assistance of Prof. Muneretto and under the supervision of Estech R&D personnel. Some home - made prototypes with magnets have been tested (see Figure 40) in order to understand the level of forces (Table 12) needed to do the task (magnetic guidance of the internal catheter by means of the external one).

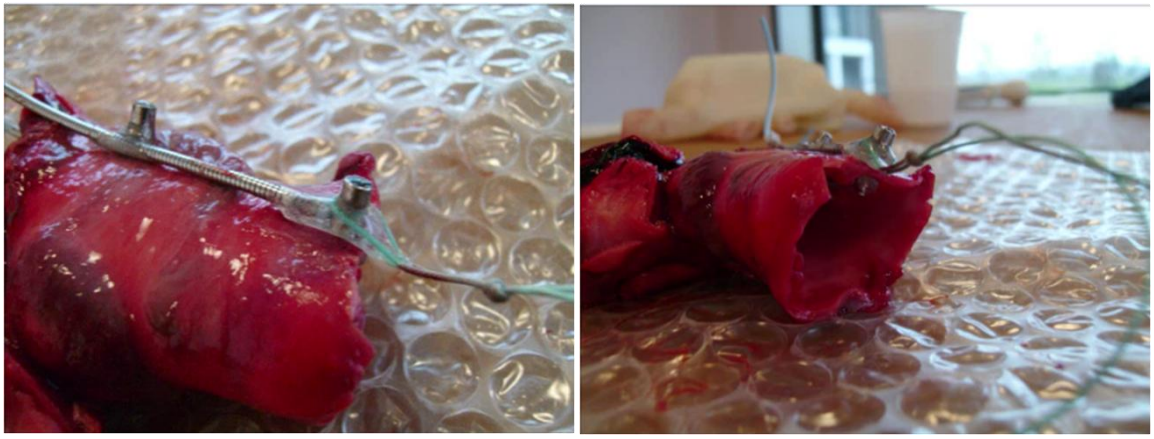


Figure 40 First prototypes

	Ft(N)	Fn(N)
Case A: d22-d24 Cylinder Ø 3- cylinder Ø 6	3	1.1
Case B:s09-d24 Disc Ø 9mm-Cylinder Ø 6	2.85	3.89

Table 12 Test session 14/03/2010

As predicted and from the results of these first two sessions, balance between friction and magnetic force is a key issue in the design of the Muneretto Beam Device.

A new series of prototypes have been manufactured using new magnets (Tests results-September 2010) with more appropriate dimensions and magnetization direction.

The magnets have been embedded in many types of moulding silicone. In Table 13 their main features are shown.

Name	Type of application	Viscosity (MPa)	Hardness Shore A	Elongation at Break
GLS 50 (Prochima)	Casting	30000	18-20	400%
CRISTAL RUBBER (Prochima)	Casting	28000	33	320%
RTV 4411 (Silbione)	Casting	7500	11	800%

Table 13 Silicones

As a results a series of new prototypes have been manufactured and tested with chicken tissue (5 mm thick). In Annex VI the main results are reported.

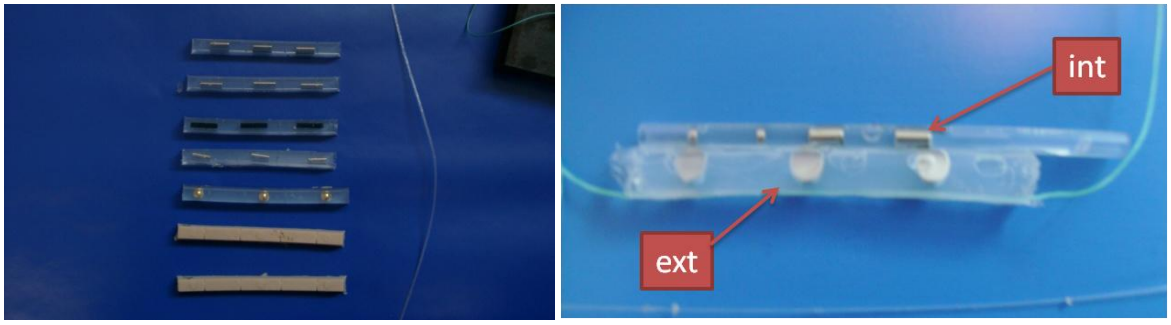


Figure 41 Silicone embedded prototypes

The intermediate results from these tests are:

- Silicone is not good for sliding
- Frosted PVC can be the solution for the catheter
- The handling, layout and coupling of the magnets during manufacturing are key issues.

Therefore a new series of prototypes have been manufactured and tests with chicken tissue (5mm thick) are made (see October 2010).

The best results are achieved with configuration 1 (see Figure 42), with magnets Z03.5x10GD-N35 for the external catheter and Z02x10ND-N35 for the internal one.

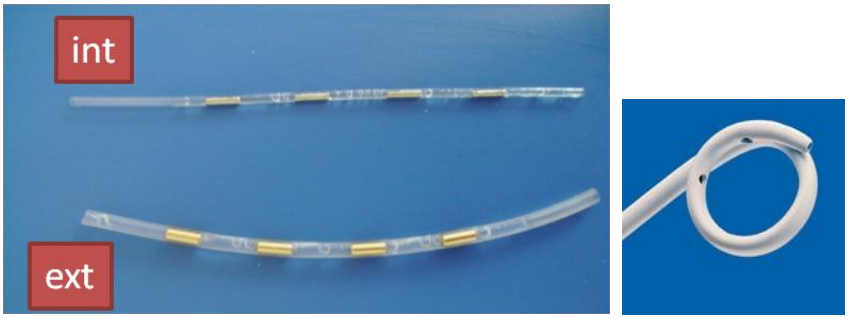


Figure 42 Configuration 1, October 2010 tests (left); Pig-tail (right)

Therefore the catheters with materials like pellethane and frosted PVC offer a good sliding and magnets of config. 1 are chosen for the integration in the device. Another important issue is the shape of the tip (a round shape is suggested for improving the sliding, see pig-tail in Figure 42) and the flexibility of catheters has to be increased:

- Reducing tube thickness
- With a modular catheter.

The magnets will be integrated on the device like a necklace. This will enhance flexibility and the magnetic coupling will not be invalidated by the stiffness of the wall. Moreover during the insertion of the internal catheter inside the atrium (4.5.2), it would be possible to reduce the diameter of the oversheath, thus reducing the scar on the wall of the heart tissue.

5 Video drain

5.1 Analysis of the medical background: Anatomy and Complications of abdominal surgical wounds

5.1.1 Anatomical district

The abdominal cavity is the largest hollow space of the body. Its upper boundary is the diaphragm, a sheet of muscle and connective tissue that separates it from the chest cavity; its lower boundary is the upper plane of the pelvic cavity. It is vertically enclosed by the vertebral column and the abdominal and other muscles. The abdominal cavity (Figure 43) contains the greater part of the digestive tract, the liver and the pancreas, the spleen, the kidneys, and the adrenal glands located above the kidneys.

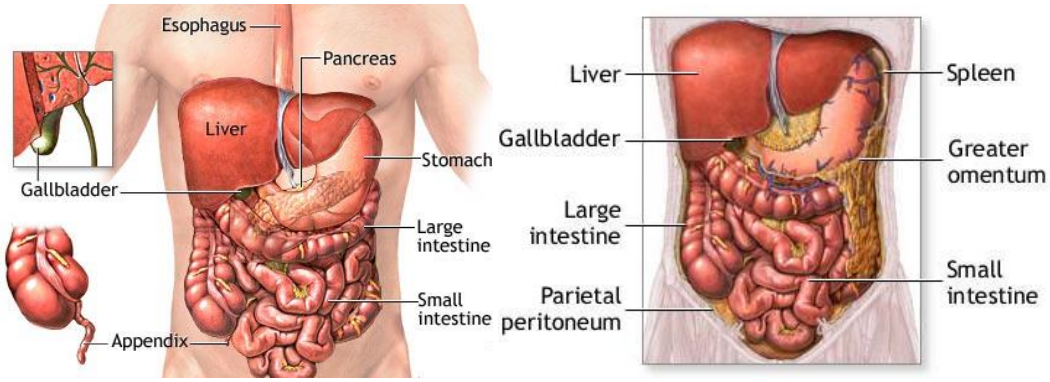


Figure 43 Abdominal Organs

The abdominal cavity is lined by the peritoneum, a membrane that covers not only the inside wall of the cavity (parietal peritoneum) but also every organ or structure contained in it (visceral peritoneum). The space between the visceral and parietal peritoneum, the peritoneal cavity, normally contains a small amount of serous fluid that permits free movement of the viscera, particularly of the gastrointestinal tract, inside the peritoneal cavity. The peritoneum, by connecting the visceral with the parietal portions, assists in the support and fixation of the abdominal organs. The diverse attachments of the peritoneum divide the abdominal cavity into several compartments.

Some of the viscera are attached to the abdominal walls by broad areas of the peritoneum, as, for example, the pancreas. Others, such as the liver, are attached by folds of the peritoneum and ligaments, usually poorly supplied by blood vessels.

The peritoneal ligaments are actually rather strong peritoneal folds, usually connecting viscera to viscera or viscera to the abdominal wall. Their name usually derives from the structures connected by them(e.g., the gastrocolic ligament, connecting the stomach and the colon; the splenocolic ligament, connecting the spleen and the colon) or from their shape (e.g., round ligament, triangular ligament).

The mesenteries are folds of peritoneum that are attached to the wall of the abdomen and enclosing viscera. They are richly supplied with vessels that carry blood to or from the organs that they enfold. The three most important mesenteries are the one for the small intestines; the transverse mesocolon (which attaches the transverse portion of the colon to the back wall of the abdomen) and the mesosigmoid (which enfolds the sigmoid portion of the colon).

The omenta are folds of peritoneum enclosing nerves, blood vessels, lymph channels, and fatty and connective tissue. There are two omenta: the greater omentum hangs down from the transverse colon of the large intestine like an apron; the lesser omentum is much smaller and extends between the stomach and the liver.

5.1.2 Ethiology and Pathophysiology

Common afflictions of the abdominal cavity include the presence of fluid in the peritoneal cavity (abscess) and peritonitis, an inflammation of the peritoneum. Intra-abdominal abscessess are an important and serious problem in surgical practice. Appropriate treatment is often delayed because of the obscure nature of many conditions resulting in abscess formation, which can make diagnosis and localization difficult. Associated pathophysiologic effects may become life threatening or lead to extended periods of morbidity with prolonged hospitalization. Delayed diagnosis and treatment can also lead to increased mortality rates. Therefore, the economic impact of delaying treatment is significant.

A better understanding of intra-abdominal abscess pathophysiology and a high clinical index of suspicion should allow for earlier recognition, definitive treatment, reduced morbidity and mortality.

Although multiple causes of intra-abdominal abscesses exist, the following are the most common:

- Perforation of a diseased viscus, which includes peptic ulcer perforation
- Perforated appendicitis and diverticulitis
- Gangrenous cholecystitis
- Mesenteric ischemia with bowel infarction
- Pancreatitis or pancreatic necrosis progressing to pancreatic abscess.

Other causes include untreated penetrating trauma to the abdominal viscera and postoperative complications, such as anastomotic leak or missed gallstones during laparoscopic cholecystectomy.

Intra-abdominal abscesses are localized collections of pus that are confined in the peritoneal cavity by an inflammatory barrier. This barrier may include the omentum, inflammatory adhesions, or contiguous viscera. The abscesses usually contain a mixture of aerobic and anaerobic bacteria from the GI (Gastro Intestinal) tract.

Surgical site infections (SSIs) are not an extinct entity; they account for 14-16% of the estimated 2 million nosocomial infections affecting hospitalized patients in the United States (31). Infections are caused by bacterial contamination mostly contracted during surgical operation (see Table 14) and, more rarely, by contamination in the postoperative period.

clean intervention	1-3%
clean-contaminated intervention	5%
contaminated intervention	15-30%
dirty intervention	20-40%

Table 14 Percentage of infection per grade of cleanliness of intervention

Local Signs of infection are erythema, tenderness, hardening of margins and pus that leaks from the wound. It becomes clinically manifest between the V and VII day. Some slow onset infections occur with skin erythema, partial wound dehiscence, and streaming days after

removal of points. The main complications can be dissemination of local or general infection, wound dehiscence with possible gutting and incisional hernia. The prognosis of wound infection is generally favourable if the treatment is appropriate. Only exceptionally a poor evolution occurs for the incidence of complications later (e.g. dehiscence, peritonitis, septic shock). In Table 15 there is a list of risk factors in surgical wound infections.

	Risk factor
Patient's status	Age, nutrition, diabetes, tabagism
Intervention	Duration of surgical washing Failure in the obliteration of dead space Preoperative shower Preoperative skin preparation Duration of the intervention Right antibiotic prophylaxis Operating room ventilation Not accurate Surgical device sterilization Surgical drainage Surgical technique Poor haemostasis tissue trauma

Table 15 List of risk factors in surgical wound infections due to patient's status and intervention

Today the only way to monitor surgical wounds are:

- To monitor the patient several times during the day in order to avoid immediate local complications
- To check color and amount of drainage in the post operative period
- Daily inspection and palpation of the wound
- Medication of the wound on the 5th day
- Partial removal of suture knots ,total removal on the 9th day

The use of drainage reflects the need for the surgeon to maintain a "Spy" on what happens in the outbreak surgery after skin closure. The drainages have the primary objective to promote the evacuation of any collecting blood, serous fluid or other. The abdominal cavity generally doesn't require aspiration, because the abdominal pressure is enough to convey the collected blood or other liquids outside. There are several kind of drainage tubes for each application. The endo-abdominal draining tubes are used for emptying the peritoneal cavity from:

- Normal substances present in the post operative phase: serositis, poor bleedings
- Residual not totally removed during intervention: blood, bile, pus, necrotic substances secondary to infectious or hemorrhagic complications occurred postoperatively

VideoDrain is a ''warning'' endoscopic system that allows the monitoring of abdominal cavity in the postoperative course. It allows for viewing inside the abdominal cavity and can be used by nurses and by the physician. With direct and real-time visualization of the abdominal cavity it will be possible to find the potential danger before the leak of liquids.

VideoDrain must be positioned parallel to a drainage tube placed after any abdominal surgery. It can be placed in the laparoscopic wounds or in an abdominal incision depending on the

organs / tissues to inspect. VideoDrain is designed to be used in post-operative course after resection of the stomach, intestine and rectum (in hazardous, both intestinal and vascular), anastomosis (special kind of suture that joins two hollow viscera thus making them communicate). In presence of ischemia, the use of VideoDrain is highly recommended, especially where there is a need to reopen and verify the result of the intervention. It is a valid alternative to "second look" interventions.

5.2 Market Analysis

A precise market analysis has been conducted thanks to the use of national hospital discharge records for the particular surgical application of the device. The SDO (schede di dimissione ospedaliera[9]) is the tool used in all Italian hospitals to document the hospitalization of each patient. The national database of hospital admissions has been established in 1994 and it carries the information of all admissions registered in Italy. It has gradually expanded both quantitatively and qualitatively. Completing the form, the hospital identifies the service offered to the patient, which can be a surgical procedure or a diagnostic intervention, with a code: ICD, International Classification of Diseases.

Regularly reviewed, the present version is ICD9CM (International Classification of Diseases, 9th Revision, Clinical Modification) whose main objective is to classify morbidity data.

The main surgical applications regarding the post-operative use of VideoDrain are listed in the Table 16.

Description of the intervention	ICD9-CM	Discharged –Italy (2005)	Discharged –USA (2005)
Esophageal interventions	42	2710	45.292
Incision and removal of the stomach	43	15347	267.547
Other interventions on the stomach	44	5816	174555
Incision, removal and anastomosis of the intestine	45	57510	628.661
Other interventions on the intestine	46	3738	57.255
Interventions on the rectum, rettosigmoid and rectal peripheral tissues	48	24135	110.528
Other interventions on the abdominal region	54	2943	96.162
Transplantations		2740	21.218
Liver	50,5	935	
Pancreas	52,8	72	
Kidney	55,6	1733	
TOTAL		114.939	1.401.218

Table 16 Comparison of principal DRG (*Diagnosis Related Groups*) for VideoDrain application between Italy and Usa 2005

5.3 State of the art: Commercial systems

The objective of VideoDrain is to monitor the abdominal cavity after a surgical intervention creating, through the insufflation of a balloon, a cavity between the organs; introducing a fiberscope inside a tube until the cavity, it allows the control of the post–operative course of the patient.
In Table 17 there is an economic comparison between some devices similar in terms of structure or components and sometimes in intended use to VideoDrain.

[9]http://www.salute.gov.it/ricoveriOspedalieri/paginaInternaRicoveriOspedalieri.jsp?menu=rilevazione&id=1232&lingua=italiano

Product	Price (€)	Companies			Annual sales Italy (pcs)
		Italy	Europe	World	
Drainage catheters	1-4 (the catheter) 20-80(the whole set depending from the type)	Chimed[10], Gps [11] Mediberg[12]	Anderseneurope[13] Astratech[14]	Boston[15] Merit[16] Angiodynamics[17]	+500 K
Endoscopic covers	9-15	Service 2001[18] Xmed[19] Endoclarix[20]	Storz[21] Insight[22] Scopeguard[23]	Medtronic[24]	1.5 M
Balloon dissectors	580		Covidien[25]	Bbraun[26]	≈8.000
Balloon systems for diagnosis and intervention	193		Pajunk[27]		

Table 17 Analysis of competitors: market evaluation

The annual sales have been calculated starting from information on national hospital public databases, regarding the annual purchases of each institute and the number (32)of Italian public and private institutes of Health (approx 1600).

Below there is a description of each concurrent device and also of alternative diagnostic techniques for post operative diagnosis of abdominal surgery complications.

5.3.1 Abdominal drainage tubes

The drainage system is generally a tube whose inner diameter can vary from about 1 mm to over 15 mm with thicknesses ranging from 1 to 6 mm and should be designed to allow easy flow of materials in the main channel of collection. In general, in the distal portion it has a variable number of side holes to facilitate the conveyance of the drainage material toward the external sterile containers.

[10] http://www.chimed.it/
[11] http://www.gpsmedical.com
[12] http://www.mediberg.it/prodotti-medicali-monouso.html
[13] http://www.anderseneurope.com/
[14] http://surgery.astratech.it/
[15]http://www.bostonscientific.com/procedure/ProcedureLanding.bsci/,,/navRelId/1000.1002/method/Procedure/id/10001061/seo.serve
[16] http://www.merit.com/products/productdetail.aspx?id=654
[17] http://www.angiodynamics.com/products/total-abscession
[18] http://www.service2001surgyline.it/
[19] http://www.xmed.it/
[20] http://www.endoclarix.com/
[21] http://www.karlstorz.com/cps/rde/xchg/karlstorz-en/hs.xsl/146.htm
[22] http://www.insightmedical.net/product.asp?ID=58
[23] http://www.scopeguard.co.uk/products/urology/cystoscope-sheath/
[24] http://www.medtronic.com/italy/
[25] http://www.covidien.com/hernia/pages.aspx?page=Catalog/Access
[26] http://www.bbraun.com/cps/rde/xchg/bbraun-com/hs.xsl/products.html?prid=PRID00005099
[27] http://www.pajunk.com/

Thanks to the monitoring of drainage fluids (33), it is possible, but not in all cases, to prevent post operative complications such as pancreatic fistulas, hematomas etc.

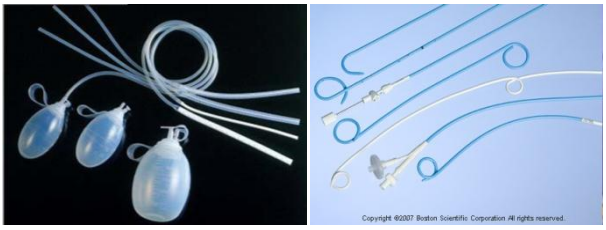


Figure 44 Example of systems for drainage

5.3.2 Endoscopic covers

The endoscopic covers (i.e. ENDOSHAFT-COVER® and ENDOSHAFT-COVER® PLUS) are sterile and disposable protective coatings for flexible and rigid endoscopes. They are easily placed on the fiberscope and usually equipped with a lens on the tip of the device in order to avoid blurring. The device provides a fast and effective way to increase the productivity of endoscopes, it provides sterility for each procedure and it is an effective barrier to microorganisms.

Figure 45 Example of fiberscopic covers

5.3.3 Trocar for extraperitoneal dissection (Balloon dissectors)

The balloon dissectors separate the layers of fascia from the peritoneum and access the site of the hernia, they promote relaxation leading to the creation of an extraperitoneal cavity in which it is possible to operate. It consists of a reusable part (Blunt cannula and mandrel) and a disposable part (rod with balloon distension and hand pump).

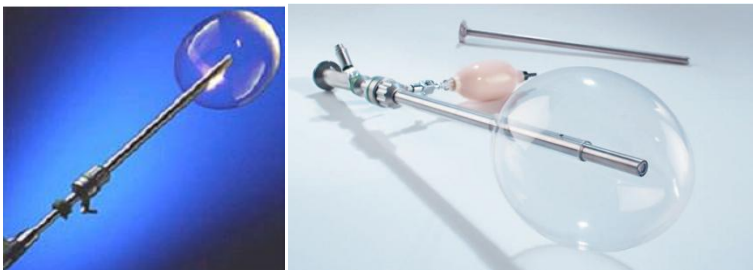


Figure 46 Balloon dissectors

5.3.4 Balloon systems for diagnosis and intervention without insufflation

Diagnostic balloon is a valid "gas-less" alternative to pneumoperitoneum. It allows the examination of the cavity during the distension of tissue through a rigid endoscope. The unique system, LapVision by Pajunk , consists of an optical trocar tip which gives the vision, once introduced the endoscope, throughout the operation of abdominal distension. The balloon has a second chamber in the distal part and the two balloons are blown simultaneously. This ensures greater stability in handling maneuvers during the surgical dissection. The diameter of the balloon reaches only 3 cm.

Figure 47 Pajunk LapVision

5.3.5 Abdominal ultrasound

Sonography of the abdomen is commonly requested for patients who have recently undergone abdominal surgery. Abdominal sonographic examination is often inadequate or impossible in the patient who has recently had abdominal surgery. Dressings, sutures, drains, raw areas, discharging sinuses, and tenderness interfere with the study. Hence the examiner has to scan between the wounds or intercostally. In addition to these limitations, scanning is impossible directly over the wound when sutures or clips are present(34).

Incisional hernias, which are hernias that occur through a surgical scar in the anterior abdominal wall, are serious complications of abdominal surgery (35) and Ultrasound examination can help the diagnosis of such complications. In post-operative patients, large hematomas may often be seen in the vicinity of the surgical scar (36).

In (37) ultrasound examinations were carried out on women on day 4 after surgery to assess the presence of abdominal wall or pelvic fluid collections.

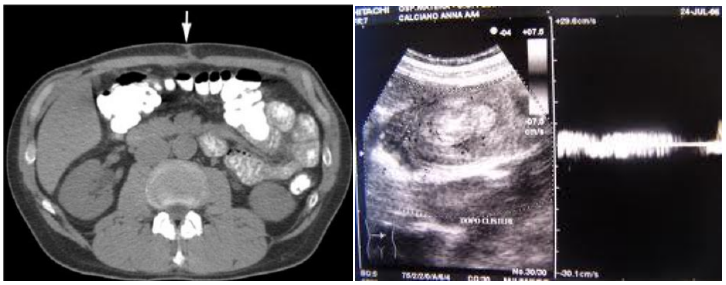


Figure 48 Abdominal Ultrasound examinations

5.3.6 Diagnostic Laparotomy

Diagnostic laparoscopy is a minimally invasive surgical procedure that allows the visual examination of intra abdominal organs in order to detect pathology. The video image of the liver, stomach, intestines, gallbladder, spleen, peritoneum, and pelvic organs can be viewed on a monitor after insertion of a telescope into the abdomen. Manipulation and biopsy of the viscera is possible through additional ports.

The indications (38) for diagnostic laparoscopy can be divided into four main groups:

3. Non-traumatic, non-gynecological acute abdominal pain like:

    - Appendicitis
    - Diverticulitis
    - Duodenal perforation
    - Mesenteric adenitis
    - Intestinal adhesion
    - Omental necrosis
    - Intestinal infarction

- Complicated Meckel's diverticulum
- Bedside Laparoscopy in the Intensive care unit
- Torsion of intra-abdominal testis

4. Gynecological abdominal emergencies
5. Abdominal trauma, abscesses and disease
6. "Second look" procedure or cancer staging.

There is some risk of infection. However, antibiotics are usually given to prevent this complication.

There is a risk of puncturing an organ, which could cause leakage of intestinal contents or bleeding into the abdominal cavity. Such a complication could lead to immediate open surgery.

5.3.7 Abdominal radiography and computer tomography scan

When an abdominal X-ray is taken, radiation is momentarily applied to the abdomen. The image that is produced is the result of passing X-rays through the abdomen to the film. Structures like bone or calcification, which are dense and have a high atomic number, absorb a lot of radiation, so that fewer X-rays reach the film, and appear white. Structures like bowel gas, which are full of air and have a low atomic number and density, appear black because most X-rays pass through without being absorbed. Liver, fat, tumor, and fluid absorb less X-rays than bone, but absorb more than air and, consequently, appear gray on the film.

Abdominal radiography uses X-rays, a type of ionizing radiation that can potentially change chemical and genetic structures in the human body. Plain abdominal X-rays can render important clues in evaluating one's condition. But in many cases, it does not provide any specific information, and only functions as a gateway examination to the next step. In the case of abdominal trauma, abdominal CAT (computer axial tomography) scan is the examination of choice because it can demonstrate internal bleeding, organ injury, or bowel perforation specifically, in an early stage.

Abdominal CT for postoperative abscess can be expected to be diagnostic in a substantial proportion of cases (39) in the first week after an abdominal intervention, the majority of which lead to percutaneous or operative drainage. Postoperative CT for intra-abdominal abscess should be obtained as clinically indicated, regardless of interval from surgery.

CT helps identify fluid collections(40), differentiate them from hernia recurrence (which may have a difficult physical examination, especially in obese patients), and confirm their resolution.

5.3.8 Analisys of competitors features

In Table 18 there is a comparison between the main features of concurrent devices and system of diagnosis of abdominal organs and wounds in the postoperative period.

System Feature	Drainages	Covers	Balloon dissector	LapVision	US	Laparotomy	TC, Xrays	VideoDrain
Visual monitoring of the surgical wound		X	X	X		X		X
Space creation in the abdomen			X	X		X		X
Diagnosis of post-operative complications	X	X		X	X	X	X	X
Difficult use for lacking of necessary accessories in the hospitals		X			X	X	X	X
High cost (both disposable and reusable parts)			X	X	X	X	X	
Invasiveness				X		X	X	
Diagnostic efficiency	Medium, sometimes a second look intervention is necessary	Not applicable for abdomen, due to the collapse of organs	Not applicable, different intended use	No data available	Low, lack of direct vision of the wound	x	x	Tbd
Disposable	X	X	X (partially)	X				X
Flexibile	X	X		Flexible trocar sleeves with flat closures remains in the patient without being disturbed.				X
Additional scars needed				X		X		
Anestesia needed				X (LOCAL)		X		
Hazardous						X	X	

Table 18 Analysis of competitors: comparison of main feature

As seen in the previous table there is not a real direct competitor for VideoDrain because the systems differ for many reasons. The TC scan and X-rays exams are very effective but very dangerous for health and the ratio cost/efficacy is very high; ultrasound is not dangerous but not very effective in case of visualization of pus, bile, blood. The balloon dissectors are fabricated with a different intended use and cannot be released in the patient for the entire

length of the postoperative period. The endoscopic covers cannot allow the inflation of the abdominal cavity and the drainage tubes are only intended for draining liquids but they cannot show the condition between the organs.

Only LapVision allows the visual monitoring of abdominal site but there are some structural and economic differences compared to VideoDrain.

The shaft is in stainless steel (Table 19) and only a flexible trocar is left into the scar on the patient for further monitoring, thus the surgeon has to reuse the entire kit in order to evaluate the patient's conditions. The cost of the kit, as reported in Table 17, is very high compared to the one of Video Drain, which will be approximate around 15-20 €.

Product	Spacemaker™ Dissection Balloon	Herloon	Pajunk LapVision
Material	Silicone balloon, latex body o the trocar (not in contact with the patient). The oval dissection balloon is rigid; the round dissection balloon is elastic.	Stainless steel shaft, plastic balloon	Stainless steel shaft, plastic balloon
Shape	Different shape of the ballon depending upon the intervention	Unique	Unilateral and bilateral balloon. Double balloon for enhanced stability and for guaranteeing a minimal space between the optic
Sterilization method	The entire device is disposable	Partially disposable	Partially disposable
Dimensions	The round dissection balloon is 4.5 (114.3mm) inches in Ø when inflated with 1000cc. The oval dissection balloon is 7.5 inches wide, 4.5 inches tall and 4.5 inches deep when inflated with 1000 ccs of air. Vmax=40 hand pumps of air (syringe up to 20cc)	Lenght 300 mm Tube Ø 10 mm	Tube Ø 11 mm Balloon Ø 30 mm
Valve			One way tap valve for insufflations of the balloon
Accessories needed			scopes Ø 3,5 mm

Table 19 Analysis of structural features of the main concurrent and similar device

5.4 Patent Search

A search of pre-existing patents has been conducted on free databases like:

- http://www.freepatentsonline.com
- http://www.wipo.int/pctdb/en/
- http://www.espacenet.com/index.en.htm7
- www.patentstorm.com

Taking into account only the class A61-Medical or veterinary science; hygiene- of the International Patent Classification (IPC)- in Table 20 there are the main results of a wider patent search.

Keywords	Search engine				Relevant results among the first 200
	1	2	3	4	
post-operative diagnosis device abdominal vision	154	293	0	425	(41) (42)
patient abdominal vision system cover	547(3)	0	0	1438(0)	(43) (44)
Drainage Endoscope	4237	0	17	3464	0
Balloon Dissector	1075	195	9	877	(45) (46) (47) (48)
Multilumen drainage tube	395	63	0	260	0
Balloon Wound Surgical Tube	5776	4219	0	8816	0
Endoscopic balloon Cover	4778	2236	2	7306	(49) (50) (51; 52) (53) (54)
Scope sheath balloon diagnosis	2066	1314	0	1000	(55)
drainage endoscope monitoring post-oper	391	109	0	279	0
Wound scope observation post-oper	1730	2447	0	3676	0
Expanding balloon abdomen monitoring device	803	1347	0	1954	(56) (57)

Table 20 Results of patent search

The main patent found is (43) described as follows:

It is directed towards a medical scope guide for use in viewing the internal body tissues of a patient. The scope guide comprises an elongated hollow tube having opposite inner and outer ends. A transparent balloon is secured to the inner end of the tube. The tube serves as a conduit of air for inflating and deflating the balloon. A scope device is slidably received in the tube and extends into the balloon for viewing internal body tissues.

In use, the scope guide is inserted through a surgical incision into a patient's body. During such insertion, the balloon is retracted into the inner end of the tube. The balloon is inflated, and preferably engages the body tissue to be viewed. After the tube is in place, the scope device is inserted into the tube such that the end of the scope device is positioned within the transparent balloon. Thus, with the balloon inflated and the scope device positioned in the balloon, the internal body tissue can be easily viewed. The scope guide can remain in position with the inner end thereof located within the patient's body and the outer end located outside the patient's body, so that the internal tissues can be viewed at a later time. In such a situation, the incision can be closed around the tube and then closed completely after the scope guide is finally removed.

Preferably, the scope guide is made of a flexible plastic material and is disposable. Also, aspiration and irrigation passages may be provided on the scope guide.

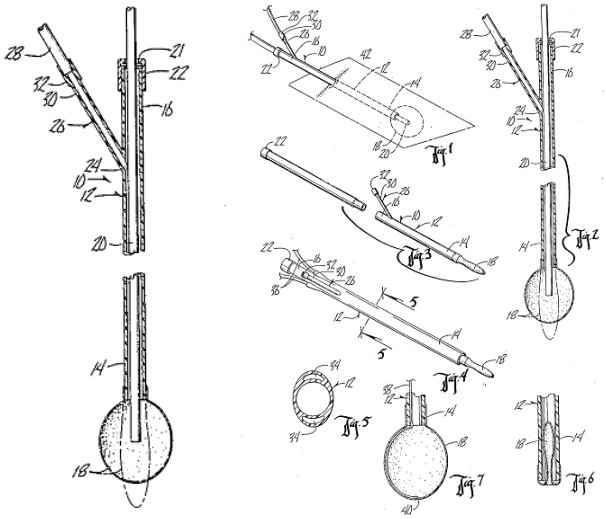


Figure 49 Patent Images

As described, the patent refers to a device very similar to VideoDrain but it is expired due to failure to pay maintenance fee, as seen on (58).Thus it is not possible to patent again the device but the production is free of any legal or economic constraint.

Thanks to the advice of an expert in patenting, it has been stated that it may still be possible to submit an application for patent as an invention, applying some changes to the intended use (restricted to a certain series of risk interventions) and other technical changes. At the same time as an alternative, it is also possible to submit a request of Utility Patent.

5.5 Design of the device

Initial specifications of the Product are:

- Biocompatibility, both in the materials and in the design
- Minimal invasiveness into the abdominal cavity and outside
- No incision / trauma to the patient more than the one reported after the intervention
- Rapid diagnosis in cases of post-operative problems in the abdominal cavity.

VideoDrain must be able to see organs placed inside the abdominal cavity and interconnected between them in order to keep the physiological balance of the body. Each dimension is well defined and the spaces between the various tissues are minimal. It is necessary an enlargement of the field of vision for a precise diagnosis and, hence, the need for a system able to create volume in the area concerned.

The tools that perform a separation of tissues and membranes inside the human body are known as dissectors. In no way the system can damage bodies which it comes into contact with and then a balloon dissector has appeared to be a minimally invasive solution because it is able to:

- Apply mechanical action of rapid and temporary separation
- Adapt to the surrounding organs without damaging
- Allowing for a clear view of the abdominal cavity
- Protect the vision system
- Maintain microbial insulation and protection from external agents in the abdomen.

5.5.1 Analysis of potential configuration and Computer assisted design

The main components discussed below are:

- A plastic tube
- A balloon
- A one-way valve system
- A vision system.

In the design of the device several configurations have been examined, evaluating whether each of them met the basic specifications.

The potential versions can be:

1. Multi-lumen (M): the catheter incorporates the collection of drained fluid and visualization of internal organs.
2. Single-lumen (S): the catheter allows the endoscope to visualize organs within the abdominal cavity.

The first approach has been adopted to consider the integration of the drainage system and the vision system in order to reduce the number of tubes to bring inside the patient at the end of the intervention. Therefore, the completion of the postoperative tasks results simplified.

Two different (M) versions containing drainage and vision system in one device (see Figure 50) have been designed. An external diameter of the tube of 10 mm has been established for both versions for minimal invasive purposes. The internal channel for the commercial fiberscope varies from 3 to 5 mm (see 5.5.4).

In the first version (A) there is a single channel for the collection of drainage fluids coming from the lateral holes and the channel for the fiberscope is eccentric compared to the tube. In version B, four channels have been designed in order to allow an easier flow of drainage fluids, due to the symmetrical order of the holes. The main disadvantage of the second solution is the thickness of the tube wall (0.45 mm versus 1mm of the version A, see Annex VII), which is too low for a good result of the process of extrusion (3.3.3.1). For further information about drawings see Annex VII)

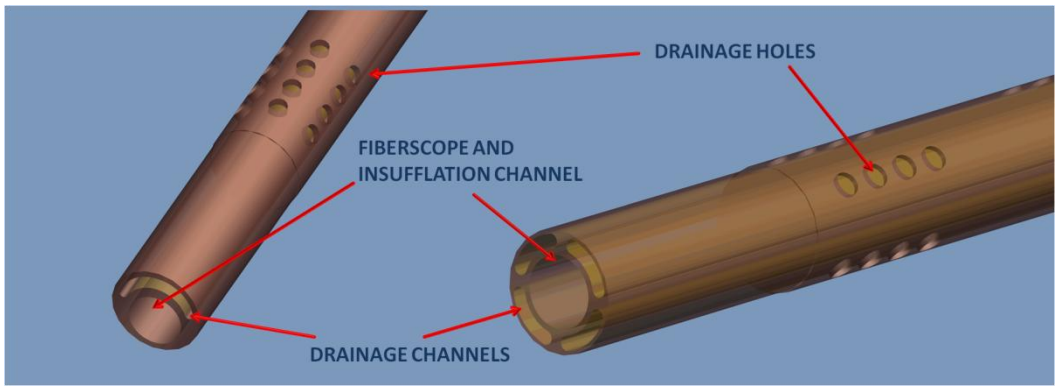


Figure 50 Distal end of multilumen (M) tubes: version A on the left and version B on the right

Other two (M) versions have been investigated (Figure 51):

3. C version, which has a channel for the fiberscope and one for the sliding of a guide wire

4. D version, with a lumen for the introduction of a commercial drainage tube and one for a commercial fiberscope

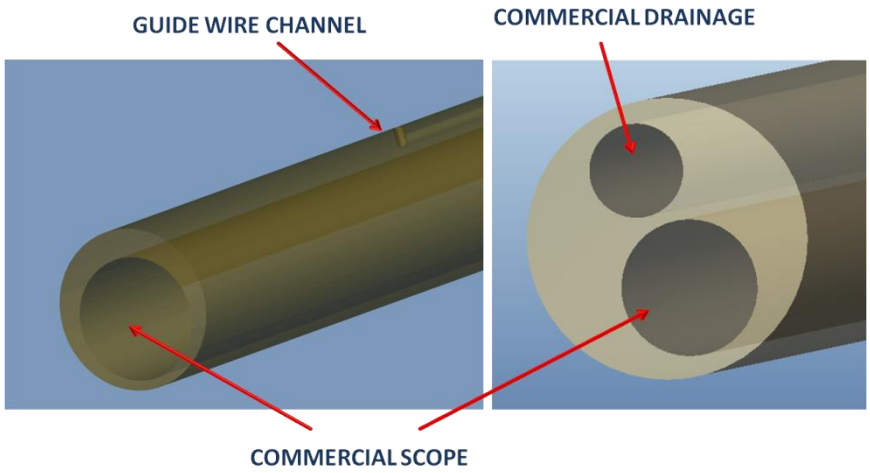


Figure 51 Multi-lumen version C (left) and D (right)

Because of the difficulty to find a fiberscope in the hospitals, another draft (E version, Figure 52) has been made in order to embed an economic mini vision system. The system consists of:

1. A miniature camera
2. A lighting system using LEDs.

After careful concerns regarding the resolution, size and cost, the chosen camera is the model MO-BS802-105 of MISUMI (Figure 52 on the right); its specifications are shown in Table 21.

Video system	NTSC
Effective Number of pixels	320x240
Image Sensor	1/18" Color CMOS Camera
Resolution	240 TV Lines
S/N Ratio	>48dB
Minimal illumination	2 Lux/F1.2
dimensions	3.5X5.2 mm

Table 21 Misumi MO-BS802-105 specifications

This solution has two main disadvantages: the external diameter of the whole device results too big (15mm) and the device too expensive for the DRG which it has been thought to.

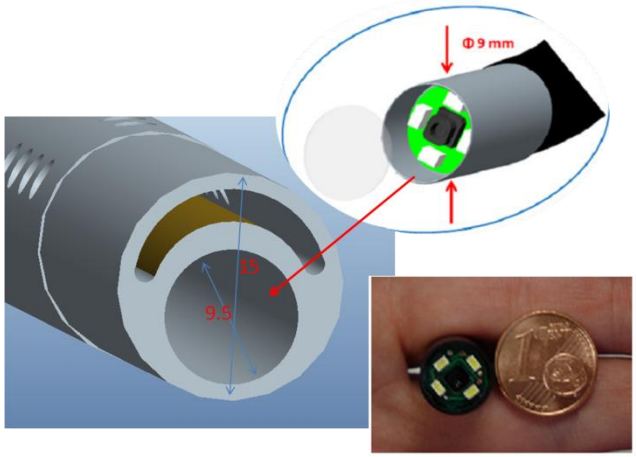


Figure 52 Multilumen (E) with embedded vision system

The major benefit of the multi-lumen solution is that the device integrates drainage and diagnosis (solution A,B,D,E),thus the introduction of a single tube causes less discomfort to the patient.

There are many disadvantages:

- Assembly and manufacturing are more complex, thus the cost is higher
- Need of additional evidence to assess the power of drainage system
- The size of the outer diameter increases

It is more difficult to find the proximal end connector between standard connectors because it has to be also a collection system for drained liquids: it cannot be commercial, thus the cost increases.

Another configuration (S) provides a tube with an internal channel for the endoscope and for insufflation of a distal balloon for the monitoring. In order to reduce the wall thickness, whilst maintaining the integrity and mechanical flexibility of the tube, a steel spiral has been included during the extrusion in the wall of the tube (Figure 53).

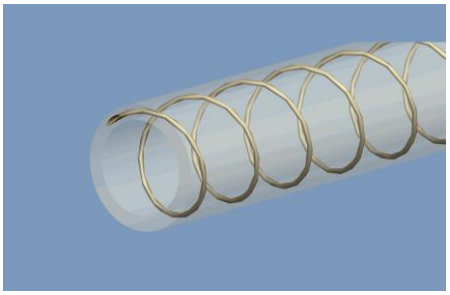


Figure 53 Single lumen(S) braided reinforced tube

The single-lumen configuration has many advantages:

- Construction and manufacturing are relatively simple
- Lower overall costs
- Meets the specification on the maximum external dimension: <<10mm
- One-way valve system for the connector part already commercially available.

The only disadvantage is that it must be parallel to a commercial drainage catheter, thus causing less comfort to the patient during the insertion of two tubes.

5.5.2 Analysis of materials

Biocompatibility plays a key role in the development of medical devices and is an important input requirement for its design. In order to take into account the biocompatibility (59) one must not only consider the applied materials, but especially the complete medical device as a whole and its intended use in the human body. In addition one should keep in mind that biocompatibility of a medical device depends on the time that it is exposed to the human body and the location in the body where it is applied or implanted.

Apart from the materials and its intended use, the biocompatibility of a medical device is also influenced by its production process. During this process the quality of materials may decline and, as a consequence, the applied materials must be judged in their final state. Degradation can be caused by heat, temperature or contact with other materials. Cleaning, packaging and sterilization may alter the quality of materials. Therefore, the complete production process

has to be taken into account when the biocompatibility of a medical device is established. In the ISO 10993-1 there is a flow chart (see Figure 54 in yellow circles VideoDrain evaluation) which guides selecting the tests to evaluate the biological response to medical devices.

Either directly or through the release of their material constituents, the device materials should not:

- Produce adverse local or systemic effects
- Be carcinogenic
- Produce adverse reproductive and developmental effects.

Therefore, evaluation of any new device intended for human use requires data from systematic testing in order to ensure that benefits provided by the final product will exceed any potential risks produced by device materials.

In general, the tests include: acute, sub-chronic and chronic toxicity, irritation to skin, eyes and mucosal surfaces, sensitization, hemocompatibility, genotoxicity, carcinogenicity and effects on reproduction including developmental effects. However, depending on varying characteristics and intended uses of devices as well as the nature of contact, these general tests may not be sufficient to demonstrate the safety of some specialized devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity, may be necessary for some devices**.**

There are devices which are made of materials that have been well characterized both chemically and physically in the published literature and that have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all the tests suggested by the ISO 10993 standard.

A systematic analysis of biological risks can be found in the general principles set out in clause 3 of ISO 10993-1 (see Table 22, in red the indications about the minimal tests for the materials of VideoDrain components).

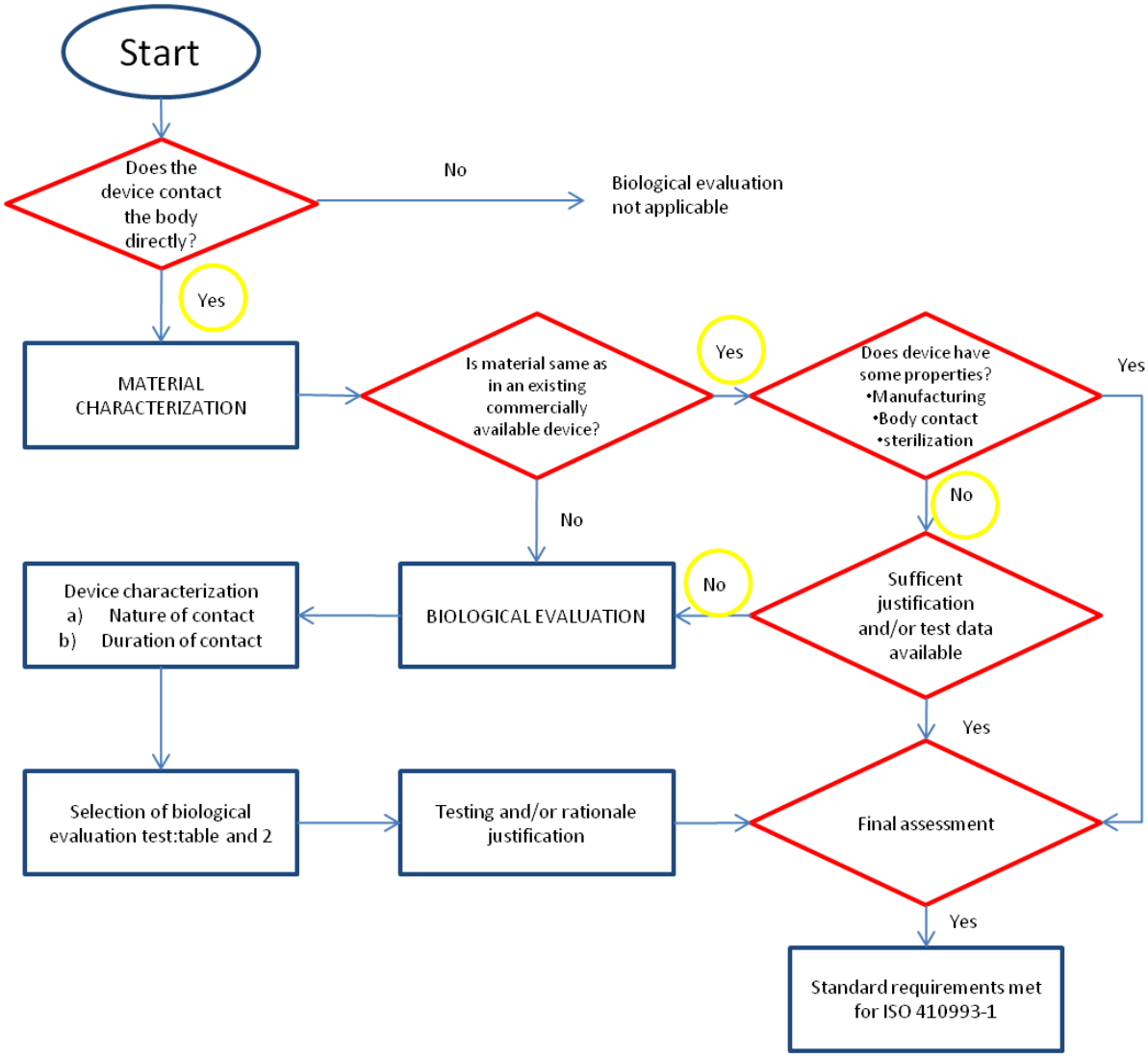


Figure 54 Annex B ISO 10993 Flow chart for the selection of toxicity tests

Device Categories			Biological Effect							
Nature of Body Contact		Contact duration A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reaction	System Toxivity (acute)	Sub-chronic toxicity (sub-acute)	Genotoxicity	implantation	Haemocompatibility
Surface devices	Skin	A	x	x	X					
		B	x	x	X					
		C	x	x	X					
	Mucosal membrane	A	x	x	X					
		B	x	x	X					
		C	x	x	X		x	x		
	Breached or compromised	A	x	x	X					
		B	x	x	X					

		C	x	x	X		x	x		
External communicating devices	Blood path, indirect	A	x	x	X	x				x
		B	x	x	X	x				x
		C	x	x		x	x	x		x
	Tissue/bone/ dentin communicating	A	x	x	X					
		B	x	x				x	x	
		C	x	x				x	x	
	Circulating blood	A	x	x	X	x	.		.	x
		B	x	x	X	x		x		x
		C	x	x	X	x	x	x		x
Implant devices	Tissue/ bone	A	x	x	X		.	.	.	
		B	x	x				x	x	
		C	x	x				x	x	
	Blood	A	x	x	X	x	.	.	x	x
		B	x	x	X	x		x	x	x
		C	x	x	X	x	x	x	X	x

Table 22 ISO 10993-1 Biocompatibility Matrix

In the prototyping phase, several kind of materials have been used in order to choose the right characteristics (stiffness for the tube, transparency and elongation for the balloon). Silicone is among the most extensively tested materials used in medical device applications, in particular in tubing for minimally invasive devices. Chemical analysis demonstrate a low loss of residues and the absence of plasticizers and additives. The majority of medical devices made in silicone show:

•Low bacterial adhesion

•Low thrombogenicity.

Therefore, silicone is the ideal material for creating VideoDrain, considering its repellent and excellent stability both from a chemical and a mechanical point of view. In fact, silicone is used in a context similar to VideoDrain as surgical drainage, urethral probes and all applications in which there is prolonged contact with the body (60). Indeed is flexible, elastic, resistant and can be autoclaved repeatedly.

The main mechanical specification for VideoDrain are:

- For the catheter: flexibility and stiffness (shore A between 30 and 80)
- For the balloon: transparent, expandable (max. pressure 20mmHg, external diameter from 30 to 90 mm so an high elongation to break is needed)

Mechanical characteristic	Rtv 4411	Rtv4440
Hardness Shore A	11	37
Tensile Strength [N/mm]	3.0	5.5
Elongation [%]	800	400
Tear strength	12	22
Colour	Transparent	Transparent

Table 23 Materials for the prototyping phase

The first prototypes designed to assess the feasibility of the system were produced using the line of Silbione® Bluestar Silicones (Table 23), respectively RTV 4411 for the balloon and RTV 4440 for the catheter. Both the silicones are certified for medical products. For the

manufacturing of the balloon various attempt have been done. At first, a mould has been designed and realized with a 3d printer, and a casting has been done. The results have been not so encouraging, due to the high number of air bubbles (see Figure 55, left) depending to lack of openings for air. The technique of dipping showed better results (Figure 55, right).

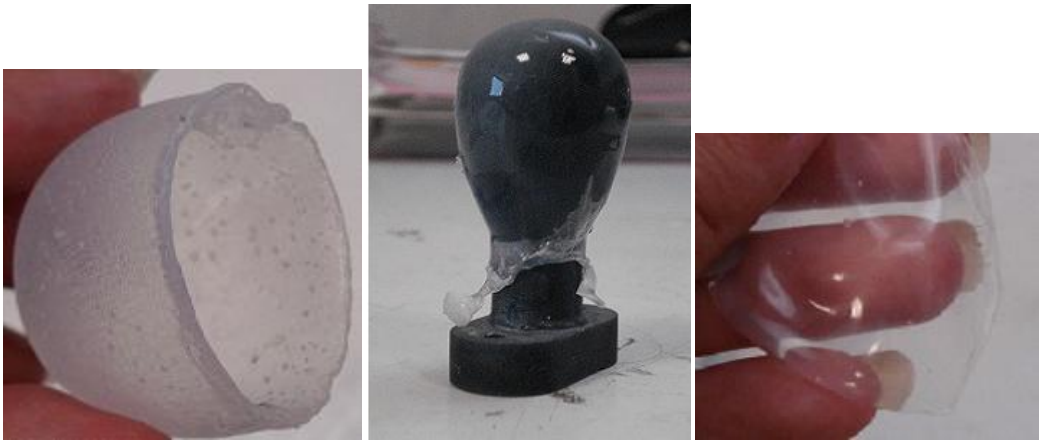


Figure 55 Balloon prototyping

A manual immersion does not allow the control of the thickness and for the tube the results obtained were very bad, due to presence of air bubbles and bad dimensional tolerances.

5.5.3 Final configuration and prototype

After the analysis of all the possible configurations for the tube, the S version has been chosen as the solution which better matches the intended use of the device and better optimizes the potential manufacturing costs and quality parameters. A search for commercial components has been completed in order to produce the device drawn in Figure 56 (see Annex VII for further details), fulfilled with auxiliary systems (valves, balloon, connectors).

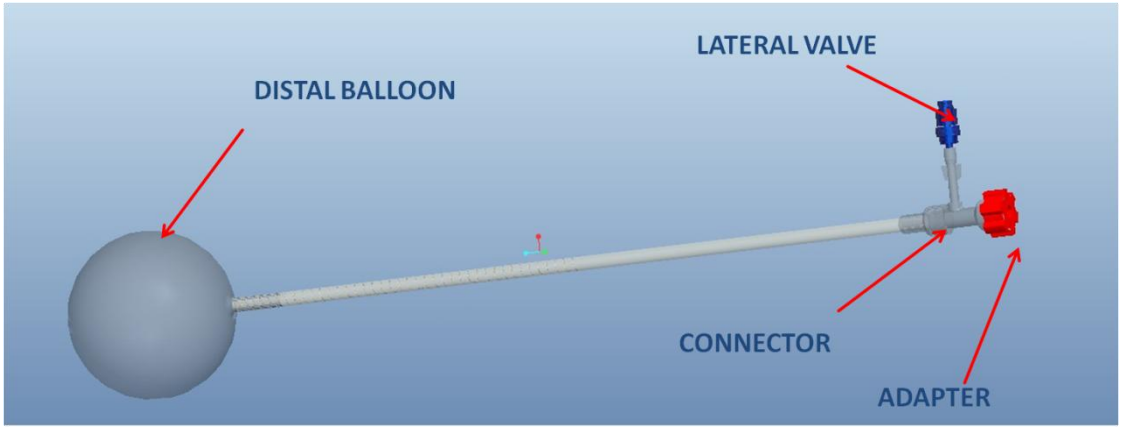


Figure 56 Final CAD drawing of VideoDrain

The Lateral Valve(61) is a one way valve which utilizes a female luer lock compatible connector and a male luer lock adapter. It mates securely with all standard luer syringes and connectors providing a hermetic seal between syringe luer tip and valve.

Figure 57 Lateral valve: cad drawing and commercial component

The single lumen tube is reinforced (Figure 58) with an helical metal wire coextruded with the tube.

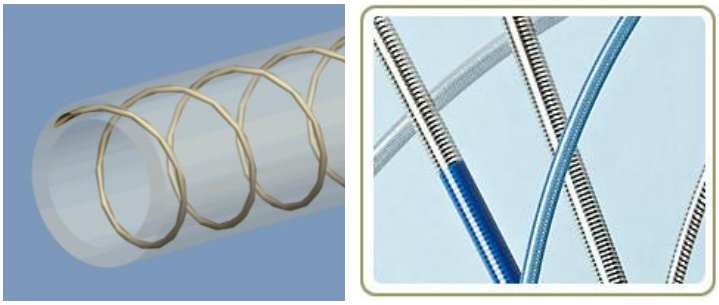


Figure 58 Braided reinforced tube

The distal balloon (Figure 59) is made by medical grade silicone. It allows an expansion from 35mm of diameter to 90mm.

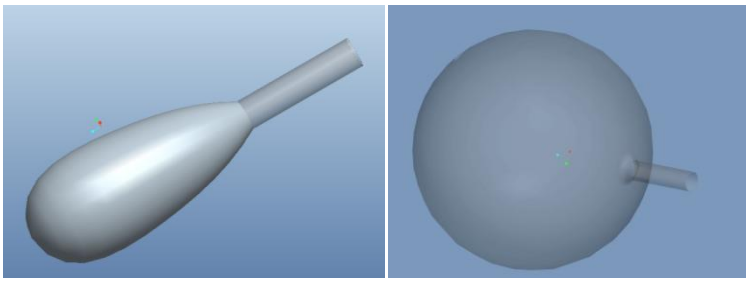


Figure 59 Balloon: deflated (left) and inflated (right)

The connector is made by three parts (see Figure 60 left image):

1. One bonded with the single lumen reinforced tube
2. One attached to the first part with a thread, it contains a silicone membrane (4 in Figure 60 right)
3. One laterally glued to the second part, it has a luer lock attachment to fit the lateral one-way valve

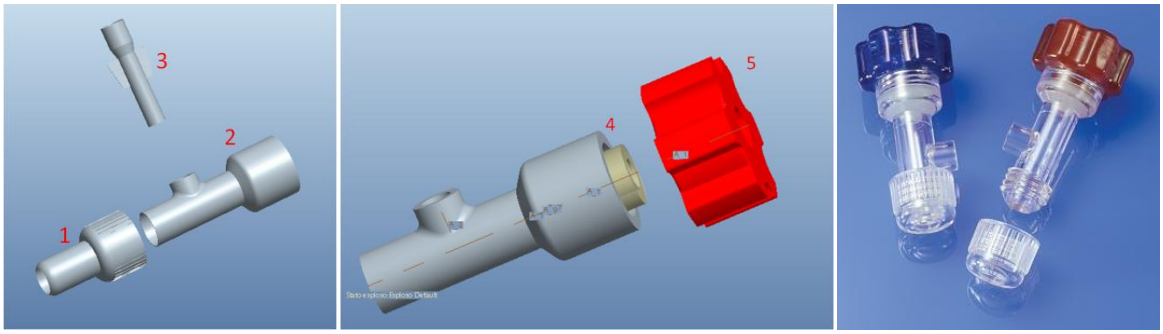


Figure 60 Exploded view of the connector (left) and the adapter (centre). Commercial adapter (right)

At the proximal end of the connector there is a red cap which allows the regulation of the opening of the silicone membrane, thus allowing the insulation for fiberscope of different diameter.

The commercial component chosen for the device is a Tuohy Borst Adapter (Figure 60) (62) which allows the regulation of internal diameter for the entrance of the fiberscope with an external diameter from 2.2 to 5.6 mm.

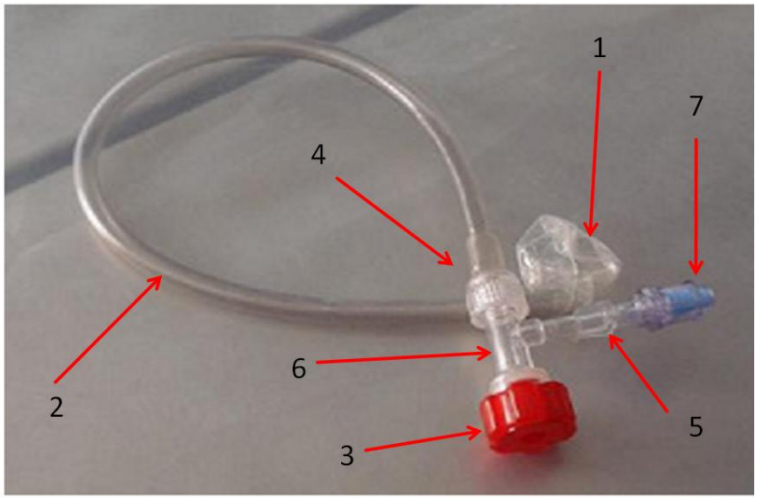


Figure 61 Final Prototype of VideoDrain

In Table 24 we report all components of the pre-industrial prototype (Figure 61) . VideoDrain final prototype (Figure 61) has been manufactured by a company which applies the new quality standards and safety for the medical device sector (ISO13485, MDD 2007/47).

Component (Figure 61)	Critical dimensions	material
1-Balloon	External diameter 35mm Thickness: 0.3-0.4mm	Silicone
2-Reinforced tube	23Fr (7.59 mm)	Body: PU AISI 304
3-Thuohy Borst adapter for catheters	Internal diameter from 7 to 17 Fr (2.33 to 5.66 mm)	Body: PC Membrane: Silicone
4-Sleeve T.B. adapter-catheter body		PVC
5-Female luer lateral connector		PVC
6-Connector between adapter and lateral luer		PVC
7-Anti-reflux luer lock valve		Body: PC Valve: silicone

Table 24 Components of the final prototype

5.5.4 Accessories

In order to insufflate the distal balloon, an inflation device is needed. It must have a male luer lock attachment in order to fit the female luer of the one way valve. A commercial syringe with a big volume (50 ml,(63)) has been chosen.

Alternatively another way to control the insufflation can be an inflation device like the one in Figure 62 (left)(64) which allows a monitoring of the pressure inside the balloon.


Figure 62 Inflation device (left); flexible endoscope (right)

For the monitoring of wounds, a vision system is needed. It must be flexible and the outer diameter must be between 2.3 and 5.6mm. In the healthcare facilities there are a lot of flexible endoscopes, available for various applications (see Table 25), which can be used with VideoDrain.

Scope	External diameter(mm)	Length(mm)
Broncoscope	3.6-5	550
Rhinolaryngoscope	3.4-5.2	250-300
Cystoscope	3.3-5.1	350
nasopharyngoscope	3-5	300
Choledochoscope	3.7-4.5	300-1880
Hysteroscope	3.1-4.9	200
Fiber Intubation Scope	3.4-4	600
Uteroscopes	3.3	700

Table 25 Medium values of dimensions of commercial flexible endoscopes

5.6 Tests

5.6.1 Mechanical tests

Some mechanical tests has been done on the connections of the final prototype in order to ensure their resistance to break.

The UNI EN 1617 (Sterile Drainage Catheters and Accessory Devices for Single Use) refers to drainage catheter and auxiliary disposable devices. Catheters of external diameter below 2mm, suction catheters for the respiratory tract and tracheal tubes are excluded. Therefore, VideoDrain can be included. The regulation provides information on various made tests indicating what should be the minimum strength at break between connections of the components of the device.

External nominal diameter	Tensile strength at break (N)
From 2 to 4	5
>4	15

Table 26 UNI EN 1617; minimum force needed to break connections

The UNI EN 1618 (Catheters Other than Intravascular Catheters - Test Methods for Common Properties) indicates the test methods to ensure an uniform assessment of the characteristics of catheters, such as resistance to corrosion of metal components, determination of the traction, resistance to leakage of fluid under pressure, determining the water flow in catheter and tests for safe connections.

The useful data extrapolated from this standard is the speed to be imposed during the tensile test (Figure 63) on the connections of VideoDrain:

20mm * L / min

where L is the length exposed to tension.

Figure 63 Tensile test on the connection between tube and sleeve

On the device the tensile strength test of the connection between the adapter 4 in Figure 61 has been carried out. The expected minimum value of breaking stress for the connection is 0.288 N/mm^2 (calculated starting from the data in Table 27). As depicted in Figure 64 the breaking value of stress is much higher than the limit imposed by the UNI EN 1617, so the connection is safe.

Sample Length	15 mm
Speed trial	300 mm/min
Sample Section	52 mm2
Minimum strength to break UNI EN 1617	15 N
Minimum allowed break limit for connections	0.288 N/mm2

Table 27 Connection break test parameters

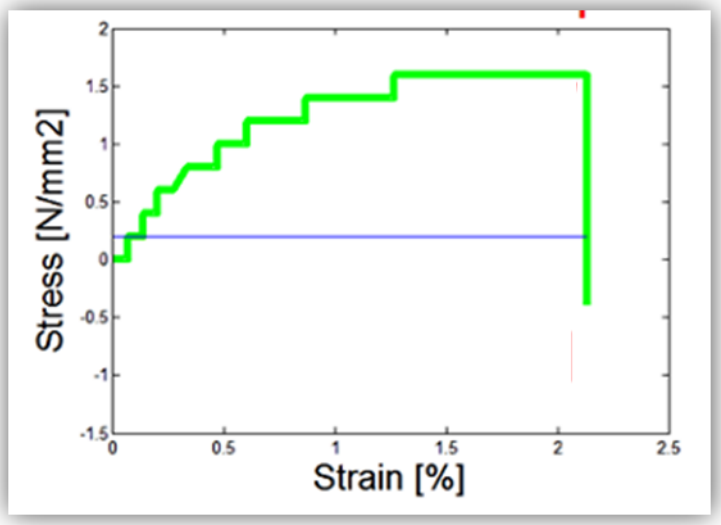


Figure 64 Stress Strain curve for the tensile test of connection

5.6.2 Animal trials

A device as VideoDrain doesn't need preclinical testing to enter the EC market, because its risk class is IIa (see Certification aspects). However in order to test the usefulness of the device before its possible marketing, the device has been tested in vivo.

The significance of the results derived from animal testing is highly dependent on the choice of a suitable animal model. The pig is a scientific model suitable for subsequent mining results in humans. Moreover, it is ease of use for the assessment of VideoDrain properties, such as transparency of the balloon, ease of use. Organs like stomach, liver, bowels and kidneys from an anatomical point of view in the pig are very similar to those of man.

Clinical trials with medical devices are subject to the following harmonized standards:

- **UNI EN 540**: Clinical Investigation of Medical Devices for Human Subjects
- **UNI EN ISO 14155-1**: Clinical investigation of medical devices for human subjects. General requirements, november 2005
- **UNI EN ISO 14155-2**: Clinical investigation of medical devices for human subjects. Clinical investigation plans, dicember 2004.

Video Drain has been tested in vivo in four sessions to verify the visualization of the abdominal organs through the prototype and to chose the protocol for its clinical use. To protect animal welfare, the prototype has been ETO sterilized and provided in a sterile packaging. The tests were conducted with the animal under general anesthesia, monitoring its physiological activities and under the supervision of a veterinarian and a surgeon, following the requirements of Decree 609/86 (EU Directive on animal experiments).

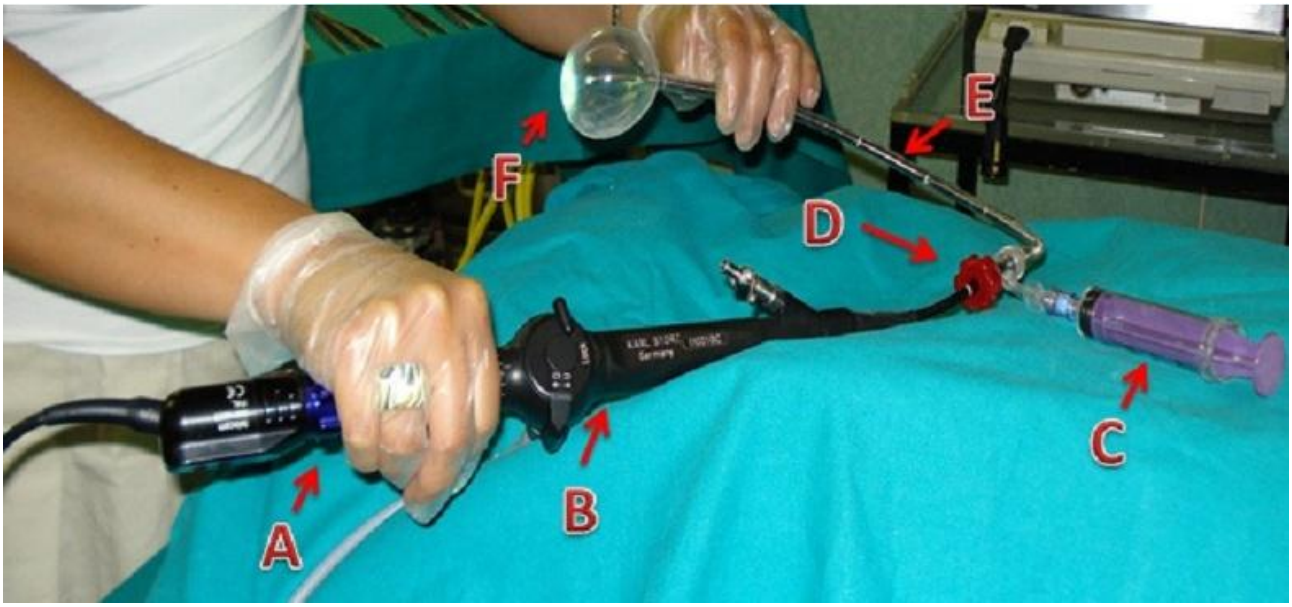


Figure 65 Experimental session: set-up phase

The tested version, with all its components, is shown in Figure 65:

1. The connection between the video input of the optical fiberscope and the surgical workstation;
2. Fiberscope;
3. Syringe for the expansion of the balloon;

4. One-way valve system;
5. VideoDrain catheter;
6. Expanded balloon (the end of the fiberscope with the lighting system is also shown).

5.6.2.1 Test procedure

Once the device is placed into a scar in the abdomen, the fiberscope is inserted into the red connector on the device. After making sure that the Thuohy Borst adapter closes properly the endoscope (to avoid the loss of air), the syringe for the expansion of the balloon should be connected through the lateral luer-lock attachment. Particular attention should be paid to all the auxiliary channels of the endoscope. In fact, they must be closed otherwise the balloon will not be inflated. VideoDrain user can directly view the expansion (see the sequence in Figure 66) of the balloon once it has been introduced into the abdominal cavity.

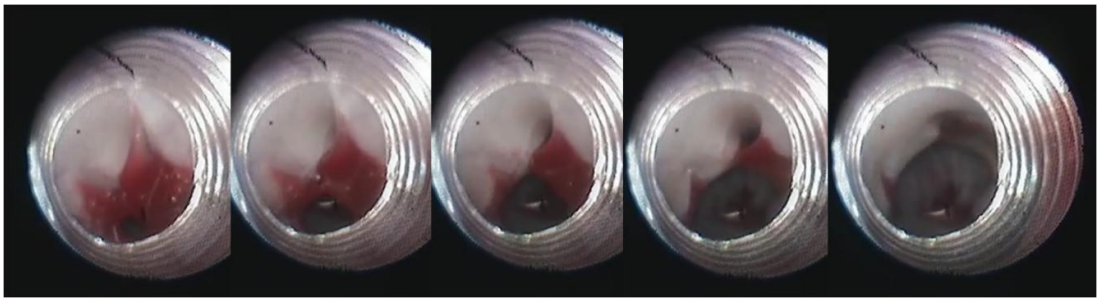


Figure 66 Insufflation of the balloon

Test	1	2	3	4
Place	San Piero a Grado	CNR Pisa	San piero a grado	Roma-Tor vergata
Date		04/06/2009		20/07/2010
Partecipants	Troia, Lencioni, Burchielli,Menciassi,Magnani	Troia, Doc. Peri, Lencioni	Magnani, Doc. Basili	Troia, Prof. Scozzarro, Menciassi
Device	VideoDrain	VideoDrain	VideoDrain	VideoDrain
Required equipment	Fiberscope, syringe 60 ml, luer lock stopcocks to close aux channels	Fiberscope, syringe 60 ml, luer lock stopcocks to close aux channels	Fiberscope, syringe 50 ml, luer lock stopcocks to close aux channels	Fiberscope, syringe 50 ml, luer lock stopcocks to close aux channels
Animal	Pig	Pig	Pig	Pig
objective	Evaluation of vision through the balloon	Evaluation of vision through the balloon	Evaluation of device ease of use and impact on surgeons	Evaluation of device ease of use and impact on surgeons
Short description of procedure	Insertion fiberscope insertion of the tube through the scar Insufflations Further insertion of fiberscope vision	Insertion fiberscope insertion of the tube through the scar Insufflations Further insertion of fiberscope vision	Insertion fiberscope insertion of the tube through the scar Insufflations Further insertion of fiberscope vision	Insertion fiberscope insertion of the tube through the scar Insufflations Further insertion of fiberscope vision
Position of the scar	Lower lateral abdomen	Higher lateral abdomen	Lower lateral abdomen	Lower lateral abdomen
Target organs	Abdominal cavity	Abdominal cavity	Abdominal cavity	Abdominal cavity
Estimated	15-20	15-20	15-20	15-20

procedure time (min)				
Results	Good view	Good view	Good idea for the surgeon	Good but see after for details
Problems			Air loss due to fiberscope channels	Buorst adapter broken,balloon cannot be insufflated due to air loss in the proximal part

Table 28 VideoDrain animal lab sessions

For creating an anatomical volume three complete injections are necessary. After each pump, the syringe has to be unscrewed from the luer-lock, recharged and connected again to the blue valve. The maximum number of injections is seven.

5.6.2.2 Test results

As soon as the balloon is expanded, the user will have a view similar to Figure 67.

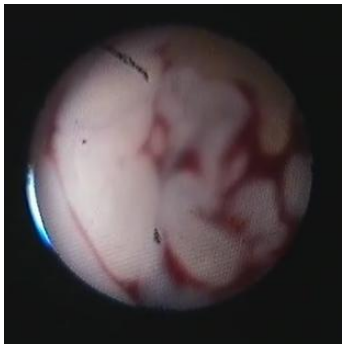


Figure 67 Image obtained through VideoDrain

Slightly rotating the catheter and directing it to the right, left, up and down, detailed images of the organs surrounding the insertion point of the device can be obtained.

The first test was carried out by inserting the fiberscope in a scar on the abdomen (Figure 68) charged by the veterinarian and the device was positioned to be the end of the balloon on the wall of kidneys.

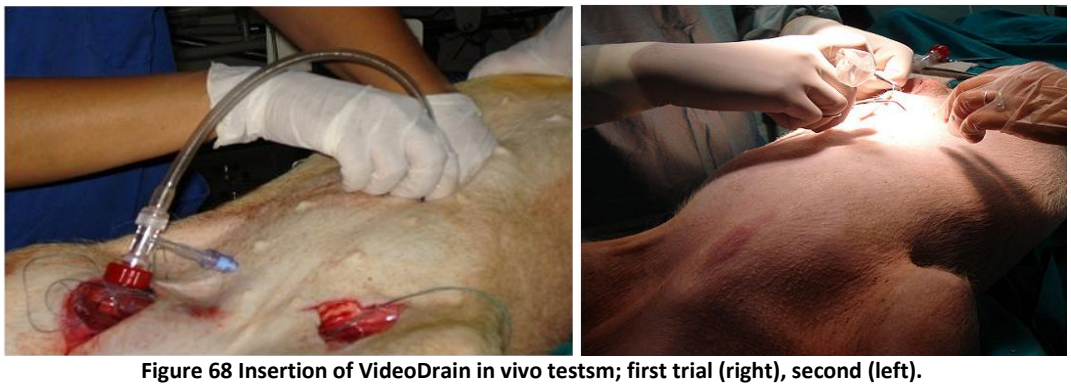


Figure 68 Insertion of VideoDrain in vivo testsm; first trial (right), second (left).

The vision (Figure 69) is distorted compared to a normal 2D acquisition but the view of the organs is quick and easy to understand. The images contain information about physiology and pathology of the cavity explored with details and color immediately comprehensible to doctors and nurses.

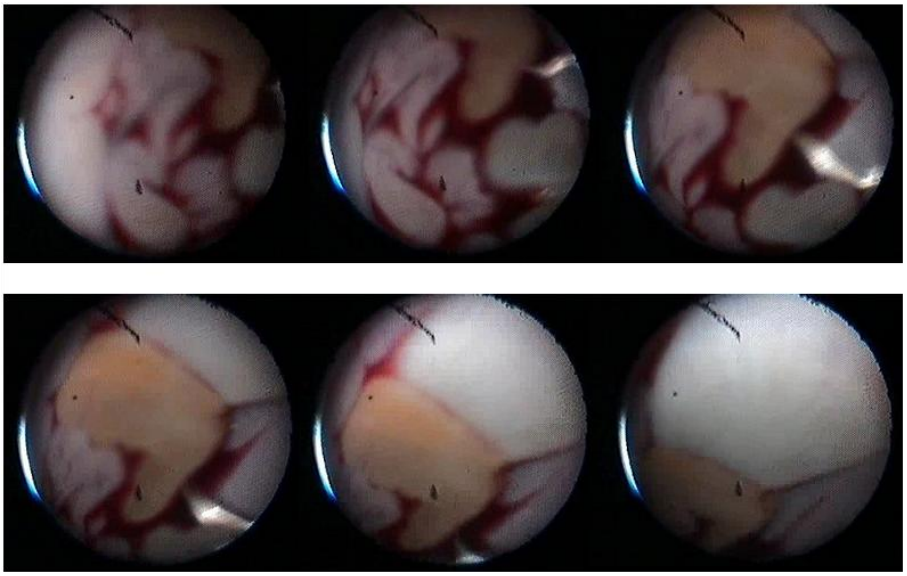


Figure 69 View of viscera from VideoDrain

In the second test, the protocol was similar but the scar was in the higher part of the abdomen thus liver and gallbladder could easily be seen.

The system successfully creates an anatomic volume within the abdominal cavity and it adapts easily to the surrounding organs allowing for the monitoring. As a results of the first two trials, as follows, there is the definition of the experimental protocol which has been used in the subsequent trials with surgeons:

- Remove VideoDrain from the sterile packaging
- Remove the protection in the distal part of the system
- Insert the device into the abdominal cavity through the laparoscopic incision
- Insert the fiberscope into the device adjusting the red adapter to the diameter of the vision system
- Advance the fiberscope to the distal end of the catheter in order to have an image of the expanded balloon
- Press the plunger of the syringe (60ml recommended) inflate the balloon monitoring the dilatation on the image on the screen to avoid damaging the surrounding organs. Unscrew the syringe and proceed to the next expansion.
- Push and position the fiberscope within the expanded balloon and keep on with the inspection.

The fourth test has been carried out in Rome with the assistance of two expert surgeons. At first they have performed a colecistectomy before, thus the VideoDrain has been inserted through a laparoscopic hole left by the trocar in the lower left side of the abdomen.

There were problems with the inflation of the balloon, probably because of air leakage from the bronchoscope channel. The vision appeared satisfactory. Prof Scozzaro[28] was impressed by the idea of the device but he suggested some further improvements for product marketing.

[28] Endoscopist of University of Rome

First of all he suggested to keep the balloon with a plastic sheath before the use and during the insertion into the wound. Prof. Scozzarro also suggested to include the device in a higher market segment, changing a little bit its intended use (restricting from the case of post-operative complications to the one already advanced after the hint of complications such as bile). Thanks to a guidewire insertion (0,035") with a-traumatic tip (type TERUMO), the device can be inserted after the removal of the drainage tube in the same area, ready for the inspection. For the previous design the VideoDrain should have an additional lumen for inserting the guidewire externally (C tube in Figure 51).

5.7 Risk Managment

5.7.1 VideoDrain intended use

Starting from the definition of medical device, VideoDrain falls within the scope of Directive 2007/47 EEC and its guideline has been followed both in its design and implementation.

The acronym VideoDrain derives from Video monitoring of a Drainage site after surgery; the device doesn't need any additional scar because it is introduced through a surgical hole for a maximum of seven days. It is designed to accelerate the identification of potential bleeding or complications that may arise as a result of an operation.

The device, inserted Following the annexed IFU (Instruction of Use), introduces a balloon inside the collapsed cavity; once positioned the catheter following anatomical knowledge, the endoscope is introduced, later the balloon is expanded. The doctor can conduct the inspection moving the endoscope to reach the desired point inside the inflated balloon. Once positioned the catheter remains in place, and periodically re-inserting endoscope and reconnecting the expansion of the balloon it is possible to monitor the abdominal cavity. VideoDrain is indicated for the detection of post-operative bleeding, it is recommended

- after anastomotic dehiscence; the suture might yield causing an hazardous situation, for example when esophagus and rectum are involved,
- to control the plenty visceral perfusion for example in the post-operative course after a mesenteric ischemia,
- to control the pulsation of the arteries, especially after vascular interventions and transplantations.

VideoDrain can be an alternative to the so-called "second look " interventions (operations carried out shortly after the primary to control its outcome); for example, after visceral ischemia where it is necessary to reoperate the patient to check the status of the suture after the removal of the infarcted section. In these cases the device can be inserted into the patient after the first intervention so that it can represent an "eye" for the entire post-surgery. The use of the device is associated with a system vision (max 5 mm) that the manufacturer does not provide; it is possible to use any endoscope present in intensive care units (Table 25).

5.7.2 Classification

The device VideoDrain, in accordance with Directive 2007/47 which scope covers medical devices and precisely with the Art. 8 and Annex IX, belongs to the class IIa, because it is a Surgically invasive device the use of which is to be classified in the short time term. The device has been classified (Table 29) as mentioned in 3.4.1.

Duration	Short term
Invasiveness	**Invasive surgical device**
Risk class	**Class IIa**

Table 29 VideoDrain classification

5.7.3 Functional Analysis

The manufacturer must identify the hazards associated with analyzing characteristics of MD that could affect patient safety. In ISO 14971 there is a questionnaire (Table 30) that can help the functional analysis of a MD in understanding the potential hazards associated with its use. Probing the phases of manufacturing and planning the use of the device, manufacturer can deduce what are the potential dangers of MD.

Question	Answer
What is the intended use and how is the medical device to be used?	VideoDrain has been designed for the monitoring of the abdominal cavity in the post-operative phase. The distal balloon is inflated through a syringe and a fiberscope in inserted through the tube; the device has a non-return valve and an adapter for the scope, which make the system perfectly sealed
Is the device intended to be implanted?	no
Will the device be in (direct) contact whit patient or other persons?	Yes, it can be inserted into the scars left in the abdomen after laparoscopic surgery. Also the medical people can touch the device during the follow-up.
What are the materials or components used ?	See Table 24
Is Some kind of energy given or detracted to the patient?	No
Is Some kind of matter given or detracted to the patient?	Yes: blood, bile, pus, etc.
Does the device manage some biological material for a subsequent use?	No
Is the device sterile or is it sterilised by the end user?	Yes, It is sterilized with ETO
Is the medical device intended to be routinely cleaned and disinfected by the user?	No
Does the device modify the environmental conditions of the patient?	It applies some pressure to the abdominal cavity organs when the balloon is inflated for the monitoring
Is a measurement	No

device?	
Can the device make an interpretation?	No
Can the device control or is it in connection with other devices?	Yes, it is connected to a fiberscope
Can the device be subject at unexpected leak of energy or matter?	No
Can the device be subjected by ambient conditions?	Yes, during storage and transport the temperature must not exceed room temp.
Does the medical device influence the environment?	No
Are there some consumables or accessory associated to the devices?	Yes, a syringe for insufflation of the balloon and a fiberscope.
Are periodical set-up or re-conditioning necessary?	The medical personnel should check the positioning inside the patient
Does the device use a software?	No
Has the device an expiration date?	Yes, Max 5 years in a sterile condition and kept as close to delivery
Can the device produce some delay effects due to the long-term use?	No
To what mechanical forces will the medical device be subjected?	VideoDrain is subject to mechanical pressure at one end and the control is performed by the user with a syringe on recommendation of the manufacturer; a maximum pressure of 20 mmHg can be applied
What determines the lifetime of the medical device?	For a new device, the lifetime of the medical device is driven by the sterilization process and its level of Bioburden; during use, life span depends on the need of medical / other person carrying the protocol, in any way is a limited time.
Is the medical device intended for single use?	Yes
Is safe decommissioning or disposal of the medical device necessary?	Yes
Does installation or use of the medical device require special training or special skills?	The installation and use of the device requires specialized knowledge and the following of IFU
How will information for safe use be provided?	Through the label and the IFU leaflet
Will new	No

manufacturing processes need to be established or introduced?	
Is successful application of the medical device critically dependent on human factors such as the user interface?	No
Does the medical device use an alarm system?	No
In what way(s) might the medical device be deliberately misused?	Not following the IFU
Does the medical device hold data critical to patient care?	No
Is the medical device intended to be mobile or portable?	no
Does the use of the medical device depend on essential performance?	no

Table 30 Questionnaire for functional analysis

6 Floseal GI (Gastro Intestinal) catheter

6.1 Analysis of the medical background: bleedings in upper and lower gastrointestinal tract

6.1.1 GI Endoscopy

GI endoscopy is a minimally invasive diagnostic and therapeutic procedure used to evaluate the interior surfaces of any organ in the gastrointestinal (GI) tract by inserting a small scope in the body, generally through a natural body opening (mouth/anus).

Through the scope, one is able to see lesions; an instrument may not only provide an image but also enable taking small biopsies and perform a surgical procedure. Many endoscopic procedures are relatively painless and only associated with mild discomfort, though patients are sedated for most procedures. Complications are rare but may include perforation of the organ under inspection with the endoscope or biopsy instrument. If this occurs, surgery may be required to repair the injury.

All GI organs can be inspected and treated with an endoscopic procedure; an Upper GI endoscopy is a test that allows the vision of oesophagus, stomach, duodenum (the first part of the small intestine). The lower gastrointestinal tract includes most of the small intestine(duodenum, Jejunum, ileum) and all of the large intestine (Cecum, Colon, Rectum, Anus)(see Figure 43).

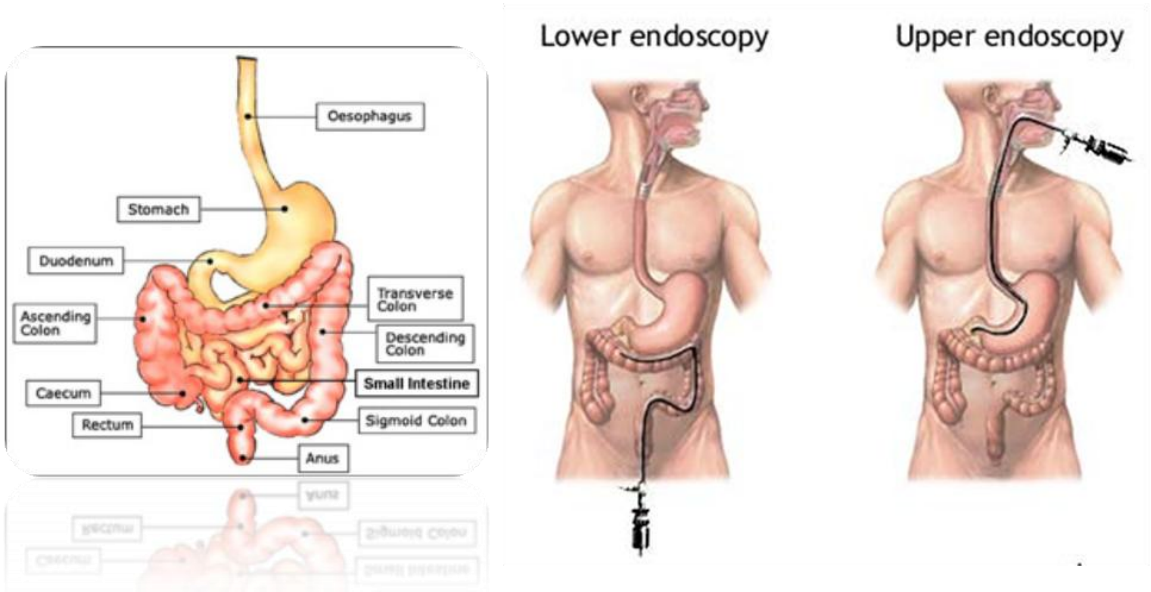


Figure 70 Gastrointestinal tract: anatomy and endoscopy

6.1.2 Ethiology and Pathophysiology

GI bleeding can be spontaneous (due to an underlying condition or disease) or surgical (due to a resection *of* tissue to treat a disease).Upper gastrointestinal (UGI) and lower gastrointestinal (LGI) spontaneous bleeding is a very common disorder which has many different causes.

Bleeding is generally severe and patients present to the Emergency Room and then undergo an endoscopy after resuscitation and stabilization.

GI bleeding can originate anywhere from the mouth to the anus and can be overt or occult. The manifestations depend on the location and rate of bleeding.

Hematemesis (65) is vomiting of red blood and indicates upper GI bleeding, usually from an arterial source or varix. Coffee-ground emesis is vomiting of dark brown, granular material that resembles coffee grounds. It results from upper GI bleeding that has slowed or stopped, with conversion of red Haemoglobin to brown haematin by gastric acid. Hematochezia is the passage of gross blood from the rectum and usually indicates lower GI bleeding but may result from vigorous upper GI bleeding with rapid transit of blood through the intestines. Melena is black, tarry stool and typically indicates upper GI bleeding, but bleeding from a source in the small bowel or right colon may also be the cause. About 100 to 200 ml of blood in the upper GI tract is required to cause melena, which may persist for several days after bleeding has ceased. Black stool that does not contain occult blood may result from ingestion of iron, bismuth, or various foods and should not be mistaken for melena.

GI bleeding is not a disease, but a symptom of a disease. GI bleedings can be characterized in two major groups: spontaneous bleedings and surgical bleedings.

There are many possible causes for spontaneous bleedings (Table 31), which are divided into upper GI (above the ligament of Treitz), lower GI, and small bowel. Bleeding of any cause is more likely, and potentially more severe, in patients with chronic liver disease (e.g., from alcohol abuse or chronic hepatitis), in those with hereditary coagulation disorders, or in those taking certain drugs.

Upper GI tract (70%)	Duodenal ulcer (20–30%)
	Gastric or duodenal erosions (20–30%)
	Varices (15–20%)
	Gastric ulcer (10–20%)
	Mallory-Weiss tear (5–10%)
	Erosive esophagitis (5–10%)
	Angioma (5–10%)
	Arteriovenous malformation (< 5%)
	Gastrointestinal stromal tumors
Lower GI tract (percentages vary with the age group sampled≈24%)	Anal fissures
	Angiodysplasia (vascular ectasia)
	Colitis: radiation, ischemic, infectious
	Colonic carcinoma
	Colonic polyps
	Diverticular disease
	Inflammatory bowel disease: ulcerative proctitis/colitis, Crohn's disease
	Internal haemorrhoids
Small-bowel lesions (rare)(5%)	Angiomas
	Arteriovenous malformations
	Meckel's diverticulum
	Tumors

Table 31 Main causes of spontaneous Gastrointestinal bleeding (66)

For surgical bleeding the main and fastest growing procedure is EMR (Endoscopic Mucosal Resection), which can be performed in the UGI (Barrett's oesophagus, early gastric cancer etc.) or LGI tract (flat adenomas, polyps etc.).

Upper gastrointestinal haemorrhage (UGIH)(67) is an urgent disease that is often encountered in daily medical practice. Endoscopic hemostasis is currently indispensable for the treatment of UGIH. Many methods of endoscopic hemostasis are in wide use, including hemoclip, injection and thermo-coagulation methods. Although UGIH develops from a wide variety of

diseases, such as oesophageal varices and gastric and duodenal ulcer, hemostasis is almost always possible. Identification of the causative diseases, primary treatment and characteristic features of endoscopic hemostasis are needed to allow appropriate treatment.

Gold standard therapies are available for hemostasis of ulcers and varices. Other causes of GI bleeding are generally treated with combination therapies. Surgical bleeding during an EMR is managed the same way as ulcer bleeding. Hemostasis is of critical importance during all surgical procedures. A fundamental principle of good surgical technique is minimization of blood loss, and gastroenterologists have a wide variety of agents and tools to aid them in this endeavour. Although used less frequently than simple electro cauterization, topical haemostatic agents are useful in minimizing blood loss and in turn surgical morbidity.

Ulcer bleeding is an arterial, spurting, difficult to manage type of haemorrhage where Floseal' s strong efficacy profile could make a difference and innovate endoscopic hemostasis management. Preclinical works confirmed this hypothesis(68); gelatin matrix hemostatic agents are considered to be very effective to control bleedings that occur during surgical operation.

6.2 Market Analysis

GI bleeds are a growing phenomenon and the incidence rate trend has been going up dramatically over the past decades. Epidemiologic data from Europe indicated an UGI annual incidence of 48 to 145 per 100.000 population in the 1960's and 1970's (69).Despite recent advances in the therapeutic approach, mortality associated with UGI bleeding remains significant at 5% to 11 %, and it is the highest in patients with liver disease and oesophageal or gastric varices (70). A list of possible intervention which allow the use of Floseal GI catheter is shown in Table 32. The data are taken from Italian[29] and American[30] database of hospital discharged in year 2005.

Description of the intervention	ICD9-CM	Discharged –Italy (2005)	Discharged –USA (2005)
Closed Biopsy Of Esophagus	42.24	206	654
Closed Gastric Biopsy	44.14	1142	956
Suture Peptic Ulcer Nos	44.40	233	*
Suture Gastric Ulcer Site	44.41	1143	4.051
Suture Duodenal Ulcer Site	44.42	1287	7.701
Endosc Control Gast Hemorag	44.43	2651	46.263
Transcath Embo Gast Hem	44.44	89	334
Other Control Gast. Hem.	44.49	107	211
Proctosigmoidosc Thru natural orifice	48.22	7	*
Closed Rectal Biopsy	48.24	702	11.904
Radical Electrocoag-Rectal Lesion	48.31	103	*
Other Electrocoag Rect Les	48.32	90	499
Laser Destruc Rectal Les	48.33	103	*
Cryosurg Destruction Rect Les	48.34	9	*
Local Excision Rectal Lesion	48.35	1504	2.587
Polypectomy Of Rectum	48.36	986	6.575
TOTAL		10362	81736

[29] http://www.salute.gov.it/ricoveriOspedalieri/ric_informazioni/sceltaint.jsp

[30] http://hcupnet.ahrq.gov/HCUPnet.jsp?Id=FCB06E8AF5B3E88A&Form=SelDXPR&JS=Y&Action=%3E%3ENext%3E%3E&_DXPR=PR1

Table 32 Comparison of principal DRG (*Diagnosis Related Groups*) for Floseal GI Catheter application between Italy and Usa 2005

6.3 State of the art: Commercial systems and therapies

The aim of Floseal GI Catheter is to introduce and apply an Haemostatic matrix (Floseal) which is the gold standard in the field of surgical Hemostasis.

Endoscopic therapy (71) can be broadly categorized into injection therapy, thermal coagulation, and mechanical hemostasis. When analyzed separately, injection therapy, thermal-contact devices, and laser treatment all decrease the frequency of recurrent bleeding and rate of surgical intervention.

Mechanical method	Injection method	Thermo-coagulation	Hemostyptic sprays
Hemoclip	Ethanol	APC	Thrombin
Balloon tamponade	Epinephrine	Heater prove	Sodium alginate
Ligation (EVL, detachable snare)	Monoethanolamine oleate	Hemostatic forceps	Fibrin glue
Polymer	Polidocanol	Microwaves	
	N-butyl-2-cyanoacrylate	Laser (Nd-YAG, diode)	

Table 33 Summary of methods of endoscopic hemostasis

Clips, cauterization, APC, and injection therapy have been useful with good efficacy. Using principles established by these tools future devices may better address current limitations by enhancing tissue capture and providing greater compressive forces. Several novel endoscopic devices are under development may lead to improved endoscopic outcomes. These include memory clips, flexible suturing devices, high compression cauterization, injectable polymers and telecommunicating biosensors(72).

Below there is a description of each concurrent device and also of alternative diagnostic techniques for post operative diagnosis of abdominal surgery complications.

6.3.1 Endoscopic injection needles

Endoscopic sclerotherapy, a well-established treatment for bleeding GI varices, accomplishes vascular obliteration by injection of a sclerosing agent. Sclerosants are tissue irritants that cause vascular thrombosis and endothelial damage, leading to endofibrosis and vascular obliteration when injected into or adjacent to blood vessels. To control bleeding from a varix, a sclerosant is dispensed with a sclerotherapy needle passed through the working channel of an endoscope. Sclerotherapy needles consist of an outer plastic sheath and an inner core channel attached to a needle at the tip. The conventional sclerosants, ethanolamine oleate, polidocanol, sodium tetradecyl sulfate, sodium morrhuate, and absolute alcohol, are indicated for acute endoscopic hemostasis and elective obliteration of bleeding esophageal varices. They have also been used alone or in combination with ligation or cyanoacrylate for the treatment of bleeding esophageal or junctional (esophagogastric) varices. The sclerosants are not indicated for primary prophylactic treatment of varices that have not bled.

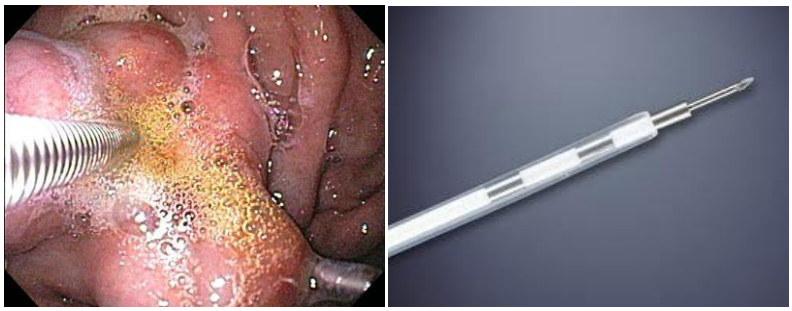


Figure 71 Injection needle hemostasis

The use of sclerosants (including absolute alcohol) in injection therapy (Figure 71) for bleeding ulcers should, however, be discouraged: extensive and uncontrolled tissue necrosis caused by sclerosants injected to the ulcer base can result in ulcer perforation and complications relating to adjacent tissues.

EUS (Endoscopic Ultrasound) directed polymer injection may allow temporary hemostasis in massive haemorrhage when visualization is not possible. Thermo-sensitive reverse phase polymers rapidly transform from a liquid into a gel-plug at body temperature. This new endoscopic method of temporary hemostasis does not require direct visualization of the bleeding site and may provide more time for thorough endoscopic evaluation and definitive treatment.

6.3.2 Thermo coagulation

Thermal devices can be divided into contact (heater probe, monopolar and bipolar electro coagulation) and noncontact types (Figure 72,laser treatment, argon plasma coagulation [APC]). Heating leads to edema, coagulation of tissue protein, and contraction of vessels, resulting in a haemostatic bond.

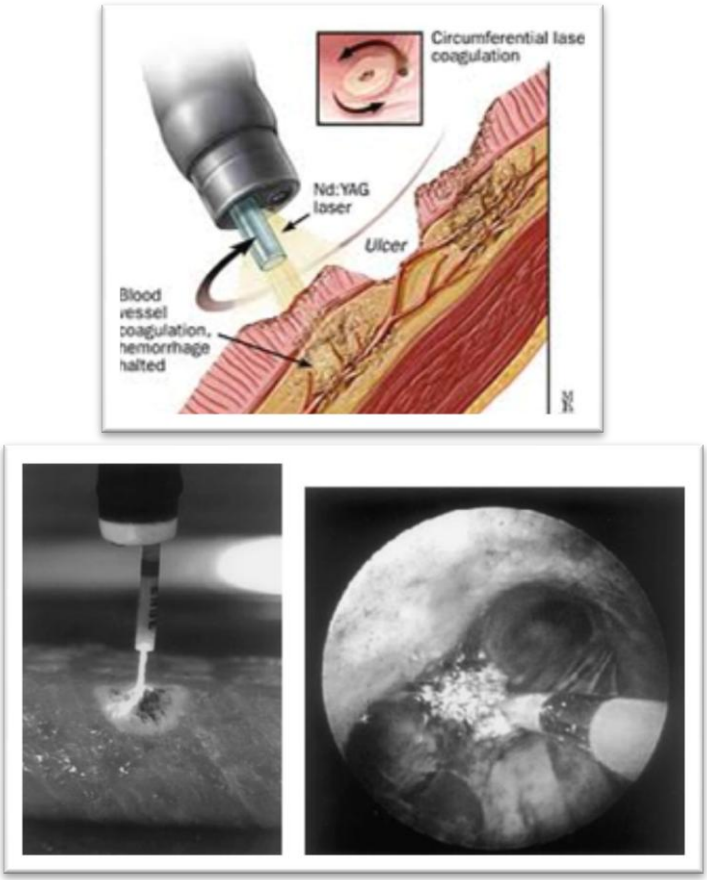


Figure 72 Laser hemostasis (YAG) on the left; Argon Plasma hemostasis (right)

While the haemostatic effects of contact probes are well established by clinical trials, the use of APC in the treatment of peptic ulcer bleeding has only recently been reported. There has been only one randomized, controlled study comparing APC with heater-probe coagulation, and it suggested that APC is equally as safe and effective (73).

Tissue coagulation requires a temperature of approximately 70˚C. Repeated application of these devices can result in the build-up of coagulum at the tip, which can impede conductivity and necessitates removal of the probe and cleaning the tip (74).

Another flexible (75) device under development for hemostasis are high compression endoscopic bipolar forceps. Insulation between conductive plates and jaws prevent radiation of heat and allow for trans-endoscopic sealing of large blood vessels. Applicable to future natural orifice surgery, this device may prove useful for advanced intraluminal procedures.

6.3.3 Mechanical Devices

Mechanical devices have been used for the treatment of variceal haemorrhage (71), but rarely in the treatment of peptic ulcer disease. Hemoclips (Figure 73) have gained popularity in the past few years. The deployment of hemoclips on fibrotic ulcer floors can be difficult, however, particularly when they are used tangentially or with the endoscope in a retroflexed position.

The efficacy of hemoclips seems to be limited by difficulty of successful application. With improvements in design, this technical problem might be overcome. More studies are required to give a fair verdict on the effectiveness of hemoclips.

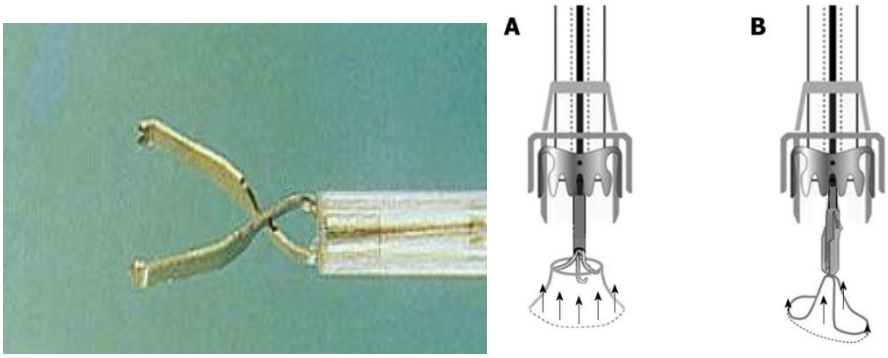


Figure 73 Endoclips

Nitinol clips like OTSC are the newer device for hemostasis of non-variceal bleeding(76). These are cut by electrical discharge machining and are mounted in a loaded position on the endoscope tip. They capture large amounts of tissue and achieve compression with serosal apposition.
Other developments have lead to flexible sewing(75) tools. This device has 4 degrees of freedom with articulating jaws that pass a barbed one-way locking suture preventing tissue from moving retrograde once acquired. This trans-oral device could find clinical application for hemostasis and closure of perforated ulcers.

6.3.4 Combined Therapy

The benefit of combination therapy has been evaluated in many trials (77) .

In (73) patients with actively bleeding peptic ulcers, ulcers with adherent clots, or ulcers with no bleeding visible vessels were randomly assigned to epinephrine injection plus heat probe coagulation or epinephrine injection plus argon plasma coagulation. The primary outcome measure was recurrence of bleeding. Secondary outcome measures were initial hemostasis, endoscopic procedure duration, number of patients requiring surgery, mortality within 30 days, and ulcer status at 8 week follow-up endoscopy. Epinephrine injection plus argon plasma coagulation is as safe and effective as epinephrine injection plus heat probe coagulation in the treatment of patients with high-risk bleeding peptic ulcers.

Currently, the standard therapy most widely used is injection with diluted epinephrine, followed by thermo coagulation with a 3.2 mm heater probe.

6.3.5 Hemostyptic sprays

Preparations containing collagen play a prominent role among local hemostyptic agents in surgery (78). The combined application of a sheet of collagen with fibrin glue improved local hemostasis to a great extent. Large areas of capillary bleeding can be treated successfully with this method. Despite the very good results, this method has not been applied on a broad scale. This is due to the necessary skill and experience and the relatively cumbersome preparation required at the operation site.

6.3.6 Analysis of competitors features

Following (Table 34) there is a comparison of prices between the main competitor techniques of the Floseal GI cath. even if due to the variety of treatment modalities, often combined, it is very difficult to estimate an average cost of treatment.

Product	Price (€)	Companies
Endoscopic injection needle cath	40-60 (disposable cath.)	Olympus[31] TeleMed Systems[32] Boston Scientific[33]
Electrosurgical haemostatic devices	200-300 (disposable)	Olympus[34] ConMed [35] Cook Medical[36]
Endoscopic clip fixing devices	100-200	Olympus[37] Boston Scientific[38] Ovesco[39]
Floseal GI cath.	50	MicroTech

Table 34 Analysis of competitors: market evaluation

In Table 35 there is a comparison ((79) (74)) between the main features of concurrent devices and system for the treatment of peptic ulcer disease.

System / Evaluation parameter	Injection therapy	Thermo coagulation	Clips	Hemostyptic sprays	Floseal GI cath. (results of first trials)
Good Initial hemostasis[40]	xx	xxx	xx	xxx	x
Difficult Maintaining of front view			xxx	x	
Risk of perforation	xxx	xx	xx		
Rate of recurrent bleeding	xxx	xxx	xx		
Requirement for emergency surgery	xx	xx	xx		
Mortality within 30 days		xx	xx		
Ulcer status at 8 week follow-up endoscopy	x	x	x		
Length of hospital stay		x	x		
Transfusion requirements		xx	x		
Ease of use	xx	xx	x		xxx
Hazard		xxx			

Table 35 Analysis of competitors: comparison of main feature (x=low, xx=medium, xxx=high).

[31] http://objects.olympus-europa.com/endo/documents/injector_force_max.pdf
[32] http://www.telemedsystems.com/sclerotherapy_needles.htm
[33]http://www.bostonscientific.com/Device.bsci?page=HCP_Overview&navRelId=1000.1003&method=DevDetailHCP&id=10074442&pageDisclaimer=Disclaimer.ProductPage
[34] http://www.olympuskeymed.com/index.cfm/page/products.index.cfm/id/754/navid/754/parentid/752
[35] http://www.conmed.com/EndoTech_SuperConductor.php
[36] http://www.cookmedical.com/esc/dataSheet.do?id=698
[37] http://www.olympusamerica.com/presspass/press_pass_cut/documents/QuickClip2%20Long%20brochure.pdf
[38] http://www.cookmedical.com/esc/dataSheet.do?id=700
[39] http://www.ovesco.com/
[40] endoscopically verified cessation of bleeding for at least 5 minutes after the first endoscopic treatment

All of the current standard treatments for endoscopic hemostasis, although effective to a certain extent, have some relevant drawbacks and limitations:

- Failure rate (intra-op or delayed re-bleeding is very common)
- Necessity to do open surgery in case of persisting untreatable haemorrhage (e.g. gastrectomy)
- Not easy to adopt (injection therapy, ligation etc. may turn out to be difficult due to lack of viable tissue, poor vision through the endoscope in the blood, application of devices on the scope)
- Safety (tissue damage).
- Floseal, if used with appropriate delivery devices which allow easy and fast application through a scope, have the potential to perform hemostasis and bleeding prophylaxis in an effective, safe and innovative way in GI endoscopy.

Recently in parallel with the development of the Floseal GI cath. a new similar device has been designed and an in vivo animal study has been deployed (80). This device (Figure 74) is a catheter of 2mm in diameter and length 1350mm.It can be used only with gastroscope, while the Floseal GI cath. can be used in colonscope too (see 6.5). From these first in vivo tests , it is easy to understand that the original IFU of Floseal are not followed. In fact they use 5 ml of thrombin (instead of the indicated 4) and saline solution to help the extrusion of the hemostatic agent into the channel. The hemostatic efficiency results invalidated; in fact the quantity of Floseal they have to use (from 1 to 4 doses of 2,5 cc each), in order to achieve some reasonable results, is much higher than the maximum four applications of 0.5cc of the Floseal GI cath. (indications from a validation protocol of Doc. Spera). Moreover the cost of each package of Floseal is very high and the healthcare system recommend a wise use of the hemostatic drug.

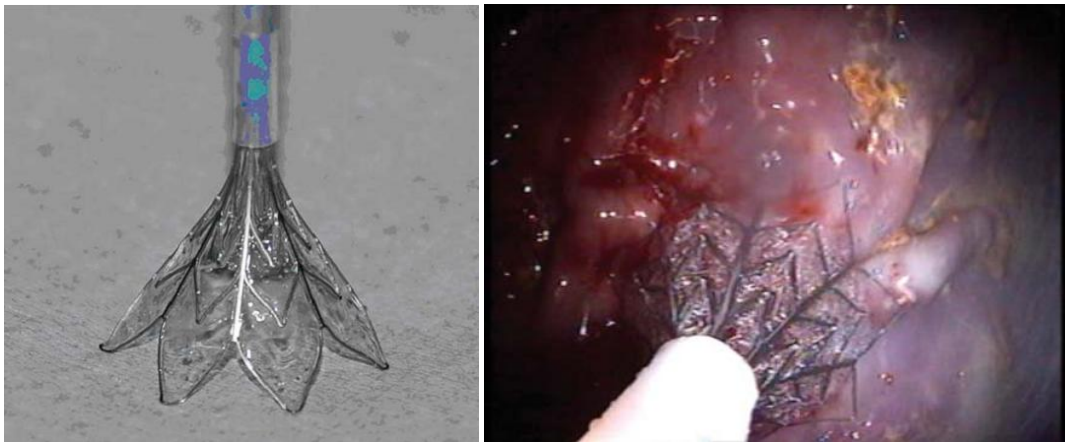


Figure 74 Floseal endoscopic applicator by Maslanka

6.4 Intellectual property

The Floseal GI Cath. is the development of a patented idea (81) of a “Gastrointestinal applicator and Method of using the same”. The patent is related to methods and apparatuses for applying therapeutic compositions having viscosities too large to be pushed through an entire length of a relatively long and thin catheter, such as one configured to reach the inside a person's gastrointestinal track.

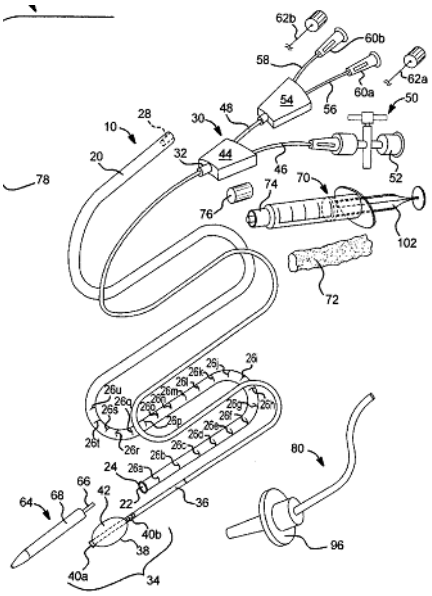


Figure 75 Patent principal drawing

One of the claim regarding the catheter is the 10th:

"A medical catheter assembly comprising: an outer tube having a proximal end and a distal end; and a balloon catheter located within the outer tube, the balloon catheter moveable within the outer tube so as to create an open space within the outer tube at the distal end thereof, the open space sized to hold a composition configured to be applied to an internal wound site of a mammalian body in an amount sufficient to cover the wound site; and an applicator configured to seal to a distal end of the outer tube to deliver the composition to the open space."

6.4.1 Accessory device: Floseal Matrix

Floseal Matrix [41]consists of a bovine-derived Gelatine Matrix component mixed with a human-derived Thrombin component. Floseal Matrix is indicated in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

The device is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis. It is effective on surgical bleeding, from oozing to spurting, and is not intended to be used as a prophylactic haemostatic agent.

Floseal is the gold standard in the field of haemostatic agents; it is proven(82) to stop bleeding in two minutes (median time to hemostasis) in patients undergoing cardiac, vascular, or spinal/orthopedic surgery. A prospective, randomized, controlled, multi-centre, multi-specialty study was conducted using a formulation of Floseal Matrix containing bovine thrombin. Patients were randomized only after it was determined that the bleeding could not be controlled using conventional approaches (e.g. direct pressure, sutures and/or cauterization) because of their ineffectiveness or impracticality. Success at achieving hemostasis was defined a cessation of bleeding within 10 minutes following application of the agent. The primary endpoint was hemostasis success for the first treated bleeding site. A

[41] Baxter Biosurgery

secondary endpoint was time to hemostasis for the first treated bleeding site. Although multiple bleeding sites in the same patient were treated, only the first treated bleeding site was used to determine primary effectiveness, as this was the only site that was truly randomized.

The Floseal Mechanism of Action is the Biophysical Hemostasis:

- It is applied to the tissue surface at the base of the lesion. Its granules fill the wound and conform to its shape
- the granules expand approximately 20% within 10 minutes and physically restrict the flow of blood. Blood percolates through the spaces and is exposed to thrombin
- A clot forms around the mechanically stable matrix provided by the granules. The structural integrity of the gelatin fibrin matrix enables it to remain in place at the tissue surface
- Floseal granules not incorporated in the clot can and should be removed with gentle irrigation without disrupting the hemostatic seal
- FLOSEAL is resorbed by the body within 6–8 weeks, consistent with the time frame of normal wound healing.

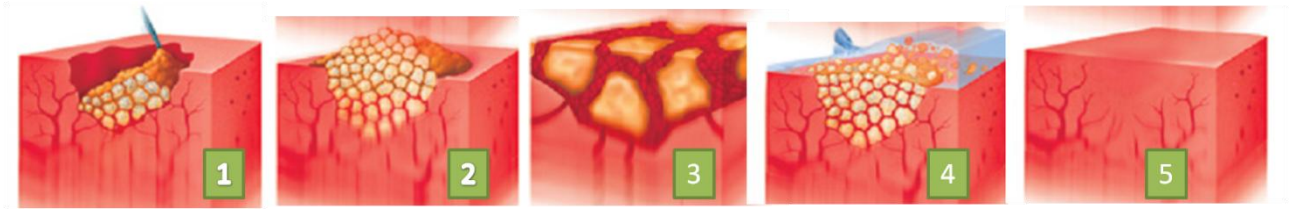


Figure 76 Floseal action

A gauze sponge must be applied to approximate the Floseal Matrix against the bleeding surface, conforming it to the lesion. In the case of the Floseal GI cath. the gauzes are represented by the balloon because it is not possible to introduce gauzes in gastroscopic procedures.

6.5 Design History

6.5.1 Initial Specification

A reverse engineering process on a "0" prototype provided to MicroTech by Baxter and specification extrapolated from the analysis of the patent N. US 0106213- "Gastrointestinal applicator and method of using same"- of Baxter int., which authors are Prof. Spera and Doc. Ariano, created the design of Floseal CS GI cath. device. The device has been designed to release haemostatic drug (Floseal) in the cavity of the gastrointestinal tract. The prototype had following characteristics:

- Primary corpus: catheter with distal latex balloon in part and luer proximal access
- Plastic tubular oversheath (Teflon)
- Cover

- Syringe to inflate balloon
- Haemostatic valve
- Syringe for Floseal.

At first the Floseal dosage to inject was equal to 2 cc, for every delivery, for a total of two extrusions.

First of all dimensional restraints of catheter have been fixed. Passing by operative channel of a gastroscope or colonscope, a first market survey about these last devices has been made to identify lengths and dimensions of the operative channels.

Company	Gastroscopes (operative channel)		Colonscopes (operative channel)	
	Lenght (m)	Diameter (mm)	Lenght(m)	Diameter (mm)
Olympus	1.1	2-2.8	1.3-1.7-2.4	2.8-3.2-3.7
Pentax	1.5	2-2.4-2.8-3.8	1.3-1.5-1.7	2.8-3.8-4.2
Storz	1.1	2.2-2.8-3.8-4.2	2.2	2.8

Table 36 Commercial scopes features

It has been made a survey among endoscopists to have a further indication about lengths and possible versions of the device to make available.

Surgeon	Spera[42], Cipolletta[43]	Repici[44]	Occhipinti[45]	Zambelli[46]	De Pretis[47]
Indications	Two versions for gastric and colonscopic procedures	One version	One version	One version	One version
Lenght(m)	1.80 e 2.40	1.80	1.80	2.10	2.10

Table 37 Survey on possible length device

For most of surgeon the gage length is 2.10m both for gastro applications and colon; some of them think that an excessive length of the catheter could make more difficult the procedure, beyond the fact that most of bleedings is in the superior gastrointestinal tract (in which lengths of 1.60m would be sufficient).

6.5.2 Underlined problems

The main complication to exceed during the design of device is the hard extrusion of the haemostatic fluid. Due to its viscosity, administration of Floseal, through a device that fits

[42] A.O.Gemelli, Roma
[43] Presidio Ospedaliero "Maresca" di Torre del Greco, Napoli
[44] A.O. HUMANITAS, Rozzano
[45] A.O. Crema
[46] Ospedale civile Trento
[47] Ospedale S.Maria del Carmine, Rovereto

working channels of therapeutic and diagnostic scopes, is only possible if the distal end of a catheter is preloaded.

Increases in the viscosity(83) of a fluid causes increases in the maximum pressure required during passage in a catheter. This can be explained by increased resistance in the catheter, as represented by Equation 12:

$$R = \frac{128\eta L}{\pi * d^4}$$

Equation 12 Fluid resistance in a catheter

This equation was derived from Hagen–Poiseuille's law (Equation 13):

$$\Delta P = 128\eta LQ/\pi d^4$$

Equation 13 Poiseuille law

where: ΔP is the pressure drop, L is the length of the tube, η is the dynamic viscosity, Q is the volumetric flow rate, d is the diameter, and π is the mathematical constant. As electricity was originally understood to be a kind of fluid, this hydraulic analogy is still conceptually useful. Then Hagen–Poiseuille's law corresponds to Ohm's law for electrical circuits (V = IR), where the pressure drop (ΔP) is analogous to the voltage (V), and the voluminal flow rate (Q) is analogous to the current (I). The resistance, then, is represented by Equation 12. Although Floseal is a suspension (ie, not completely homogeneous) and the flow may not be steady, the Hagen–Poiseuille equation was used for simplification. This means that the resistance (R) is proportional to the viscosity of the Floseal (η) and the length of the catheter (L), and is in inverse proportion to the inner diameter of catheter (d) raised to the fourth power. Lower fluid viscosity (η) can result in easier injection which can also be influenced by its temperature and dilution ratio, and the concentration of particles. Microcatheters with shorter lengths (L) and larger inner diameters (radius [a]) are recommended for easier injection, but this is not the case of Floseal GI cath. because it has to be inserted in a scope working channel .

The most probable causes for a weak pushability, analyzed after the production and test on prototypes of different type (see Annex VIII), divide themselves between the high friction to interface of oversheath-catheter and a weak thrust of fluid. Analyzing with greater detail, the efficiency absence of some of first prototypes can be given to:

- Floseal seeping
    - Friction between external sheath and catheter
    - Friction between balloon and external sheath
    - Sheath material
    - Balloon material
    - Catheter material
    - Dimensions gap between internal and external catheters
    - Balloon folding in the subsequent deliveries

- Buckling
    - Shape of the tip
    - Tip dimensions
    - Catheter and sheath length
    - Material and dimensions of metal guide-wire
- Required dosage of Floseal
- Fluid rheology linked to conservation temperature.

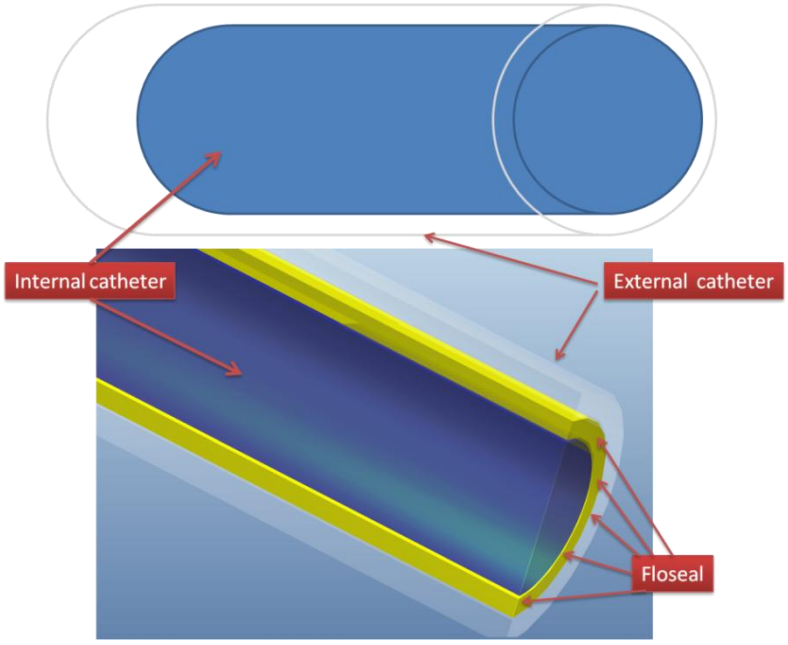


Figure 77 Floseal lateral infiltration

In order to reduce the friction between the lateral surfaces of sheath and catheter caused by sliding, different hypothesis and system configuration have been analyzed.

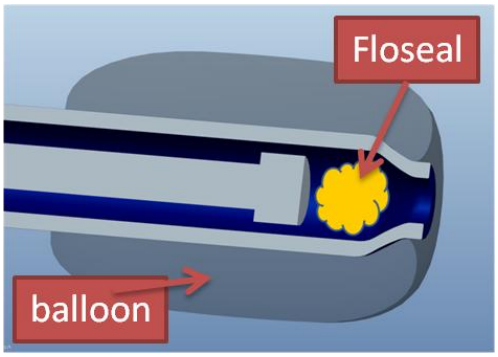


Figure 78 A possible solution to avoid friction between balloon Floseal and sheath

In the solution in Figure 78, a further catheter, in the blue one, has been used to realize the thrust of Floseal avoiding the friction between balloon, Floseal and oversheath. This solution was more expensive because of the additional micro-catheter, less effective, for the fact that the lumen available for the Floseal had a very inferior volume. More applications of the drug would be necessary, because the diameter of tip of micro-catheter was of 1mm and the

efficiency of the thrust would be so certainly weak, thus this configuration has been dismissed.

Another important characteristic to be considered is the material of different components that, in spite of it has characteristics of biocompatibility and safety, it must guarantee the correct working of the device.

With regard to oversheath, surface sliding has a particular importance. Teflon is one of plastic materials with less surface friction. Making tests with sheath of this kind of material, extrusion of fluid is favorite. The only PTFE(Teflon) hitch is economic; it is quite difficult to extrude micro catheters in this material, due to its high viscosity when molten. Moreover Teflon is a material with lowest adhesive properties, so it is hard to paste it to others materials. In the device considered, a Teflon tract would have pasted to a luer connector in PVC. A three layer material with surface low friction strata is preferred (see 6.5.4).

The material of the balloon, in the initial prototype of Baxter, is latex, inactivity material in the sector because it could create allergy in particular subjects. Actually that material has surface characteristics of friction better than materials now in business for the fabrication of balloons; in agreement with supplier, it has been chosen a material which can offer the right compromise between workability (extrusion) and low surface friction, a synthetic polyisoprene. As well, the particular balloon setup could cause difficulties in the extrusion of the fluid, especially in the second delivery, in case of missed return to zero of the balloon after the first inflation.

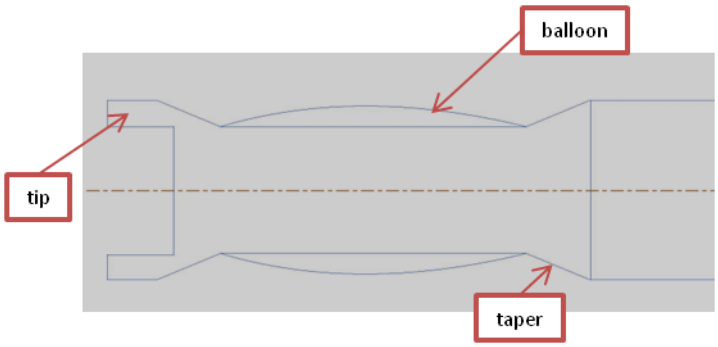


Figure 79 Setup balloon image

Another solution to be considered has been to lower the diameter of the balloon to be not in contact with sheath, but the particular setup would have been still more difficult.

We tried to accent the inclination of the only one taper (Figure 79) corresponding to ligature of the balloon, or to increase the length of taper, to allow that the balloon in pause does not extend the diameter of catheter (obviously from both extremities of the balloon) but, during the phase of prototyping, for a mechanical matter, the tube cannot be tapered more than that obtained with the first prototyping.

Maybe the material of the catheter is the least important to lower the total friction but also this element could invalidate the quality of relative movement among parts. Consideration made before for the sheath about Teflon, also are worth for the catheter. An option can be a micro milling to lower the effective of contact, thus augmenting the sliding between catheter and sheath (in Figure 80 see the cause of a bad sliding between surfaces); but this idea has not been investigated till now. For the material chosen during the prototyping, refer to 6.5.4.

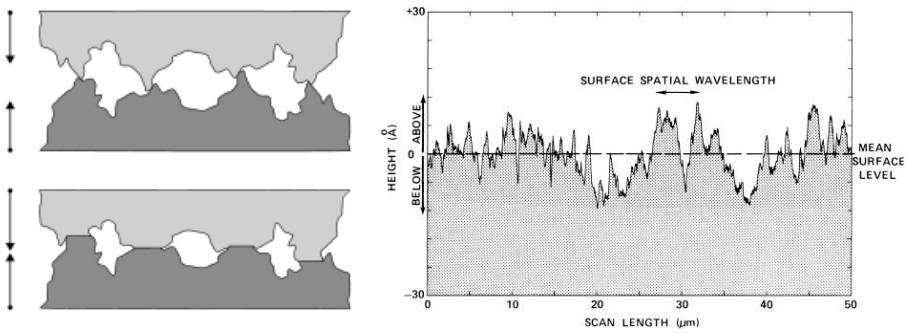


Figure 80 Expanded roughness

Another instability cause in the extrusion is the instability of buckling. Buckling is a stress of pressure applied to the head of a pivot. It is practically impossible that pivot is stressed by this pressure with a normal pure stress; the stress will be probably a force applied to distance from the barycentre axis and this creates a bending moment. For the device in question, stress is represented by the resistance of the volume of fluid to be pushed.

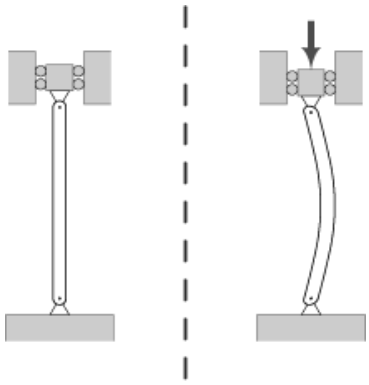


Figure 81 Image of buckling applied to our cat

To protect oneself from this phenomenon, it is important to forecast the project loadings and the stressed actions in a correct way, modifying the parameters of the project. For example:

- Reducing the pressure
- Lowering the eccentricity of loading
- Increasing the cross sectional area
- Reducing the length of the object
- Adding restraints with other near axis or with the ground
- Reducing the free deflection length of the beam.

The only way to reduce this effect in the catheter is to increase the surface of the tip and make it as flat as possible because the pushing force is transmitted in the best way without dispersion on the borders due to tangential force component (see Figure 82).

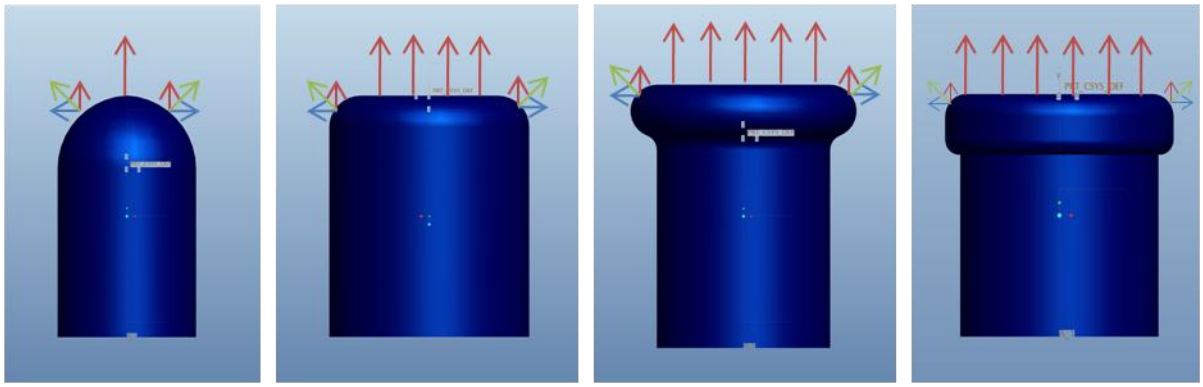


Figure 82 Pushing force distribution on different shape for the tip of the catheter

Different made tests show the tip as a crucial element for the push. Tips with different diameter and shape have been taken as prototype and soldered in the distal part of the catheter for thermoplastic fusion. Some different tests (Annex IX) have been made with modified pits (Figure 83) and the concavity of pit is very important; it must be dimensionally calibrated with the whole lumen of the sheath. In fact the diameter which, from the tests, is right for an ideal extrusion of Floseal, is equivalent to 1.9 mm.

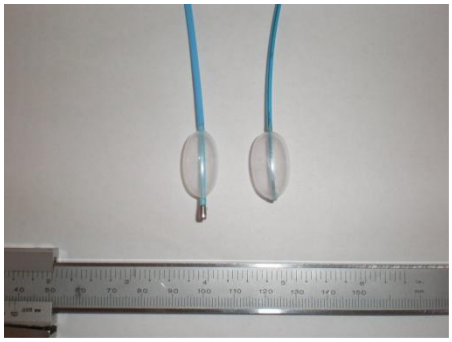


Figure 83 Metallic tip

Besides of the dimensions of the tip, the gap between external diameter of the catheter and internal diameter of the sheath is important. It is important to keep a least difference to avoid that an excessive quantity of haemostatic fluid seeps and creates a very viscous layer between the two main components of the device. It is necessary not to exceed a determined limit for the external diameter of the catheter (1.63mm) because of the thickness of balloon and its particular setup. It could be only increased in the proximal part but this would involve a further working.

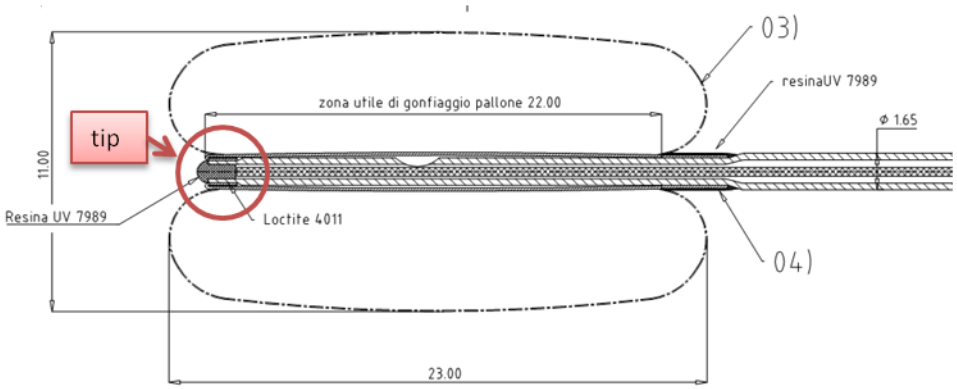


Figure 84 Inflated balloon Drawing

It is important to consider that the shape of the tip (Figure 84 and Figure 82) must be a-traumatic to avoid damaging to the tissue during the use.

Another possible cause of ineffectiveness in the thrust of the haemostatic is the shape, dimensions and material of metallic mandrel which is in the internal part of the balloon catheter. However it must be quiet flexible to play up the catheter in the bend made by gastroscope and anatomic ones; Hence, a right compromise between flexibility and rigidity, so a capacity of thrust is necessary.

In the first prototypes of the device, the mandrel, a medical metallic wire in AISI 304 o 316, was too short or slim (see Annex VIII for the different prototypes manufactured). Because the internal lumen of the blue catheter with balloon has an inferior diameter in the distal part, it is necessary to have a mandrel with a different diameter which can reach the tip. Several trials have been made to get the ultimate stage. At the beginning a 0.4mm wire has been bent in two parts, so one length was about 70cm and the other the entire length of the catheter. This solution was not very functional to thrust; even if for a length of 70cm the section was nominally doubled, with two of 0.4mm wires, their contribution to the “Pushability” of the catheter was bit superior than that of only one with the same diameter.

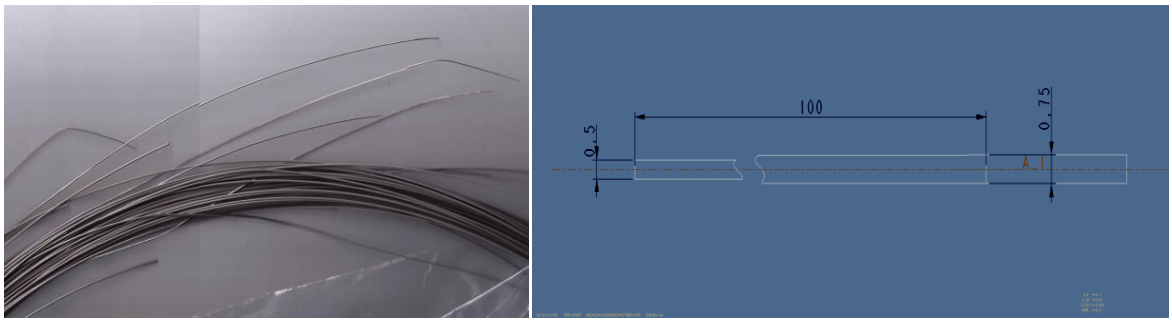


Figure 85 Welded mandrel particular (left); drawing of a tapered mandrel (right)

Successively guide-wires made up of two metallic wires have been created; in proximal and distal part there are different diameter wires (match proximal/distal part in mm: 0.8/0.5, 0.75/0.55, 0.6/0.4 o 0.4/0.3) welded with laser (Figure 85). Actually, this solution has taken an improvement in the extrusion of fluid but the technology of laser welding is expensive and hardly available for medical applications . Furthermore the welding was often not very resistant, already in the phases of prototypes assembly. The welded joint is very fragile, in fact from the SEM analysis in the welded zone (Figure 86) there is a very deep crack probably caused by formation of martensite.

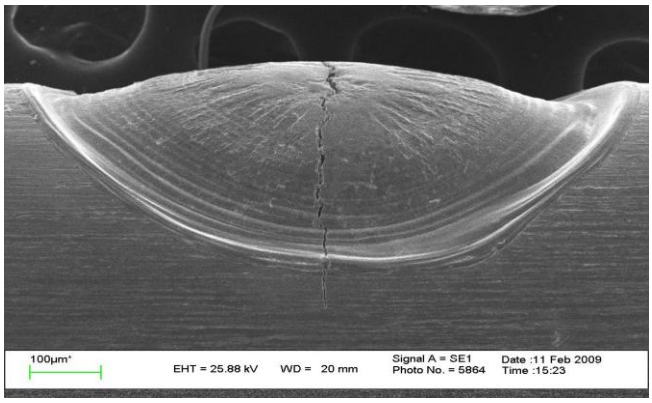


Figure 86 SEM analysis (scanning electron microscope) welded zone mandrel welding

Contextually the possibility to use metallic mandrel tapered in tip has been considered, but the sharpening of the tip is an expansive and hardly available process of production. If we consider a taper reduction equal to (see Figure 85, right)

$$\frac{1}{k} = \frac{0.75 - 0.5}{100} = 0.0025$$

Equation 14 Taper reduction

the price of 30 pieces of mandrel (smallest number of prototypes) is about 1600 euro (to make matrixes for rotary swaging which realizes plastic deformation of a 0.75mm AISI 304 annealed wire. The annealing process consist of :

1. An heating process with temperature major than the one in the critical range
2. Permanency at that temperature for an appropriate time,
3. Final cooling at ambient temperature; more or less rapid to allow a major cold workability, removing any possible internal tension.

The final prototype has a solution similar to first one considered: only one 0.50mm diameter wire, bent in two. In this solution two wires are twisted for a length equal to 2120mm, starting from the proximal part and in the distal part there is only one

The problem of hard friction and the following extrusion of the fluid could be partially overcome using silicone lubricants, nowadays used in gastroenterology, or physiological saline.

Actually, after several trials and prototyping, also on different batches of Floseal, some anomalies has been found, also with the same initial geometrical and physical conditions. If the haemostatic fluid is kept under 4°C temperature, it is much more granular and less liquid and as a result, its extrusion is invalidated. The important indication about the preservation of the fluid has been introduced in IFU (instruction of use), even if it was already present in the Floseal package. Also the time of use is very important (given by American producer): the thrombin takes at least 10 minutes to hydrate itself.

Besides, after consultancies with Doctor Spera, we got to a more detailed clinical algorithm which provides an inserting of following quantities of Floseal of 0.5 cc (against the initial ones of 2 cc); this change of quantities simplifies the problem of the seeping making the extrusion easier.

The introduction of haemostatic valve was very difficult, so, for augmenting device effectiveness, the rounding (Figure 87 option 2), previously considered necessary for the atraumatic of the catheter, has been removed, to get an entrance for the metallic cylinder of the valve as easy as possible (number 1, Figure 87). Safety was not invalidated also with a distal cut sheath, because the introduction of the catheter would be gradual and even if this does not happen, the traumatic tip is irrelevant in this case.

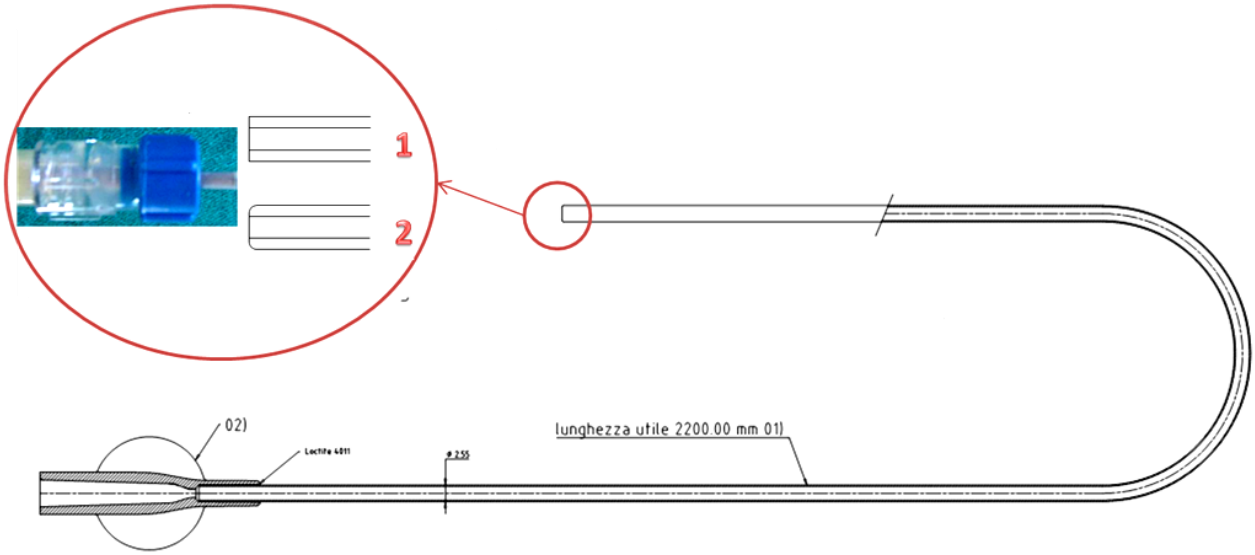


Figure 87 Enlarged image of the tip of the oversheath and connection to haemostatic valve

A pebbled grip for better catching the catheter has been considered but never realized because less pushing force is now needed due to the reduction in Floseal dosage.

6.5.3 Connections

Floseal GI catheter has several connections:

- Non-return valve for pump of balloon
- Haemostatic valve to connect Floseal syringe to distal part of sheath.

Both valves and cocks to pump and deflate the balloon were in the first prototypes; first solution was chosen for a better ease of use.

The two connections are provided with a Luer 6% mechanism. The Luer taper is a standardized system of small-scale fluid fittings used for making leak-free connections between a male-taper fitting and its mating female part on medical devices. Key features of Luer Taper connectors are defined in the ISO 594 standards.

Some black notches on sheaths have been introduced in the final phase of the device:

- One in distal part to indicate the shot of haemostatic valve
- One to indicate the introduction of 0.5 cc.

And a white notch on the blue catheter in the proximal part to indicate until where to shrink the catheter to 1 cc for the insertion of the sheath.

In any case, the device in question, was developed in a way that does not provide connections to other medical devices, in addition to the components present in the device itself.

6.5.4 Analysis of materials

In the following section some considerations about the choices made for the materials.

6.5.4.1 Balloon

Silicone, the main material in the balloon production for the medical, would be not suitable in the device considered; it must be as sliding as possible so it would be better to orient on:

- Polyurethane
- Latex
- Polyisoprene (synthetic latex).

Today Latex, as said in 3.3.2, is in disuse because of possible allergies of the personnel and of the patients. A polyurethane balloon is not so compliant, it shrivels up when it goes back to zero position. Floseal could penetrate and stick on it, so this solution hasn't been considered useful.

The material used is such a polyisoprene, a mixture between **Chemiton** and Tefabloc. Chemiton gives the right elongation about 700% (it should be at least 400%, because the balloon has to be inflated from 0 to 400cc), while Tefablock gives the right low friction properties.

6.5.4.2 External sheath

Oversheath material must be the right compromise not to invalidate the axial thrust (overstretch). The choice has been very difficult, due to the high viscosity of the Floseal. The right compromise between low friction and good extrudability has been a three layer material, an acetal resin Teflon loaded:

1. Ely2694 (thermoplastic polyamide elastomer, flexible without the addition of plasticizers)
2. 50%Ely+50%Hostaform
3. Hostaform (POM, polyoxymethylene, a thermoplastic material with good friction behavior)

A good solution would have been to use a cover in POM with PTFE, but it would not be easy to extrude for the chosen external manufacturer. Also coatings as parylene have been considered but, after the change of the dosage of Floseal, no further action has been necessary about the improvement of the sliding of the surfaces.

6.5.4.3 Catheter

From the analysis of the various tests done, friction is not the key issue in the choice of the material of the catheter, but it is very important its pushability and the avoidance of kinking (minimizing $Kflex$ and $Ktorq$, see 3.3.1).

Also in this case a three layer material has been chosen (from internal to external):

1. Ely2694
2. grilamidTR90+SdB+white
3. grilamidTR90+blue.

Grilamid is a stiff thermoplastic polyamide, it offers a high flexural fatigue strength, good to avoid unwanted lateral bending (kink) of the catheter.

6.5.4.4 Biocompatibility evaluation

Commonly, biocompatibility is a material's lack of interaction with living tissues by not being toxic, injurious, or physiologically reactive, and not causing immunological rejection: this is not restricted to the chemical/biological response, but also to energy interaction (mechanical, thermal, electromagnetic,….). Basically, it means that "the material can be used with an appropriate and predictable response in a specific device application without patient harm". It is important to underline that any material adopted is related with a specific application (time dependent). No single test may be sufficient to define biocompatibility: the same material can be perfect for a specific device/application, but not for a different one.

To minimize any potential hazards to the patients, it's essential that biocompatibility assessments be conducted for all materials which are used in a medical devices. That's why it's possible that multiple tests would be needed to determine the biocompatibility of the material.

In the ISO 10993-1 there is a flow chart (see Figure 54 in yellow circles Floseal GI cath. evaluation) which guides selecting the tests to evaluate the biological response to medical devices. Due to the novelty of some materials used in the device, it has been necessary to conduct all the tests listed in Table 22.In paragraph 6.6.3.3 and 6.6.3.4 there is the complete list of chemical and biological test made to prove biological compatibility of materials both of the device and of the packaging. The biological tests has been conducted by an external certified laboratory.

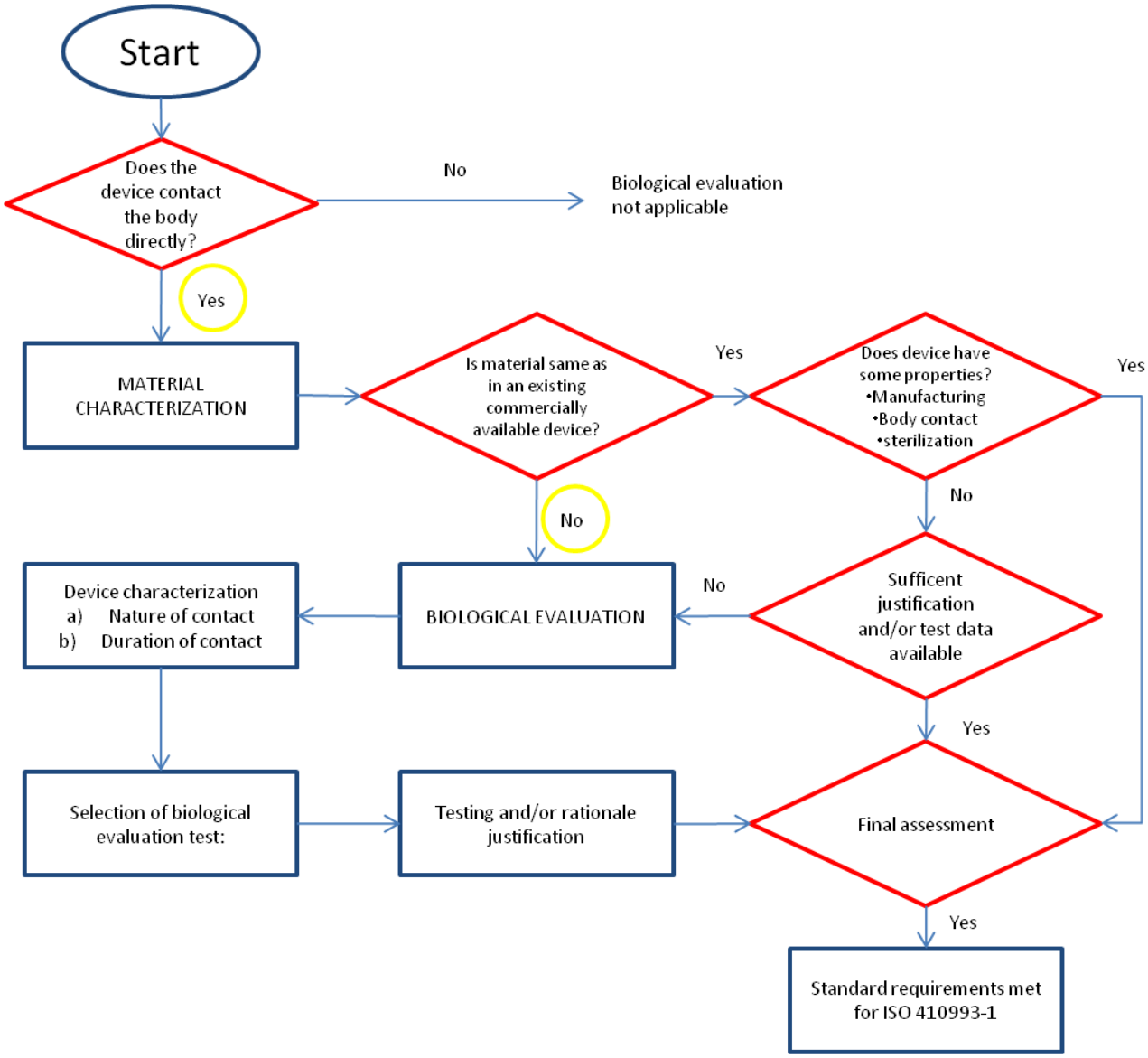


Figure 88 Annex B ISO 10993 Flow chart for the selection of toxicity tests

Device Categories			Biological Effect							
Nature of Body Contact		Contact duration A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reaction	System Toxivity (acute)	Sub-chronic toxicity (sub-acute)	Genotoxicity	implantation	Haemocompatibility
Surface devices	Skin	A	x	x	x					
		B	x	x	x					
		C	x	x	x					
	Mucosal membrane	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		

	Breached or compromised	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
External communicating devices	Blood path, indirect	A	x	x	x	x				x
		B	x	x	x	x				x
		C	x	x		x	x	x		x
	Tissue/bone/ dentin communicating	A	x	x	x					
		B	x	x				x	x	
		C	x	x				x	x	
	Circulating blood	A	x	x	x	x	.		.	x
		B	x	x	x	x		x		x
		C	x	x	x	x	x	x		x
Implant devices	Tissue/ bone	A	x	x	x		.	.	.	
		B	x	x				x	x	
		C	x	x				x	x	
	Blood	A	x	x	x	x	.	.	x	x
		B	x	x	x	x		x	x	x
		C	x	x	x	x	x	x	X	x

Table 38 ISO 10993-1 Biocompatibility Matrix

6.5.5 Final configuration and prototype

Several following versions and production of so many prototypes was necessary to get an efficient and safe version of device.

Floseal GI cath. final prototype has been manufactured by a company which applies the new quality standards and safety for the medical device sector (ISO13485, MDD 2007/47). The main characteristics of the final prototype, are the following:

- Catheter length: 2270mm
- Sheath length: 2200mm
- 1.2cc Luer female syringe
- 5 ml Balloon inflation syringe
- Storage device
- Haemostatic valve.

In Figure 61 the 3D drawing of all the components of the device is reported.

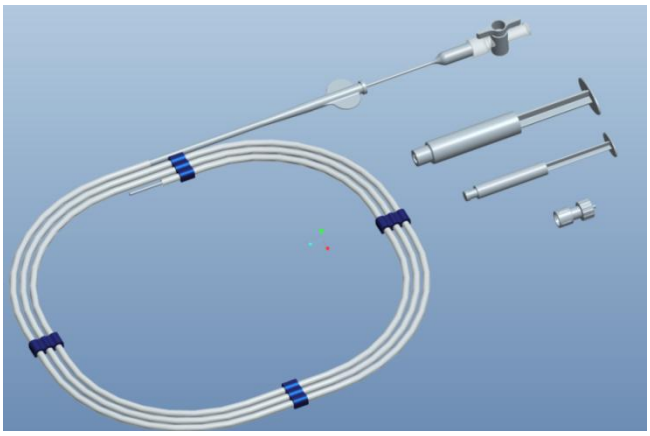


Figure 89 Drawing of final prototype of Floseal GI cath.

A detailed description of the components used in the production of medical device Floseal GI cath., complete with technical drawings and specifications for materials, has been reported in Table 39 and in the technical file.

Denomination	Material
External sheat	E2694-(50%Ely+50%Hostaform)-Hostaform
luer lock 2.65 transp.	ABS Terlux
balloon	50% chemiton+50%tefablock
tying wire for bonding	Nylon
catheter tube	Ely2694-(GrilamidTR90+SdB+white)-Grilamid TR90+blue
guide wire	AISI 316
luer lock 1.75 blue transp.	ABS Terlux +blue
one way valve	various
haemostatic valve 7 Fr.	various
valve tube	AISI 316
valve tube reducer	Grilamid E2694
syringe 5cc	various
syringe 1.2cc	various
dispenser tube	eraclene BC82-bynel CXA104-Grilamid L25
catheter stop	ely2694+ orange
3 channel clip	politene
shrink 3/16	politene

Table 39 Components of the final prototype

Starting from the analysis of the material chosen and their datasheet, it's possible to declare that the products are free of phthalates.

6.5.6 Manufacturing process

The industrial prototype of the Floseal GI cath. has been made through different manufacturing process which have involved the transformation of plastic materials in different shapes and sizes.

The first process to ensure has been the extrusion of the blue catheter, the external shaft and the balloon (Figure 90). The tolerances for the extrusion are very strict and depend on the dimension of the component and on the particular machine used by the manufacturer.

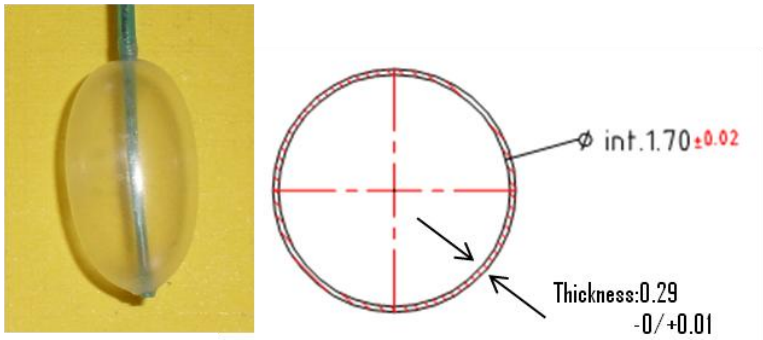


Figure 90 Balloon manufacturing tolerances

The dispenser tube (Figure 91) is extruded, whirled and 3 channel clips are applied.

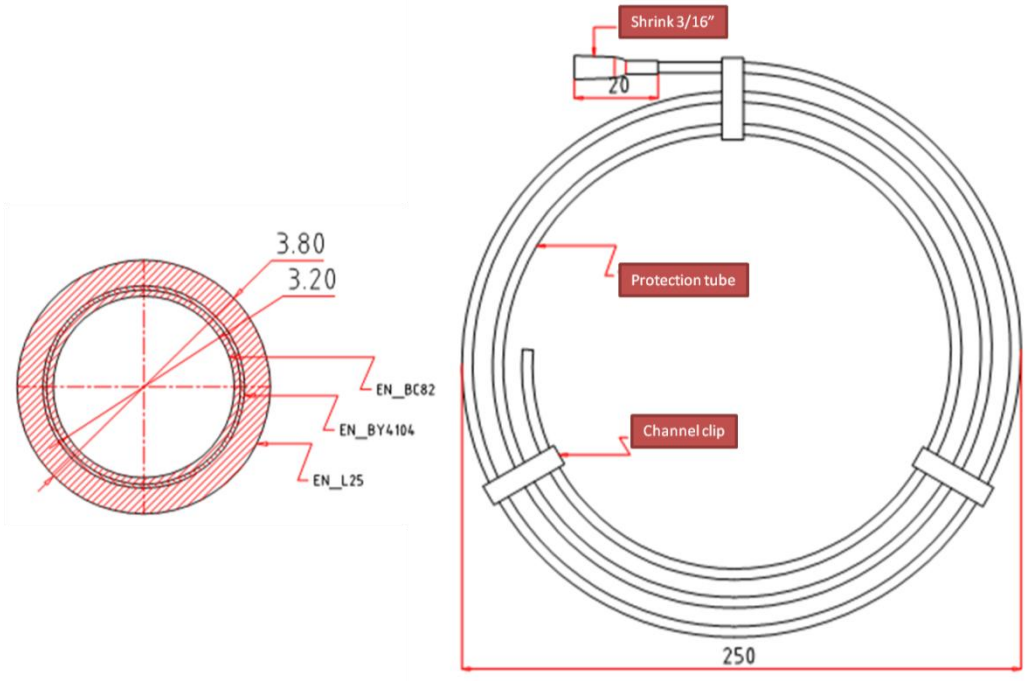


Figure 91 Dispenser tube

The next steps are the extrusion of the orange stop for the catheter inside the external shaft (Figure 92) that will be thermoformed, cut to length and squashed with small forceps.

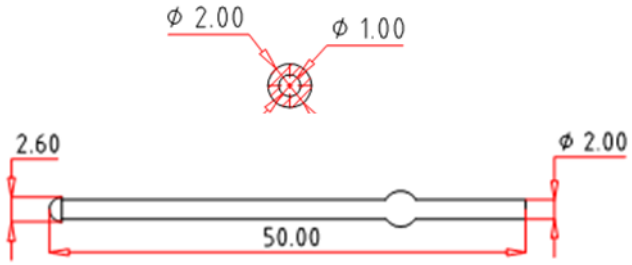


Figure 92 Stop of the catheter

In order to insert the commercial haemostatic valve to the oversheath the extrusion of a steel cylinder is necessary(Figure 93).

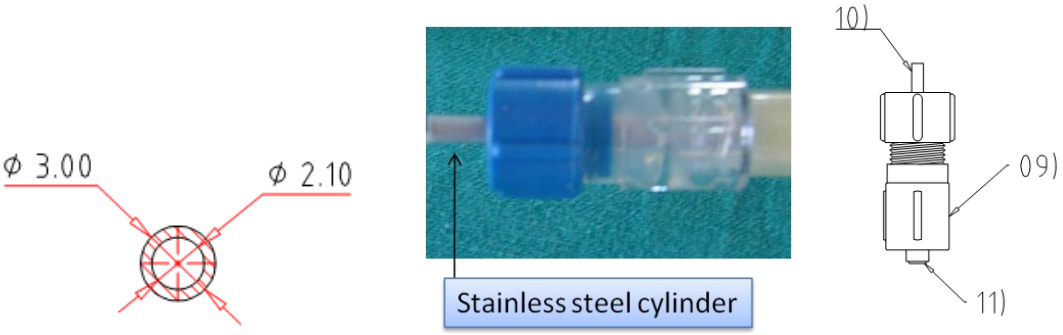


Figure 93 Dimensions the adapter cylinder for the haemostatic valve.

Following the injection molding of the luer-lock adapter for the blue catheter (Figure 94, up) and for the external sheath (Figure 94, down).

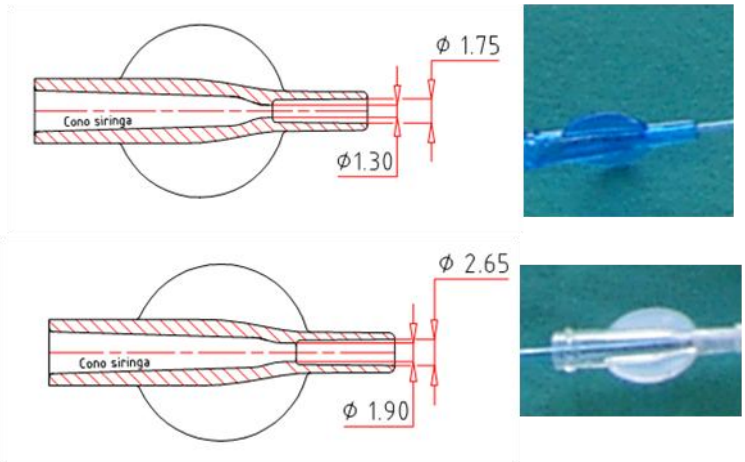


Figure 94 Luer lock adapters for the catheter (up) and the external sheath (down)

In order to mount the balloon on the internal catheter it is necessary to taper the distal end of the catheter (Figure 95) from a diameter of 1.65mm to 1.2mm for a minimum length of 50mm and then to a diameter of 1mm for 25 mm.

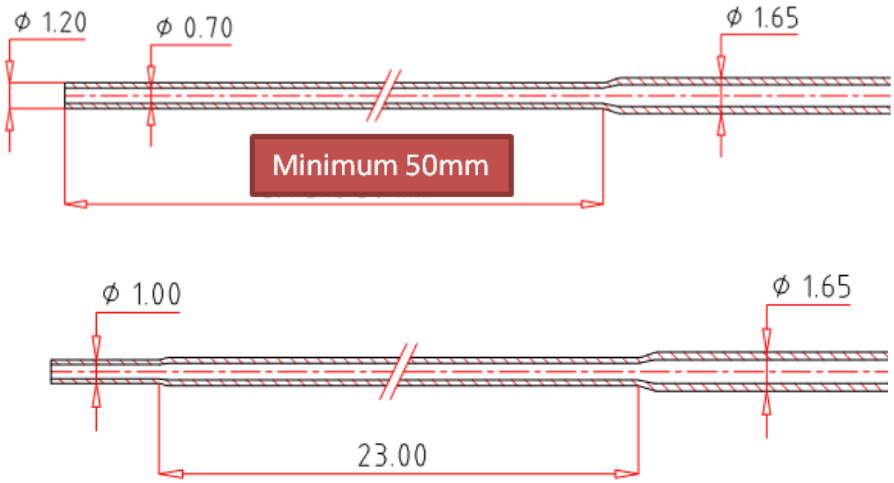


Figure 95 Tapered distal part

A tube drawing machine has been used to reduce the diameters and the distal end is cut 25mm from the point of the first drawing and closed by means of 2 consequent application of UV resin which polymerizes and leaves a round tip.

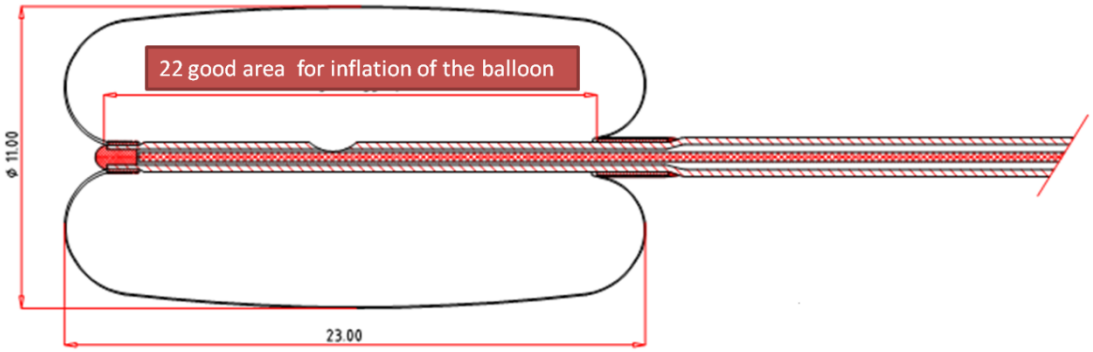


Figure 96 Balloon area manufacturing

A 0.5mm hole for the inflation of the balloon is made at a distance of 10 mm by the end of the catheter, taking care not to perforate the opposite wall. Then the tubular balloon is mounted on its area by means of glue (Loctite 4011) and spirally bonded with a nylon wire of 0.5mm diameter. Then a check of the balloon is done as in 6.6.3.2. The cutting of the catheter to length (2280mm) is next realized with a blade.

After that the blue luer connector is glued to the catheter and a check that there is not air loss is done.

Starting from an AISI 316 steel wire of 0.5mm in diameter, a spiral (Figure 97) is obtained using the lathe chuck. Then the guide-wire is inserted into the catheter.

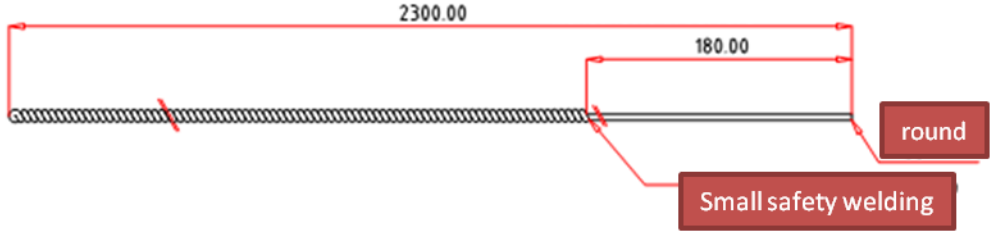


Figure 97 Guide-wire manufacturing

The cut of the oversheath (Figure 98) to length (2210mm) and a series of black notch is made: one for the limit of the hemostatic valve and one for the insertion of the right dosage of Floseal. The luer is glued to the oversheath.

Figure 98 Oversheath

The AISI 316 cilynder is cut to lenght (Figure 99 A), a UV resin is posed on one side and it is inserted into a 7Fr commercial hemostatic valve (Qosina[48]).

[48] http://www.qosina.com/catalog/part.asp?partno=80391

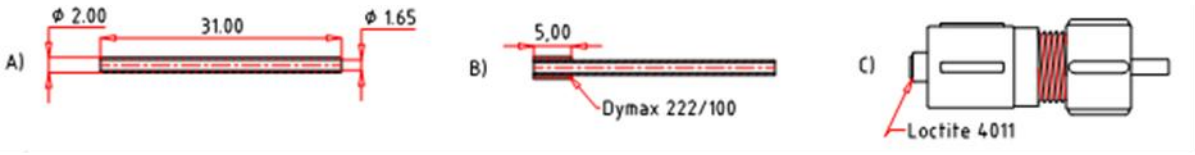


Figure 99 Hemostatic valve assembly

The two syringes are equipped. A block is made in the big one to allow an insertion of 4 cc of air into the balloon and the Floseal one is labelled with an accurate discretization to allow a precise dosage of the hemostatic agent(Figure 100).

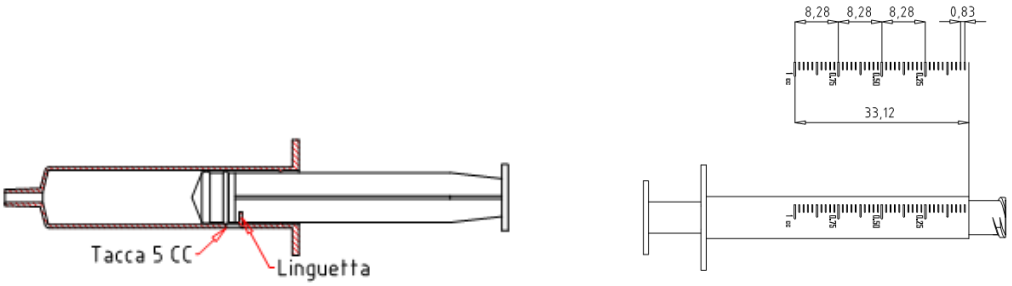


Figure 100 Syringe for insufflation (left) and for insertion of Floseal (right)

6.6 Test sessions

A device like Floseal GI cath. doesn't need preclinical testing to enter the EC market, because its risk class is IIa (see 0) and from the analysis of commercial similar devices and medical background it has been possible to achieve the CE without clinical evaluation tests (pg.118).

In order to test the usefulness of the device before its possible marketing, the device has been tested several times and with different procedures. In Annex IX the test done are fully reported.

The test sessions can be divided into test with different prototypes, which have been dove in order to find the right configuration for the device, and control test, done to demonstrate the efficacy of the manufactured device and the compliance to regulations.

6.6.1 In vitro tests

This first series of tests have been done using several subsequent prototypes of the catheter (all listed in Annex VIII). Starting from the test of the first prototype (vers. 1.0), very soon the critical feature of the device have been identified and corrective actions were taken.

For the first session of trials, the test procedure was as follows:

- Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm
- Step 2: Preparation of Floseal according to IFU

Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU

- Step 4: Expulsion of Floseal
- Step 5: Repeat steps 3 and 4 to 2 times.

The first big problem encountered was the impossibility of extruding Floseal , so several hypothesis followed regarding possible solutions(see 6.5.2.). Possible causes can be (in order of importance):

Cause	Degree of concern (1-small, 5-extremely difficult)
1. storage temperature of Floseal	5
2.dosage of Floseal	5
3. shape of the tip	3
4.dimensions of guide wire	2
5. material of the oversheath	5
6. gap between catheter and oversheath	5

Table 40 Possible causes of inefficient extrusion.

An analysis of possible solutions with the correspondent degree of importance has been reported in Table 41.

Solution	Difficulty of solution (1-easy, 5-hard)	Probable effect
Require the proper conservation	3, it is not only a problem in Baxter but also in hospitals	Probably decisive
Reduce the dosage	3, it depends on the surgeons' opinion	Decisive
Reduce the gap between the tip and catheter	4	It can help
Hardening of the guide wire	1	It can help
Use of lubricants	1	It can help, but it would be difficult to prove the complete compatibility with the materials used and in particular with the Floseal
Material change (use of Teflon)	5 (the subcontractor doesn't use Teflon)	Probably decisive

Table 41 Possible solutions

Hence decision has been undertaken:

4. implementation of miniseries (2.0) with steel tip and sleeve micro-striped
5. solicitation to Baxter about the verification of the conditions of conservation of Floseal
6. request to the clinicians in touch with Baxter on the possibility of extruding a quantity of less than 2 CC of Floseal per time.

After the acceptance of the third condition the following tests worked very good so it has been decided to reduce the dosage of Floseal to 0.5cc per application.

Other considerations can be done about the small syringe for Floseal which crashed and bent (it was too small), so it was changed with a stiffer one. The safety valve was more comfortable than the stopcock than it has been chosen. The hemostatic valve was good as adaptor between the oversheath and the syringe. The balloon was good for transparency and volume.

6.6.2 Ex-vivo tests

The catheter for the application of endoscopic Floseal through a flexible endoscope, was tested ex-vivo in an isolated pig stomach (mod. Erlangen) at the EETC (European Endoscopy

Training Centre) of the Università del Sacro Cuore in Rome, laboratory for the simulation of multiple endoscopic hemostasis interventions.

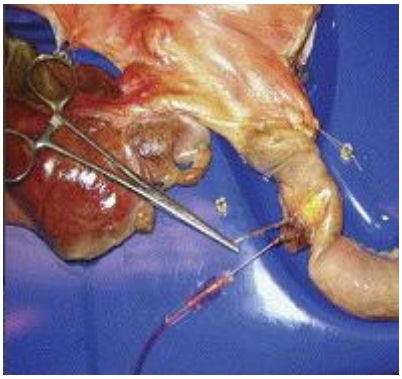


Figure 101 Erlangen model of stomach

The procedure and the results of test are illustrated in Table 42 as in Annex IX.

Date: 20/10/2009	**Place: EETC (European Endoscopy Training Centre) of the Università Cattolica del Sacro Cuore, Rome**		
People involved in the test session	Doc. Gianluca Spera (Università Cattolica del Sacro Cuore - Rome)		
Catheter version	N. 4.0	Description: see Annex VIII	N. tested cath. (same version): 2
Batch Floseal	n.		
Test Procedure	Step 1: Block the catheter on an Erlangen model of a pig stomach Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of **0.5 cc** of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and problems encountered	Test n.: 1	Cath. vers. : 4.0	The catheter work properly
	Test n.: 2	Cath. vers. : 4.0	the catheter works properly
	Test n.: 3	Cath. vers. : 4.0	the catheter works properly
Corrective Actions taken			
Results of actions	Device ready for the market		
Test Responsible	Spera	Signature	

Table 42 Final ex vivo tests

In this experiment the catheter has demonstrated efficacy and ease of use; it has revealed a remarkable handling also using a diagnostic endoscope with an operative channel of 2.8mm diameter .

The catheter is optimal for the purpose, both for the easiness of introducing the Floseal, both in its introduction and subsequent use with the endoscope.

Doctor Spera was impressed by the device that, to date , was the only system capable of allowing the use of Floseal in the digestive endoscopy and in his view, it could allow good results in the techniques of hemostasis.

6.6.3 Control tests

6.6.3.1 Physical controls

Physical controls, including visual checks, dimensional and functional, for the medical device " Floseal GI catheter ", are performed on every batch of raw material and finished product, prior to sending the same to sterilize, as required by the Qualitative Contract with the contractor company (which manages the production process from raw materials to packaging).

6.6.3.2 Floseal GI Catheter Balloon Control Procedure

After the assembling of the balloon on the catheter, the following control is performed to ensure the accuracy and especially the safety of the catheter itself.

First, during the prototyping phase, the limits of inflation and useful expansion of the balloon have been established. Therefore the syringe is prepared, making a groove in the body of the 5cc syringe, so that during inflation doctor does not enter into the balloon over 4cc of air. The syringe is connected to the catheter and then the balloon is inflated; it is left inflated for 20 minutes to verify that the diameter of the balloon just inflated remains unchanged even after 20min. The expansion of the balloon is 11mm. After the control is found to be positive, the sheath, on which is mounted the balloon, is brought within allowing the return to zero of the balloon and the complete adhesion of the balloon to the sheath itself. Thanks to the procedure showed the balloon cannot block somehow the reintegration of the sheath in the catheter itself.

Also a Break test of balloon is done: it is broken with a double delivery of the syringe kit for the pump (10ml).The material of the balloon does not divide up during the break.

6.6.3.3 Chemical controls

The components used for the device are made with own moulds or purchased on the market from certified manufacturers; all materials used are suitable for specific use both for purely structural aspects (compliance with harmonized standards) both in terms of chemical composition. The input materials are checked for the presence of the certificate that ensures compliance. In addition, a test of release of chemicals (Italian Official Pharmacopoeia; ISO 15747:2003 Plastics containers for intravenous injection) has been conducted in order to verify the compliance of the device as a whole.

6.6.3.4 Biological Control

The tests Bioburden pre-sterilization (conducted in accordance with the guidelines of ISO 11737-1 and EN 1174-1, uses the methods provided by the Italian Official Pharmacopoeia) are performed regularly (a fixed date is that which corresponds with the periodic validation of sterilization) by accredited laboratories.

Search of endotoxin (LAL Test- Pyrogen Test) and the absence of abnormal toxicity (performed according to Italian Official Pharmacopoeia)are carried out regularly by accredited laboratories.

Verification of sterility (performed according to current Italian Official Pharmacopoeia)is performed on each batch of sterilization by an external certified laboratory.

All the tests reports are kept by the Quality Assurance Manager of the producer company (MicroTech).

In addition, the tests of hemolysis (UNI EN ISO 10993-4, "Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood") and the cytotoxicity test (UNI EN ISO 10993-5 "Evaluation biological medical devices - Part 5: Test for cytotoxicity in vitro) were conducted in order to verify the compliance of the device as a whole.

6.7 Risk Management

6.7.1 Risk assessment

6.7.1.1 Risk analysis

Floseal GI catheter intended use

The Floseal GI Catheter has been designed, tested and, above all, CE labelled uniquely for a clinical use with Floseal Haemostatic Matrix. The Catheter is indicated in endoscopic surgical procedures of Gastrointestinal (GI) tract, when it allows to deliver and apply 0,5 cc of Floseal for each application. During the same surgical procedure, up to 5 total Floseal applications (of 0,5 cc) are allowed. The gastroscope working channel is 8 French (2.97 mm) minimum.

There are very similar products on the market, they all have the purpose or to seal tissues (cyano-n-butyl-cyano-acrylate) or to facilitate hemostasis (gel / fibrin glues) ; as accessories to these products there are medical devices that fulfill the need to affix and / or spread glue on the tissues in various ways. There is an established use of such devices, conceptually very similar to Floseal GI cath.: in open surgery and laparoscopy, both disposable and reusable, working with the same principle of the piston and using a syringe to make pressure on endoscopic applications.

A research carried out in collaboration with Studio Ambiente Srl and with Baxter (who already use other medical device having the same intended purpose - "to distribute glue") showed that at least one endoscopic application that works exactly with the same principle of the piston exists on the market. In this case the Floseal is applied in situ with the help of a gauze instead of the balloon, but purpose and effect are exactly the same. In Table 43 a list of medical devices similar in intended use.

Device	Company
Floseal endoscopic applicator	Baxter [49].
SurgiFlo endoscopic applicator	Ethicon[50]
Vivostat endoscopic applicator	Vivostat[51]
Glubran endoscopic applicator	Gem Italy[52]

Table 43 Similar devices

[49] http://www.baxterbiosurgery.com/us/products/Floseal/accessories.html
http://www.eaumilan2008.org/typo3conf/ext/eau_abstracts/abstracts/Poster%20session%2045/746-Wille.pdf
[50] http://www.stopcrbsi.com/biosurgicals/surgiflo/surgiflo_FB_tip_options.html
http://www.ethicon360.com/sites/default/files/userfiles/Evithrom%20Surgiflo%20pocket%20folder%20w_PI.pdf
[51] http://www.vivostat.com/composite-61.htm
[52] http://www.gemitaly.it/cms/index.php?option=com_content&task=view&id=54&Itemid=18

Even if the Floseal GI cath. has some differences from the mentioned devices it is very similar in intended use(a glue applicator). Hence it can be considered of established use and clinical validation hasn't been necessary to reach the CE label.

Although a clinical study is not needed for regulatory purposes, it is important to establish a proof of concept that Floseal is a safe and efficacious treatment for bleeding in GI endoscopy. Therefore the company decided to conduct a technical assessment by two independent specialists to check the ergonomics of the product. For marketing reasons also a multicenter study is started, involving centers throughout Italy.

Classification

The medical device "FLOSEAL GI CATHETER", subject of this Ph.D. thesis, has been classified in accordance with Rule 6, paragraph 2.2 "Invasive devices" of Annex IX of EC Directive 2007/47/EEC as a Class IIa medical device, sterile.

Application of the rule:

- The family of medical device FLOSEAL GI CATHETER, Class IIa, must meet the essential requirements set out in Annex I and be produced in compliance with the Annexes V + VII of the European Directive 2007/47/EC
- The medical device, covered by a technical brochure, is intended to be used in endoscopic surgical procedures of the digestive system, where, at the time of bleeding, it is able to carry, release and apply following amounts of 0.5 cc of Floseal
- The line of medical devices "FLOSEALTM GI CATHETER" consists of medical devices that incorporate medicines and contain no animal tissue. These devices are supplied individually wrapped and sterile
- The application was submitted in accordance with the appropriate Annexes V + VII, according to paragraph 1 of Article 11 of European Directive 2007/47/EC to the notified Body, Cermet[53].

Functional analysis

Question	Answer
What is the intended use and how is the medical device to be used?	this medical device is intended to be used in surgical endoscopic procedures, where, in case of bleedings, it allows to carry, release amount and apply subsequent doses of 0.5 cc of Floseal; device for an invasive limited time complying with regulation 6 of the classifications provided in annex IX of EEC 2007/47).
Is the device intended to be implanted?	no
Will the device be in (direct) contact whit patient or other persons?	Yes: direct contact with the patient (the device is invasive in phase of surgical endoscopic interventions),direct contact with the surgeon but only in phase of preparation and use.
What are the materials or components used ?	the medical device is manufactured with plastic materials, in contact with them there is Floseal ™ to be used on the patient in the area affected by bleeding
Is Some kind of energy given or detracted to the patient?	No

[53] CERMET Soc. Cons. srl Via Cadriano, 23-40057 Cadriano – Granarolo E. (BO)

Is Some kind of matter given or detracted to the patient?	Yes: the device is used for the application of Floseal on GI bleeedings
Does the device manage some biological material for a subsequent use?	No
Is the device sterile or is it sterilised by the end user?	Yes, It is single used, sterilized with ETO by the manufacturer. It cannot be re sterilized.
Is the medical device intended to be routinely cleaned and disinfected by the user?	No
Does the device modify the environmental conditions of the patient?	No
Is a measurement device?	No
Can the device make an interpretation?	No
Can the device control or is it in connection with other devices?	Yes, it is used with Floseal in GI endoscopic surgical procedures
Can the device be subject at unexpected leak of energy or matter?	No, the eventual unwanted leakage of Floseal is due to a wrong use of the device
Can the device be subjected by ambient conditions?	No
Does the medical device influence the environment?	No
Are there some consumables or accessory associated to the devices?	The device is complete with all the accessories needed for its use, all the connections are luer
Are periodical set-up or re-conditioning necessary?	No
Does the device use a software?	No
Has the device an expiration date?	Yes, expiration date depends on sterilization process and level of bioburden
Can the device produce some delay effects due to the long-term use?	No
To what mechanical forces will the medical device be subjected?	The device and, in particular the balloon in the distal part, can be forced during the insufflations phase
What determines the lifetime of the medical device?	For a new device, the lifetime of the medical device is driven by the sterilization process and its level of Bioburden; during use, life span depends on the need of medical / other person carrying the protocol, in any way is a limited time.
Is the medical device intended for single use?	Yes
Is safe decommissioning or disposal of the medical device necessary?	Yes, it is a special hospital hazardous disposal
Does installation or use of the medical device require special training or special skills?	The installation and use of the device requires specialized knowledge and the following of IFU
How will information for safe use be provided?	Through the label and the IFU leaflet
Will new manufacturing processes need to be established or introduced?	No

Is successful application of the medical device critically dependent on human factors such as the user interface?	No
Does the medical device use an alarm system?	No
In what way(s) might the medical device be deliberately misused?	Not following the IFU
Does the medical device hold data critical to patient care?	No
Is the medical device intended to be mobile or portable?	no
Does the use of the medical device depend on essential performance?	no

Table 44 Questionnaire for functional analysis (annex C , ISO 14971)

Identification of dangerous phenomena

Following there is a list of dangerous phenomena, known or predicted, identified following analysis of the Floseal GI cath.:

- energy factors
  - force applied during use
- chemical and biological factors
  - bio contamination; bio incompatibility; toxicity; pyrogenicity;
  - failure to maintain sterility (break packaging);
  - degradation;
- factors due to way of use
  - incompatibility with other devices with which it is intended to be used;
  - accidental mechanical. Damage
  - leakage of hemostatic Floseal .
- information
  - improper labelling;
  - inadequate instructions;
  - use by personnel without skills / untrained.
  - inadequate packaging;
  - re-use.

Risk estimation for each hazardous event

Starting from the list of dangerous phenomena identified in the previous chapter, in Table 45, the sequence of predictable events and dangerous situations are identified. For each identified hazard situation one or more hazards will be joined, which will be evaluated using information and data obtained from:

- Published Standards
- Information and scientific literature
- Data collected by the use of the device and user feedback

- Data collected by the use of similar devices already in service, including reports of accidents that have been published
- Results of studies specifically conducted
- Clinical Evidence
- Review of use
- Evaluations by experts
- Other possible.

Dangerous phenomena	Sequence of probable events	Dangerous condition	Unwanted event
Force applied during use	The device is subjected to forces which do not correspond to those expected in the activities for which it is intended	The device deforms, kinks and can break during its use (i.e. the balloon cannot be inflated and it cannot spread Floseal)	Leakage of Floseal Contamination of the patient Contamination of the operator
Bio contamination; bio incompatibility; toxicity; pyrogenicity	The device hasn't been manufactured in a controlled environment or with a wrong sterilization method	Unnoticed contamination	Infections to patie nts, allergies, irritations
Failure to maintain sterility (break packaging)	Contamination of the product during all the phases of transport of the device	Unnoticed contamination	Infections to patients, allergies, irritations
Degradation	unsuitable materials, submitted to several sterilization cycles and uses	Degradation of the device with release of chemicals	Intoxication Allergies, irritations
Incompatibility with other devices with which it is intended to be used	Component aren't adequate for the intended use and aren't compliant to regulations	Partial and unclear connections	Impossible use
Accidental mechanical damage	The device has fallen or has been broken during its use	The device doesn't work correctly during use	Impossible use
Leakage of hemostatic Floseal	The device has fallen or has been broken during its use	The device doesn't work correctly during use	Loss of Floseal Contamination of the patient Contamination of the environment, of the operator with subsequent need of decontamination
Improper labelling	Not sufficient transmitted information	Wrong use	Mistakes in the manipulation of the devices infection of the patient for the use after sterility period
Inadequate instructions	Not sufficient transmitted information	Wrong use of the device	Mistakes in the manipulation of the devices
Use by without skills / untrained personnel.	Not sufficient transmitted information	Wrong Use of the device	Mistakes in the manipulation of the devices
Inadequate packaging;	Contamination of the product during all the phases of	Unnoticed contamination	Infection for the use of a non sterile device

transport of the device			
Re-use	Contamination of the product or stress for an additional sterilization process	Unnoticed contamination or loss of technical properties	Infection for the use of a contaminated device Loss of mechanical properties

Table 45 List of identified hazards on the product (ref.: Annex E, Table E3 UNI CEI EN ISO 14971:2009)

6.7.2 Risk evaluation and control

The manufacturer has decided to accept a probability of a residual risk equal to or less than 10^{-4} (Equal to 1 for the alternative scale(see Annex III))

Eventual analysis of the benefit-risk relationship (ref. section 6.4 of the UNI CEI EN ISO 14971:2009): If the index of the residual risk is judged unacceptable on the basis of the fixed criteria, the manufacturer can collect and review information and documentation showing whether the medical benefits are greater than the residual risk. If even these tests do not confirm that medical benefits are greater than the residual risk, the risk is unacceptable.

In Table 46 some examples of risk evaluation and corrective actions, for the analyzed device, are reported. The full documentation is filed in the technical file of the product.

Unwanted event-hazard	Harm Description	IL	Causes and its occurrence	P	RE	Technical solution (Measures and contingency)	EI	Documental measures	AEI	RRE
ENERGY Force applied	Floseal leakage	(3) 10 4	rare	(2) 10 -5	(6) 10 -1	Test of good functioning during production; controls on scrap materials and finished products	(0.1) 10-6			(0.6) 10-7
CHEMICAL bio contamination; bio incompatibility; toxicity; pyrogenicity	Infection of the patient	(4) 10 6	Extremely rare (remote)	(1) 10 -6	(4) 10	Use of biocompatible materials; Sterilization; Manufacturing in controlled environment	(0.3) 10-4			(1.2) 10-4
WAY OF USE incompatibility with other devices with which it is intended to be used	Impossibility to use the device	(3) 10 4	Extremely rare (remote)	(1) 10 -6	(3) 10 -2	Controls in process and of final product before release; validation of the components on the device (Regulation); Certificates of	(0.3) 10-4			(0.9) 10-6

						Compliance issued by the suppliers of materials				
INFORMATION improper labelling	Mistakes in the manipulation of the devices	(4) 10 6	rare	(2) 10 -5	(8) 10			Labelling validation compliant to regulation	(0.1) 10-6	(0.8) 10-5

Table 46 Risk evaluation and management (see annex III for definitions)

6.7.3 Sterilisation method

The purpose of the sterilization process is to inactivate the microbiological contaminants which may be present on the device and then turn a NON STERILE product in STERILE. Since the effectiveness of sterilization cannot be verified by checking all products processed in each cycle, it is necessary to validate, monitor and control the process (as from European Directive 2007/47/EC on medical devices).

The curve of inactivation of a culture of microorganisms, through the action of a chemical or physical agent used to sterilize medical products, is often similar to an exponential relationship, which means that there is always a finite probability that a microorganism may survive regardless the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and strength of micro-organisms and the environmental conditions to which the bodies have undergone during the treatment. From this it follows that the sterility of any piece in a lot of products subjected to sterilization cannot be guaranteed and the sterility of that production batch must be defined in terms of probability that a not sterile product is in that lot.

The validation of the sterilization process is used to determine the values of some physical parameters (e.g.: Temperature, humidity, pressure, gas concentration, treatment time, etc..) necessary to transform, with a margin of warranty, the product from non-sterile to STERILE. A medical device is considered sterile when the probability of finding a sample with a living organism is equal to or less than $1x10^{-6}$ (due to the exponential relationship between the inactivation of microorganisms and sterilizing agents).

To ensure the validation of a sterilization process is extremely important that the level of bacterial contamination of the products before sterilization is maintained constantly at the minimum, and that the type of contaminant doesn't have particular strength to inactivating agent.

To demonstrate the effectiveness of sterilization, which is being validated during routine sterility control, specific, high resistant to ethylene oxide, biomarkers are used.

It is necessary to get a validation process of the sterilization treatment of the product (systematic analysis of the production phases) to get accurate and reliable indication on the physical, microbiological, chemical and biological state of the product prior to sterilization. These factors serve to make reliable the validation process and to ensure repeatability in time of the sterilization conditions guaranteeing a standard initial condition.

Hence the manufacturer (MicroTech srl) took steps to validate its sterilization with EtO (ethylene oxide) at the company SterilVerona Ltd. The details of the sterilization cycle can be found in the "VALIDATION OF STERILIZATION" filed in the Quality office of the manufacturer. In Annex X the parameters of the sterilization process are briefly reported.

6.7.4 Instruction for Use – IFU

Each device is accompanied by instructions, complete with warnings, also in accordance to what is expressly stated in the Directive 2007/47/EC, Annex I - paragraph 13. Following a short description of the IFU (instruction of Use).

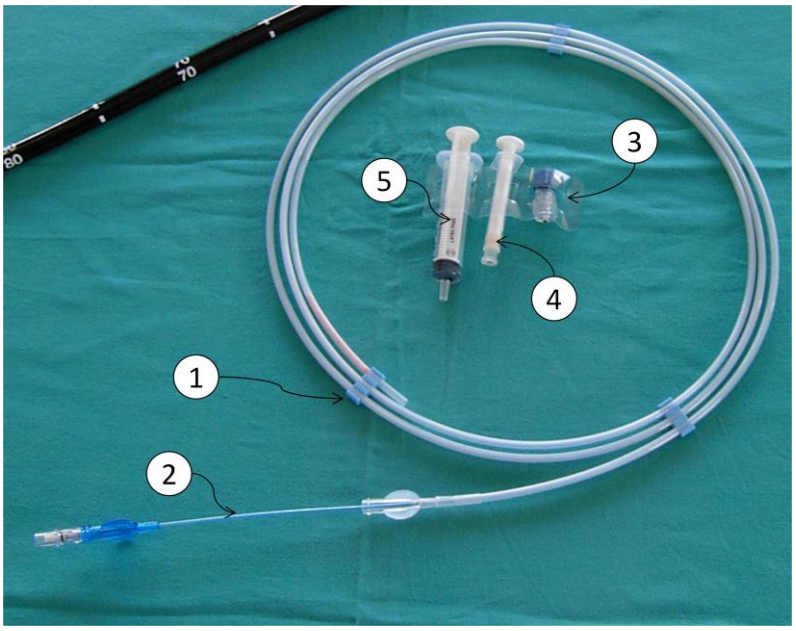


Figure 102 Device main components: 1-Case,2-catheter,3-Haemostatic valve,4-Floseal syringe,5-Balloon syringe

Step 1: Floseal preparation according to Floseal' s IFU (no difference)

Step 2: Charge of Floseal into the catheter

- remove the catheter from the case and take away the orange cup
- transfer 0,5 cc of Floseal in the Floseal syringe (comp. # 4)
- connect the haemostatic valve (comp. # 3) to the distal part of the catheter and lock it

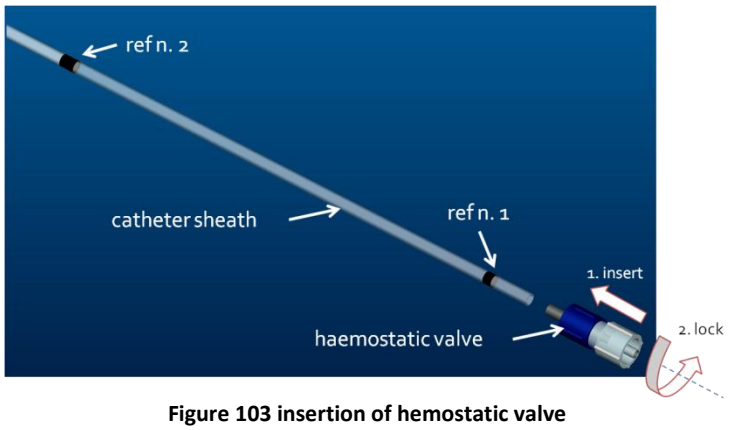


Figure 103 insertion of hemostatic valve

- connect (Figure 104) the Floseal syringe with 0,5 cc of Floseal to the haemostatic valve and lock it
- push the Floseal syringe in order to transfer the Floseal into the catheter.

Remark: it is very important that the quantity of Floseal delivered into the catheter doesn't exceed 0,5 cc. Check if the Floseal (that is visible in transparence) reaches the second reference[54] on the catheter (see Figure 103*)*

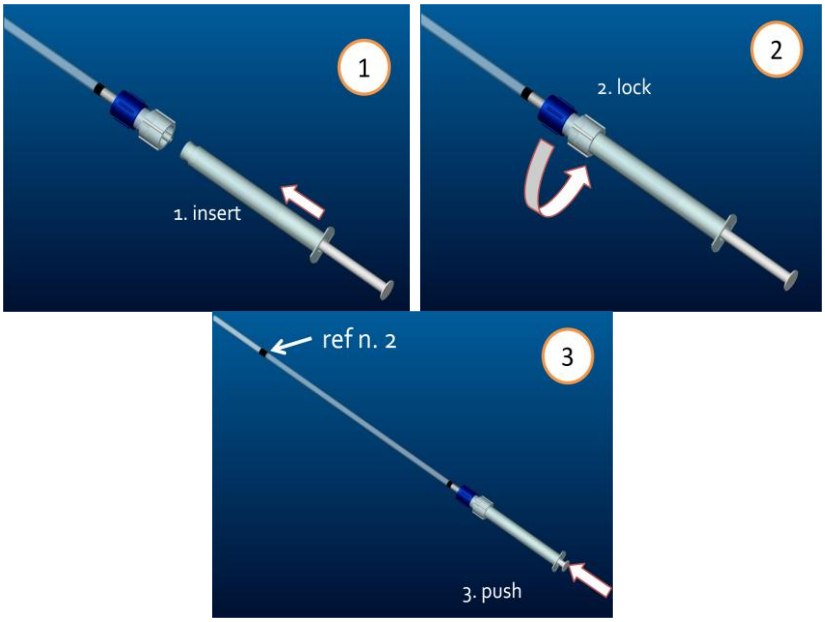


Figure 104 Connection of syringe and pushing of Floseal

- remove the Floseal syringe and the haemostatic valve.

Now the Floseal GI Catheter is ready to be used.

Step 3: Floseal delivery and application on the surgical site:

- introduce the Costamagna – Spera Floseal GI Catheter into the gastroscope through the working channel (8 French - size)
- once the catheter is completely outside the gastroscope, push the blue catheter part. The Floseal is forced outside the catheter
- using the balloon syringe (comp. #5), inflate the balloon
- using the gastroscope handles, apply the Floseal Haemostatic Matrix on the bleeding
- at the end of the procedure, using the balloon syringe (comp. #5), deflate the balloon
- remove the catheter form the gastroscope for a further application, following the same entire procedure.

[54] the sheath of the catheter has 2 references in black:
the **first** is useful to verify that the haemostatic valve reaches the correct position in order to be correctly locked
the **second** is the reference for the correct quantity of Floseal: 0,5 cc

All the procedure seems very long, but after a little training it is very easy. It is important to use a Floseal in the correct storage conditions (temperature in particular). A temperature storage low than 2°C can make the Floseal difficult to be delivered: in this case, a retraction of about 20 cm and a further introduction of the blue part of the catheter is advisable. During the "pushing" of the Floseal, in order to avoid the kink (permanent deformation) of the blue part of the catheter, the hands of the surgeon must be at the distance of 10 cm maximum (see Figure 105).

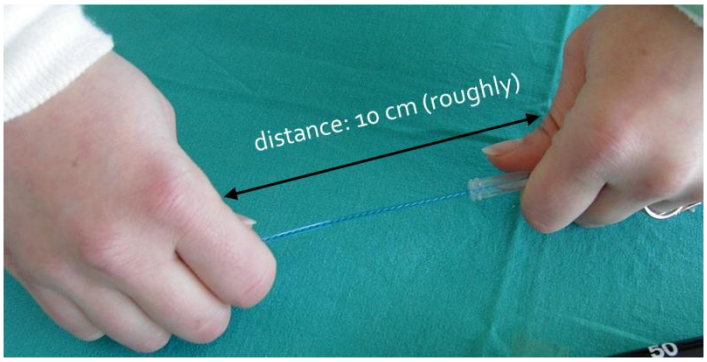


Figure 105 Distance for good handling

6.7.5 Packaging

The final packaging of the product should be able to keep it intact until use. The Floseal GI cath. is packaged in a single envelope, consisting of medical paper coupled with polypropylene / polyester. The bags are then packed in special boxes and prepared for shipment to sterilization on special pallets. Each box is marked with a label (Figure 106) identifying the product, with the following information (UNI EN 1041 and BS EN 980):

- indication of the manufacturer (MicroTech Srl)
- indication of the CE mark and number
- code of the finished product
- a description of the product
- batch production
- expiry date (valid for 5 years).

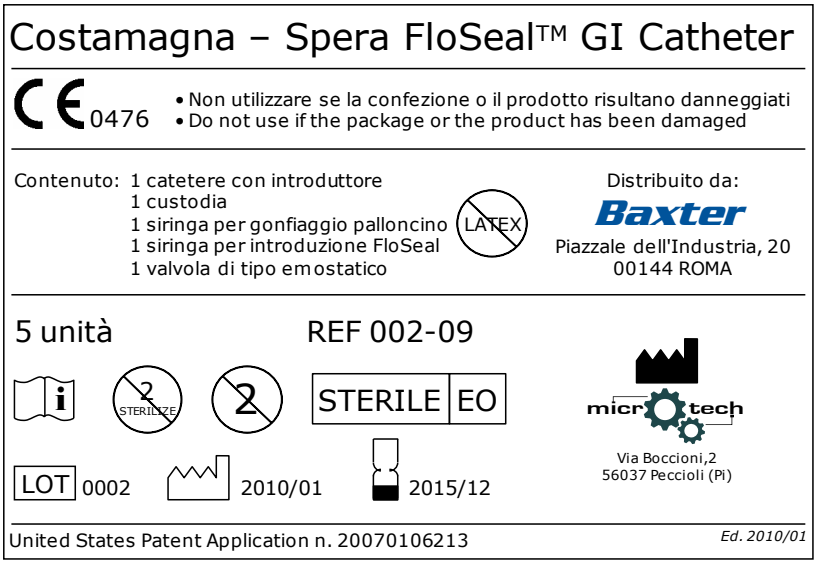


Figure 106 Label for the box with 5 units

Next to the label is affixed a strip of tape "ethylene oxide" required to verify the sterilization of the product. The strip will change color after they have been sterilized. Before shipping each pallet is wrapped with "Estenpack"[55] so as not to allow the movement of the boxes during transport.

[55] http://www.akroflex.it/english/estenpack_R-eng.htm

7 Conclusions

Medical device design methodology is a very attractive field of work, from basic research to the market profitability evaluation. Several variables have to be evaluated within all the phases, from the concept to the market roll-out, in order to ensure safety and effectiveness. The real innovation in medicine is represented by an improvement of patients' quality of life. Minimally invasive surgery and therapies move toward this direction, enabling less pain, smaller incisions and a fast post operative course, over an augmented precision and control in the interventions.

For achieving effective results it is fundamental, that the idea is born and supported by the real user of the medical devices: the surgeon.

An analytical study of the idea must be approached and the entire creative process must be sustained by the production of prototypes, with various level of accuracy, in order to help the creation of a common language between researchers and surgeons. Hence a co-inventive iterative process of design, prototyping and tests can start.

During the entire design course, evaluation of potential hazards, both mechanical and chemical, biological or electrical, associated to the use of the device must be analyzed and early solved, in order to avoid errors and possible risk to the final users.

A complete methodology for the development of innovative medical devices has been studied and presented. Three examples of research and design of innovative devices in minimally invasive surgery are fully reported in this Ph.D. work. All the phases of the design process have been implemented in order to achieve different level of results, depending on the complexity on the device.

The Muneretto Beam navigation device is a new system for magnetic guidance of electrodes for ablation of atrial fibrillation. The design starts from a commercially available device for minimally invasive ablation for cardiac surgery, which has been modified to enhance its easiness of use and mini-invasiveness. Other available systems are very expensive (robots) or too invasive (open surgery).

The critical concern in the design of the Muneretto Beam Catheter has been the magnetic coupling and the friction with biological tissues. Various configurations and prototypes have been evaluated and tested; the best magnetic coupling has been obtained and the final configuration chosen. It will be a fixed one, as described previously, so the friction between tissues and catheter and the shape of the tip are not big issues. In this work only a proof of concept has been completed, thus a lot of work has still to be done. The next steps are the development of preindustrial prototypes and the deployment of in vivo and in vitro tests in order to assess its efficiency and safety.

The VideoDrain is a new device for the monitoring of liquids and viscera in the post-operative phase, especially in case of huge interventions, where it allows the avoidance of a second-look invasive intervention. The main features of the device are: a balloon, from which it is possible to see the abdominal cavity, and a tube, for the insertion of a commercial fiberscope. A series of valves ensure the insulation from the external environment. A pre-industrial prototype has been developed and tested in vivo with medical personnel. An evaluation of regulatory issues and functional analysis have been deployed. The final industrial prototype must be developed and the certification process must start.

The FloSeal GI catheter is a novel device for the release of a commercial, gold standard, haemostatic matrix in the gastrointestinal tract. The entire process of invention, design, test, production and certification have been completed.

The critical issue in the deployment of the device has been the extrusion of Floseal, an high viscous and granulose substance. Several prototypes and tests have been developed in order to understand which would better fit the efficacy and ergonomics of the whole procedure. The device has been fully tested with surgeons and is now CE labelled. Future work will include a post-market surveillance and possible design modifications owing to difficulties found during the use of the device

8 List of publications

Development of a muscle-skeleton model of surgeon-F.Cavallo, S.Sinigaglia , G.Megali, E.Troia, P. Dario, A.Pietrabissa-Poster session GNB 2008

Improving daily clinical practice with 3D patient specific anatomical models: limits, methodologies and our experience-6th Annual HCTM Conference-Ferrari, Megali, Cappelli, Troia, Cavallo, Pietrabissa

EndoCAS navigator platform: a common platform for computer and robotic assistance in minimally invasive surgery-G. Megali,V. Ferrari, C. Freschi, B. Morabito, F.Cavallo, G. Turini, E. Troia, C. Cappelli, A. Pietrabissa, O.Tonet, A.Cuschieri, P.Dario, F. Mosca-The International Journal of Medical Robotics and Computer Assisted Surgery 2008

A 3D mixed-reality system for stereoscopic visualization of medical dataset,Vincenzo Ferrari, Giuseppe Megali, Elena Troia, Andrea Pietrabissa and Franco Mosca- Transaction on biomedical engineering 2009

Ultrasound Guided Robotic Biopsy using Augmented Reality and Human-Robot Cooperative Control, Cinzia Freschi, Elena Troia, Vincenzo Ferrari, Giuseppe Megali, Andrea Pietrabissa, Franco Mosca,EMBC 2009

Sistema di navigazione per biopsia eco-guidata,Cinzia Freschi, Vincenzo Ferrari, Elena Troia, Andrea Pietrabissa, Franco Mosca MMVR 2009

GHOST (Guidance Help for Operating Surgical Trainees)Piattaforma basata su Realtà Virtuale per il Telementoring in Laparoscopia, Andrea Pietrabissa, Vincenzo Ferrari, Andrea Moglia, Giuseppe Turini, Elena Troia, Franco Mosca, MMVR 2009

A Navigation system for Robotic-Assisted Biopsy, C. Freschi, V. Ferrari E. Troia, M. Ferrari, F. Mosca, Poster. session GNB 2010

Proficiency assessment of gesture analysis in laparoscopy by means of surgeon's musculo-skeleton model. F. Cavallo, A.Pietrabissa, G. Megali, E. Troia, S. Sinigaglia, P. Dario, A. Cuschieri, F. Mosca. (Submitted to Annals of Surgery January 2011)

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10 Annex I

Classification of Medical devices

TYPE OF CLASSIFICATION	DEFINITION	MEANING	Rules
Time- Duration	Transient	Normally intended for continuous use for less than 60 minutes.	
Time- Duration	Short term	Normally intended for continuous use for not more than 30 days.	
Time- Duration	Long term	Normally intended for continuous use for more than 30 days.	
Invasiveness	Non invasive devices		1.2.3.4
Invasiveness	Invasive devices	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body	5, 6, 7, 8
Invasiveness	Surgically invasive device	An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.	
Invasiveness	Implantable device	Any device which is intended: -to be totally introduced into the human body or, - to replace an epithelial surface or the surface of the eye, by surgical intervention which is intended to remain in place afterthe procedure. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.	
	Reusable surgical instrument	Instrument intended for surgical use by cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or similar procedures, without connection to any active medical device and which can be reused after appropriate procedures have been carried out.	
	Active devices	Any medical device the operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices	9, 10, 11, 12
	Active therapeutical device	Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap.	
	Active device for diagnosis	Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.	
	Central circulatory system	arteriae pulmonales, aorta ascendens, arcus aorta, aorta descendens to the bifurcatio aortae, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachio-cephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior	
	Central nervous system	brain, meninges and spinal cord.	

Table 47 Definitions for classification of medical devices (Annex IX of directive)

CLASS	Devices included
I	All non-invasive devices Non-invasive devices which come into contact with injured skin if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates All invasive devices with respect to body orifices other than surgically invasive devices and which are not intended for connection to an active medical device if they are intended for transient use Reusable surgical instruments for transient use
II a	Non-invasive devices: for channelling or storing blood if they may be connected to an active medical device in Class IIa for filtration, centrifugation or exchanges of gas, heat which come into contact with injured skin manage the micro-environment of a wound All invasive devices with respect to body orifices: than surgically invasive devices if they are intended for short-term use other than surgically invasive devices, intended for connection to an active medical device in Class IIa or a higher class All surgically invasive devices intended for transient use All surgically invasive devices intended for short-term use Implantable devices and long-term surgically invasive devices placed in teeth All active therapeutic devices intended to administer or exchange energy Active devices intended for diagnosis: intended to supply energy which will be absorbed by the human body to image in vivo distribution of radiopharmaceuticals intended to allow direct diagnosis or monitoring of vital physiological processes All active devices intended to administer and/or remove medicine Devices for disinfecting medical devices except for invasive devices (IIb) Devices specifically intended for recording of X-ray diagnostic images
II b	Non-invasive devices: intended for modifying the biological or chemical composition of blood which come into contact with injured skin if they are intended to be used principally with wound All invasive devices with respect to body orifices than surgically invasive devices if they are intended for long-term use except if they are used in the oral cavity as far as the pharynx (IIa) Surgically invasive devices for transient use intended to: supply energy in the form of ionising radiation have a biological effect or to be wholly or mainly absorbed administer medicines by means of a delivery system, if this is done in a manner that is potentially hazardous Surgically invasive devices intended for short-term use: to supply energy in the form of ionizing radiation to undergo chemical change in the body, except if the devices are placed in the teeth (IIa) All implantable devices and long-term surgically invasive devices Active therapeutic devices intended to administer or exchange energy in a hazardous way All active devices intended to control or monitor the performance of active therapeutic devices Active devices intended for diagnosis of vital physiological parameters intended to emit ionizing radiation Active devices intended to administer and/or remove medicine in a potentially hazardous way All devices used for contraception unless they are implantable or long term invasive devices(III) Devices intended specifically to be used for disinfecting, cleaning,rinsing or, when appropriate, hydrating contact lenses Blood bags
III	Surgically invasive devices for transient use: intended specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body in direct contact with the central nervous Surgically invasive devices intended for short-term use:

to control, diagnose, monitor or correct a defect of the heart or of the central circulatory
in direct contact with the central nervous system
to have a biological effect or to be wholly or mainly absorbed
Implantable devices and long-term surgically invasive devices:
to be used in direct contact with the heart, the central circulatory system or the central nervous system
to have a biological effect or to be wholly or mainly absorbed
to undergo chemical change in the body
All devices incorporating, as an integral part, a human blood derivative or a medicine
All devices manufactured utilizing animal tissues or derivatives

Table 48 Classification rules from article 9 and annex IX -2007/47

11 Annex II

Biocompatible materials properties

Material	PU	PTFE	PVC	Silicone	Latex
Tensile strength (psi)	4000-10000	5500-7000	2000-6000	800–1500	4400–4900
Flexural modulus(psi)	400000	100000	200000	30000	low
Ultimate elongation(%)	250-700	350/550	450%	600–1100	800–1200+
Durometer	72 ShA-84ShD	60 ShD	70-90 ShD	10 ShA-60 ShA	35 ShA
Biocompatibility	good	good	medium	optimal	weak
Abrasion resistance	high	high	good	low	good
Sterilization technique	ETO, gamma	ETO, Autoclave	ETO, gamma	ETO, Autoclave, gamma	ETO, Autoclave

Table 49 Principal characteristic of materials used

POLYMER	STEAM AUTOCLAVE	MAX. TEMP. (°F)	TYPICAL APPLICATIONS
Acetal copolymer	OK	250	Thin-wall round parts, washers and bushings
High-density polyethylene	OK	250	Orthopedic handles, instruments
Nylon	Specific grades	265	Surgical trial components
Polycarbonate	Specific grades	338	Medical tubing connectors, containers
Polyethermide	OK	275	Surgical trial components
Polyphenyl-sulfone	OK	270	Handles, implant trials, fluid handling
Polypropylene	OK	275	Handle undermolds

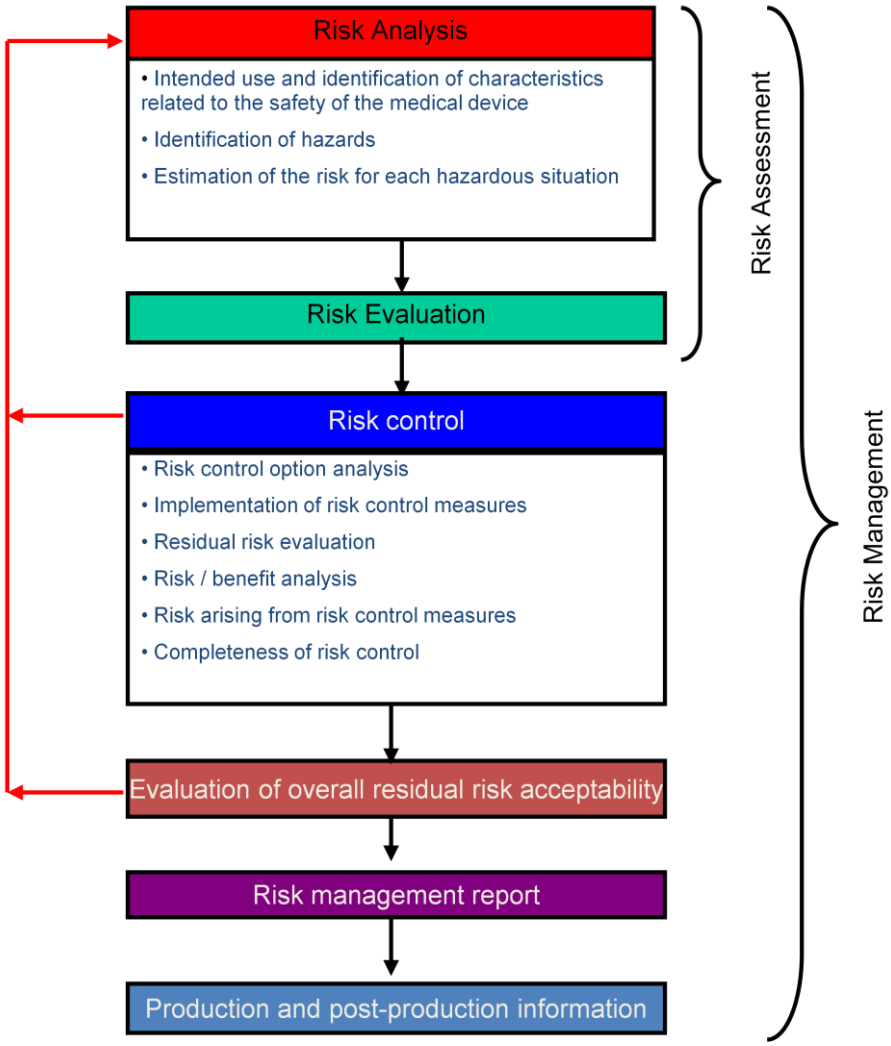
Table 50 A list f steam sterilizable materials

POLYMER	GAMMA RADIATION	MAX. RADS (Mrd)	TYPICAL APPLICATIONS
Acrylonitrile butadiene styrene	OK	5	Trays, handles
Acrylic	OK	5	Orthopedic handles, instruments
Nylon	OK	10	Surgical trial components
Polycarbonate	OK	10	Medical tubing connectors, containers
Polypropylene	OK	6	Handle undermolds, syringes

Table 51 Some gamma sterilizable materials

12 Annex III

Flow Chart – Risk Management Activities in Design and Development



Grids for Risk and Measures Assessment

Risk Assessment Criteria

Impact Level (IL) (Table 52) scale measures the level of danger of each risk starting form no risk level to the maximum potential risk (death).

100	102	104	106	108	1010
(1)	(2)	(3)	(4)	(5)	(6)
No Influence	Low (Damage slight and subjective to the persons or things)	Moderate (Slight damage and objective people or things)	High (Injury or impairment in mild / temporary)	Critical (Serious injury or disability /permanent)	Very High (Death)

Table 52 Impact Level scale (between brackets an alternative scale)

The *Probability Scale (P)* measures the probability that a event occurs, from "incredible" to "frequent".

10^{-6}	10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}
(1)	(2)	(3)	(4)	(5)	(6)
Extremely rare	Rare	Occasional	Moderate Probability	High Probability	Frequent

Table 53 Probability Scale(between brackets an alternative scale)

Risk Estimation RE (Equation 15) should be less than 10^{-4}(or fall in the green part of the Table 54).

$$IL*P=RE$$

Equation 15 *Risk Estimation*

Measures Assessment Criteria

		No Influence	Low	Moderate	High	Critical	Very High
		(1)	(2)	(3)	(4)	(5)	(6)
Frequent	(6)	6	12	18	24	30	36
High Probability	(5)	5	10	15	20	25	30
Moderate Probability	(4)	4	8	12	16	20	24
Occasional	(3)	3	6	9	12	15	18
Remote	(2)	2	4	6	8	10	12
Extremely rare	(1)	1	2	3	4	5	6

Table 54 three region risk char (it refers to *alternative scale)*

It is often very difficult to assign a value for each parameters: some indications can be obtained by previous analysis, post market surveillance and clinical studies.

Risk reduction: Technical measures (efficacy index EI) Effect of additional documentation (additional efficacy index AEI)		
Not present	(1)	10^{0}
Limited	(0.8)	10^{-1}
Fair	(0.5)	10^{-2}
Good or Effective	(0.3)	10^{-4}
Safe-compliant harmonized	(0.1)	10^{-6}

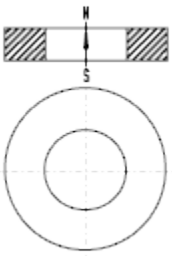
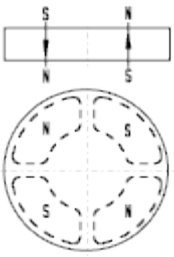
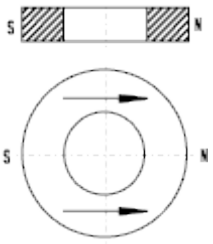
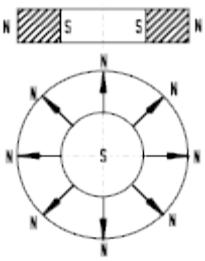
Table 55 Measures efficacy scale

Risk Estimation after Measures or Residual Risk (RRE, Equation 16) must fall in the green area (less than 10^{-4}).

$$RE*IE*IUE=RRE$$

Equation 16 Residual Risk Estimation

13 Annex IV

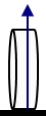
Magnetization	Pole Configuration
Axial	
Multipolar on both end planes	
Diametral	
Radial	

14 Annex V

Results of FE model validation

Comparison with datasheets

For the magnets used refer to table:

	Ø (mm)	H (mm)	Mdir	Grade	Brmax(T)
Sphere s3	4.76	-		N42	1.32
Cylinder D22	3.175	3.175		N52	1.48
Cylinder D24	3.175	6.35		N50	1.45
Disk S09	9	2.50		N52	1.45

(magn_perm) d22_d22 axially[56]

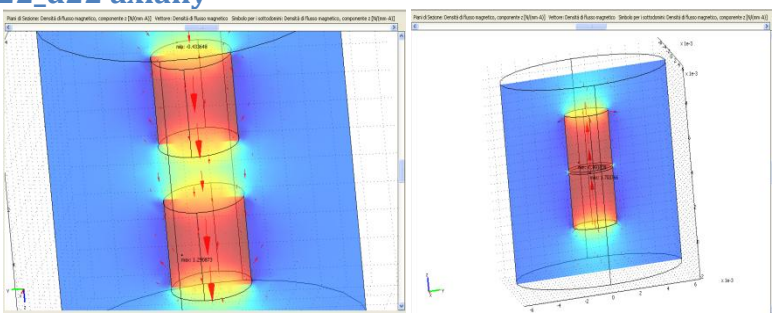


Figure 107 Comsol visualization of Magnetic flux density

Δx(mm) [57]	**0.11**	**0.3**	**1**	**2**
F(N)	4.52	3.53	1.53	0.46
$F_{datasheet}$	3.34	2.44	1.11	0.53
ΔF	1.18	1.09	0.42	0.07

Table 56 Comparison of Forces evaluated

[56] Axially stands for axially magnetized.

[57] Distance between the external surfaces of magnets in the direction of magnetization

(magn_perm) d24_d24 axially

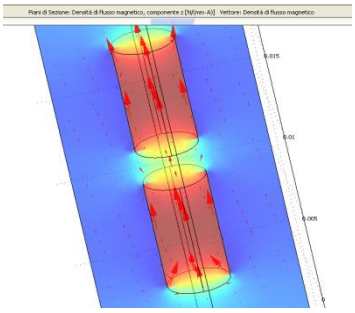


Figure 108 Magnetic flux density (B) between two d24 axially magnetized

Δx (mm)	0.1	0.5	1	2
F (N)	4.9	2.62	1.39	0.48
Fdatasheet	4.4	2.89	1.77	0.84
ΔF	0.5	0.27	0.38	0.36

Table 57 Comparison of Forces

(t.l.v.) d24_d24 diametrically[58]

In this case the procedure followed for the evaluation of forces is different from the one described in 4.5.3.

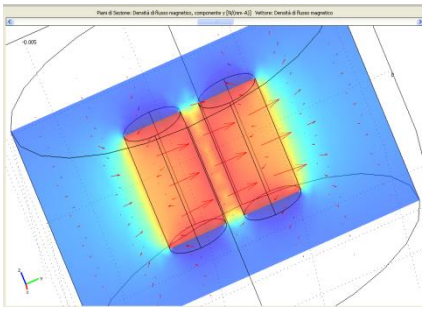


Figure 109 Magnetic flux density (B) between two d24 diametrically magnetized

Δx (mm)	0.1	0.5	1	2
F (N)	5.6	3.75	2.33	1.15
Fdatasheet	4.88	3.63	1.77	0.97
ΔF	0.72	0.12	0.56	0.18

Table 58 Comparison of Forces

Comparison with tests

Δx (mm)	0.04	0.24	1	2
F_{s3_s3}[59]	3.95	3.5	1.88	0.99
F_{D24_s09}			2.48	1.9
$F_{D22\_s3\_axially}$			7.9	5.0
$F_{D22\_d24\_axially}$	4.9		1.86	0.75

Table 59 First couplings analyzed for the validation of the model with tests

[58] Magnetization of magnets is diametral
[59] All forces are in Newton

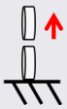
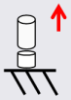
		F (N) (no tissue)	ΔF1	F (N) (with tissue, distance =1mm)	ΔF2
	s3-s3	3.93±0.04 (3.95)	0.02	3.8±0.04 (1.88)	1.92
	S09-S09	6.74±0.10		6.2±0.11	
	d22-d22	3.79±0.25 (4.52)	0.73	1.78±0.14 (1.53)	0.25
	d24-d24	4.53±0.27 (4.9)	0.37	2.0±0.14 (1.39)	0.61
	s3-d22	3.60±0.06		2.2±0.04 (7.9)	5.7
	s3-d24	4.03±0.03		2.18±0.15	
	s3-S09	4.64±0.06		2.35±0.09	
	d22-d24	4.04±0.25 (5.1)	1.06	0.71±0.07 (1.86)	1.15
	d22-S09	4.20±0.10		3.0±0.11	
	d24-S09	4.57±0.19		2.38±0.02 (2.48)	0.1

Table 60 Results of the validation. In bracket the correspondent results of FEA

Validation tests with hkcm[60] magnets

Code	Magnet Type		
Z02x02ND-48H	Cylinder		
Z02x10ND-N35	Cylinder		
Z01.2x03ND-N35	Cylinder		
Z02.5x12ED-N35	Cylinder		
S03x01.4ND-35EHT	Disc		
R03x01x03Cr-N35	Ring		
R03x01x0.15ND-N35	Ring		
R03x01.7x00.5ND-N35	Ring		
S03x02ND-N35H	Disc		
S03x02ND-50M	Disc		
Z04x04ND-N35	Cylinder		
K04.76Au-N35	Ball		

Table 61 Magnets

Magnet-Cylinder Z02x02ND-48H with iron plate

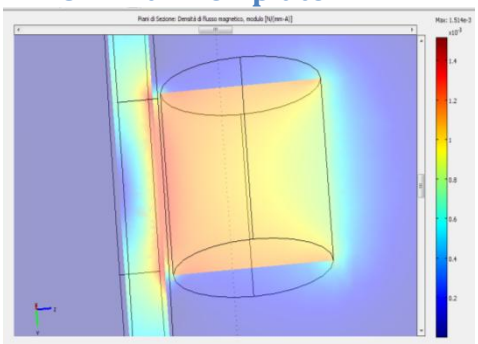


Figure 110 Magnetic flux density between magnet and a iron plate

Δx(mm)	0	1
F(N)	1.3	0.59
Fdatasheet	1.26	0.63
ΔF	0.04	0.04

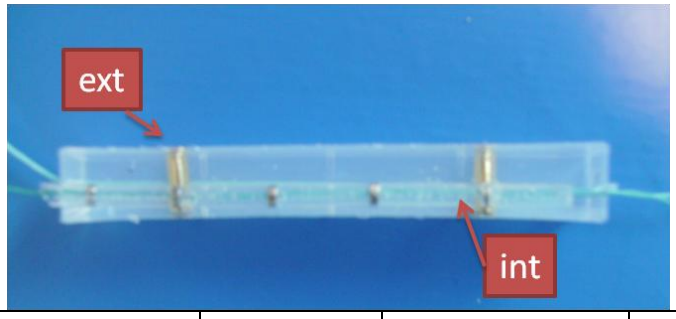
Table 62

[60] https://www.hkcm.de

15 Annex VI

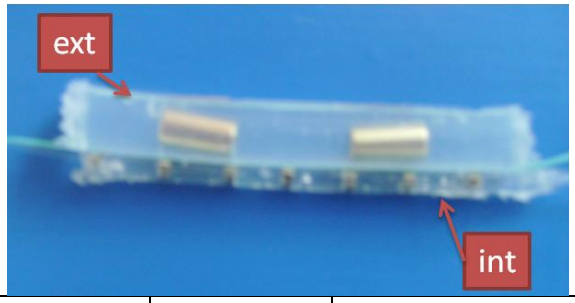
Tests results-September 2010

Configuration 1



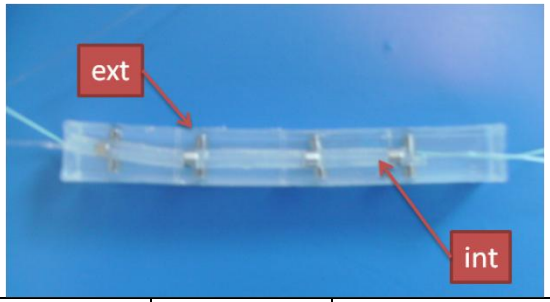
TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	2	Cylindrical	Z03.5x10GD-N35	No sliding up No sliding down
INTERNAL	5	Ring	R03x01x015ND-N35	

Configuration 2



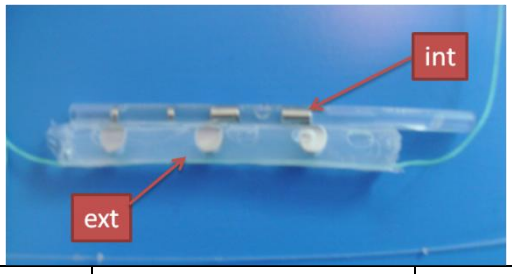
TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	2	Cylindrical	Z03.5x10GD-N35	No sliding up No sliding down
INTERNAL	7	Ring	R03x01x015ND-N35	

Configuration 3



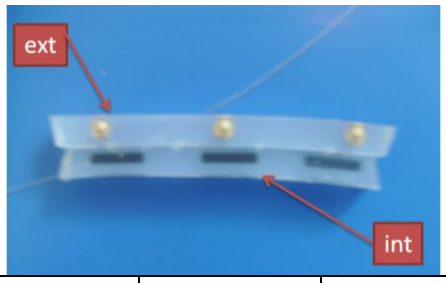
TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	4	Cylindrical	Z03.5x09GD-N35	Sliding down ok Sliding up no Bad coupling
INTERNAL	4	Ring	R03x01x03Cr-N35	

Configuration 4



TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	3	Disc	Z03.5x10GD-N35	The inner one has an external shell (in Medical PVC from a suction catheter 61) Good coupling
INTERNAL	2 2	Cylindrical Cylindrical	S03x01.4 ND-35EHT Z3.5x10GD-N35	

Configuration 5



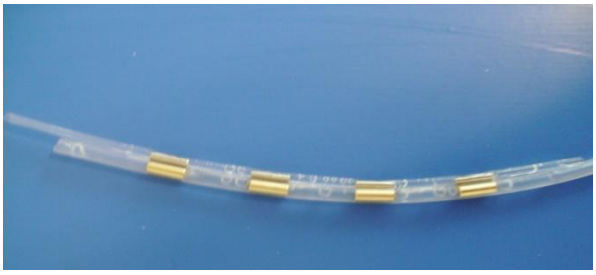
TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	3	Ball	K04.76Au-N35	No sliding
INTERNAL	3	Cylindrical	Z02.5x12ED-N35	

Configuration 6

TYPE	Number Magnets	Type Magnets	Code	Note
EXTERNAL	3	Cylindrical	Z03.5x10GD-N35	Sliding down ok No sliding up
INTERNAL	3	Cylindrical	R03x01x015ND-N35	

October 2010

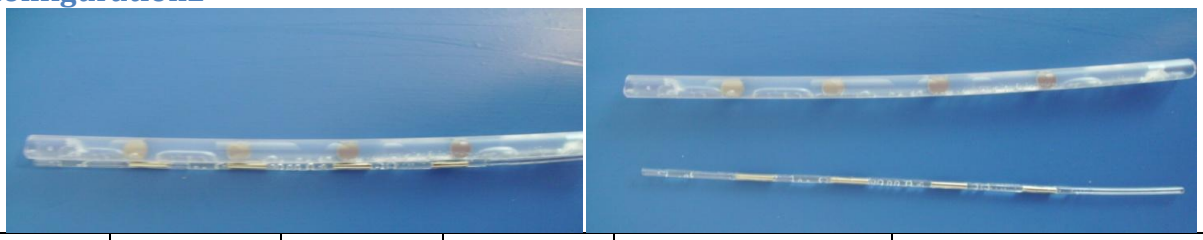
Configuration 1



[61] * http://www.dmwood.com

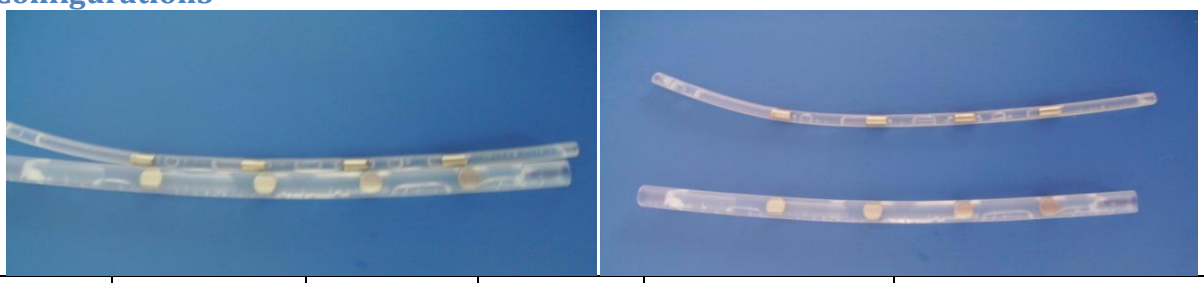
TYPE	Number Magnets	Type Magnets	Code	Tube material (Øe, Øi)[mm]	Note
EXTERNAL	4	Cylindrical	Z03.5x10GD-N35	Frosted PVC (4.6,3.1)	Good coupling No cutted Round shape for the tip suggested
INTERNAL	4	Cylindrical	Z02x10ND-N35	Pellethane 2363-80AE (2.7,2.2)	

Configuration2



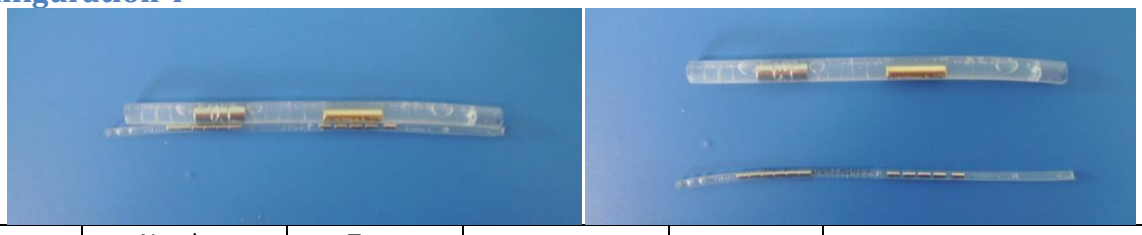
TYPE	Number Magnets	Type Magnets	Code	Tube	Note
EXTERNAL	4	Disc	MPI	Frosted PVC (8.4,6.4)	External cutted External is too rigid Good but worst than the first
INTERNAL	4	Cylindrical	Z02x10ND-N35	Pellethane 2363-80AE (2.7,2.2)	

Configuration3



TYPE	Number Magnets	Type Magnets	Code	Tube	Note
EXTERNAL	4	Disc	MPI	Frosted PVC (8.4,6.4)	Both too rigid Axial magnets are not stable
INTERNAL	4	Cylindrical	D24 (K&J) Ø 3.175x6.35	Frosted PVC (4.6,3.1)	

Configuration 4



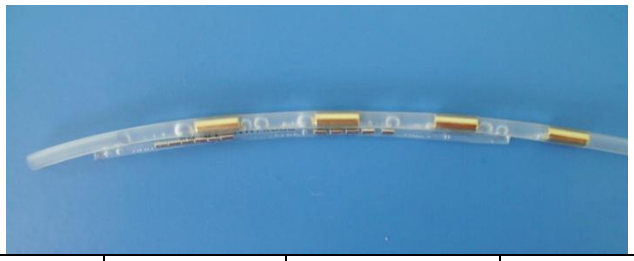
TYPE	Number Magnets	Type Magnets	Code	Tube	Note
EXTERNAL	3 1	Cylindrical Cylindrical	Z04x04ND-N35 Z03x14N52-GD	Frosted PVC (6.6,4.4)	Bad coupling External cutted, too rigid Internal magnets too small in lenght
INTERNAL	11	Cylindrical	Z01.2x03ND-	PVC	

			N35	(2.4,1.4)	

Configuration 5

TYPE	Number Magnets	Type Magnets	Code	Tube	Note
EXTERNAL	4	Cylindrical	D24 (K&J)Ø 3.175x6.35	Frosted PVC (4.6,3.1)	No good (axial magnetization)
INTERNAL	4	Cylindrical	Z02x10ND-N35	Pellethane 2363-80AE (2.7,2.2)	

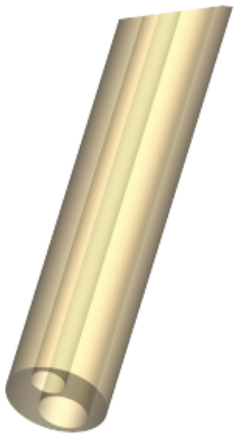
Configuration 6



TYPE	Number Magnets	Type Magnets	Code	Tube	Note
EXTERNAL	4	Cylindrical	Z03.5x10GD-N35	Frosted PVC (4.6,3.1)	Very Bad coupling
INTERNAL	11	Cylindrical	Z01.2x03ND-N35	PVC (2.7,2.2)	

16 Annex VII

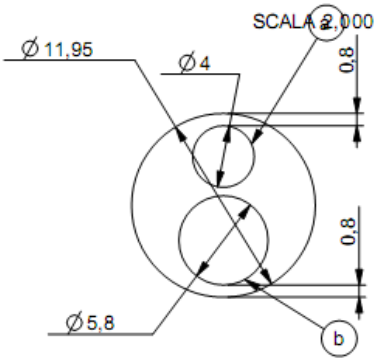
Drawings VideoDrain

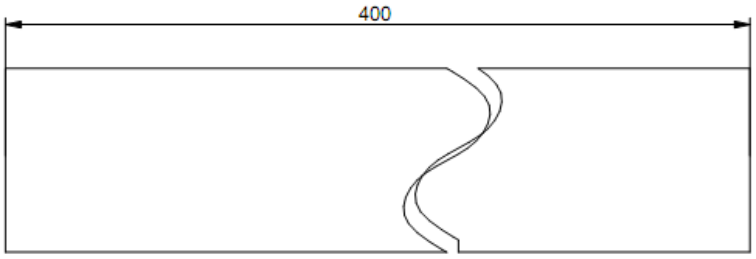


A2	1	Data	Firma	Descrizione
				a drainage channel
MicroTech S.r.l.		MULTILUMEN D		b fiberscope channel
				c
		VIDEODRAIN		d

Number	Part Name	Part Number
1	multilumen_drainage	VID_1

Format: A4 | Tolerances: Grado Medio secondo UNI 5307 | Sheet: 1/1 | Scale: 7:2 | Quantity: 1 | Material: | Treatment: | Drawing Part number: vid_4

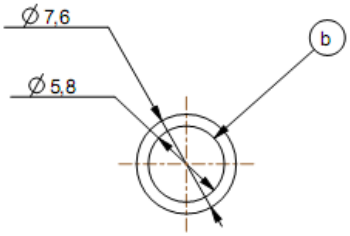


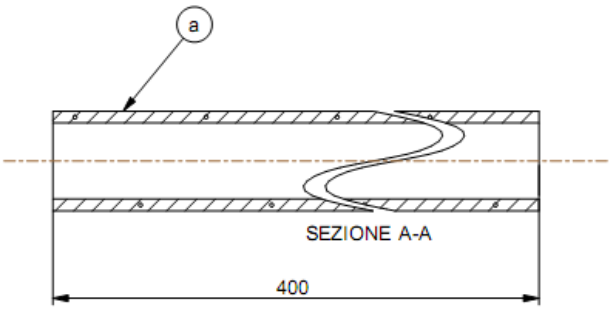


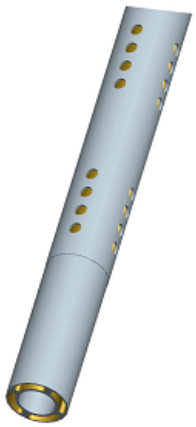
A2	1	Data	Firma	Descrizione
				a balloon bonding
MicroTech S.r.l.		single lumen		b fiberscope channel
				c metal wire
		VIDEODRAIN		

Number	Part Name	Part Number
1	single lumen tube	VID_1

Format: A4 | Tolerances: Grado Medio secondo UNI 5307 | Sheet: 1/1 | Scale: 3:1 | Quantity: 1 | Material: | Treatment: | Drawing Part number: vid_1





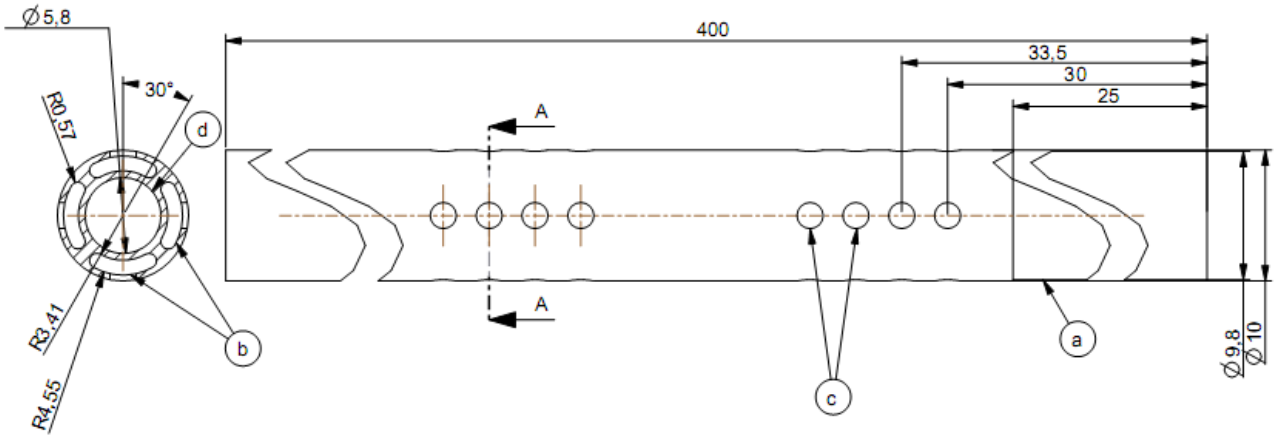


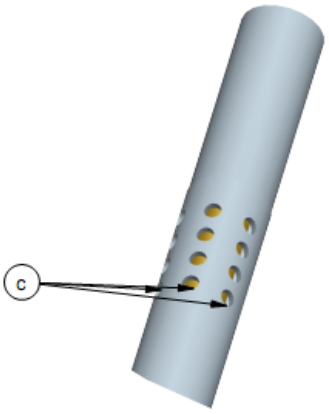
A2	1	Data	Firma	Descrizione
Posizione Position	Exp. Rev.	Data Date	Firma Elena Trois Sign	
				a balloon bonding
MicroTech S.r.l.		Complessivo Assembly	MULTILUMEN 2	b drainage channels
Via De Chirico 11 - 56037 Peccioli (PI) Tel. (+39) 0587 672 447 Fax (+39) 0587 672 450 http://www.microtechitaly.com		Progetto Project	VIDEODRAIN	c drainage holes
				d fiberscope channel

Number	Part Name	Part Number
1	tubo multilumen 2	VID_1

Formato Format	Tolleranze generali di lavorazione Generale manufacturing tolerance	Foglio Sheet	Scala Scale	Quantità Quantity
A4	Grado Medio secondo UNI 5307	1/1	3:1 3:1	1

Materiale Material	Trattamento Treatment	N°Disegno Part number
		vid_1





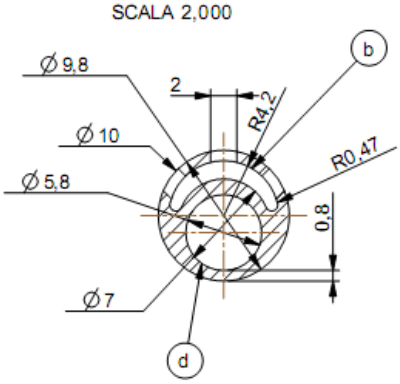
A2	1	Data	Firma	Descrizione
Posizione Position	Exp. Rev.	Data Date	Firma Elena Trois Sign	
				a balloon bonding
MicroTech S.r.l.		Complessivo Assembly	MULTILUMEN 1	b drainage channel
Via De Chirico 11 - 56037 Peccioli (PI) Tel. (+39) 0587 672 447 Fax (+39) 0587 672 450 http://www.microtechitaly.com		Progetto Project	VIDEODRAIN	c drainage holes
				d fiberscope channel

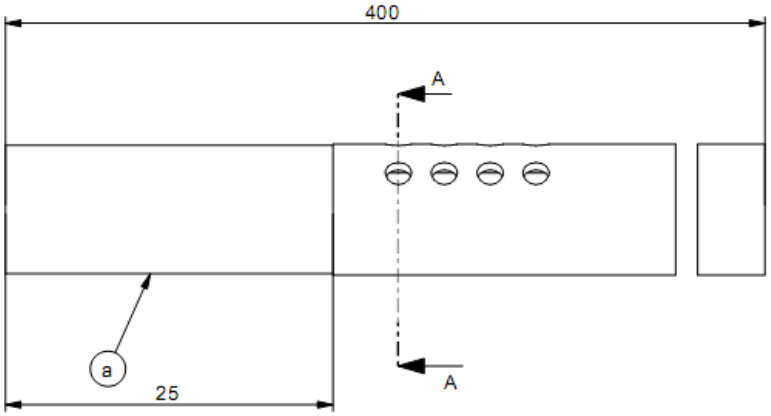
Number	Part Name	Part Number
1	tubo multilumen	VID_1

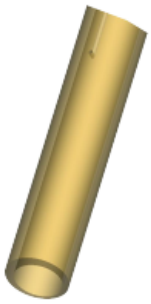
Formato Format	Tolleranze generali di lavorazione Generale manufacturing tolerance	Foglio Sheet	Scala Scale	Quantità Quantity
A4	Grado Medio secondo UNI 5307	1/1	3:1 3:1	1

Materiale Material	Trattamento Treatment	N°Disegno Part number
		vid_1

SCALA 2,000







SCALA 2,000

A2	1	Data	Firma	Descrizione		
Posizione Position	Sost. Rev.	Data Date	Firma Elena Trola Sign			
					a	fiberscope channel
MicroTech S.r.l.			Complessivo Assembly	MULTILUMEN C	b	guidewire channel
					c	
Via De Clivica, 11- 56037 Peccioli (PI) Tel.(+39) 0587 672 447 Fax (+39) 0587 672 450 http://www.microtechitaly.com			Progetto Project	VIDEODRAIN	d	
Number		Part Name			Part Number	
1		multilumen_scoz			VID_3	
Formato Format	A4	Tolleranze generali di lavorazione General manufacturing tolerances	Grado Medio secondo UNI 5307	Foglio Sheet 1/1	Scala 7:2 Scale 7:2	Quantità Quantity 1
Materiale Material	silicone	Trattamento Treatment		N°di segno Part number	vid_1	

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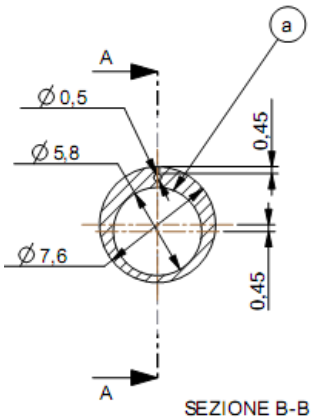
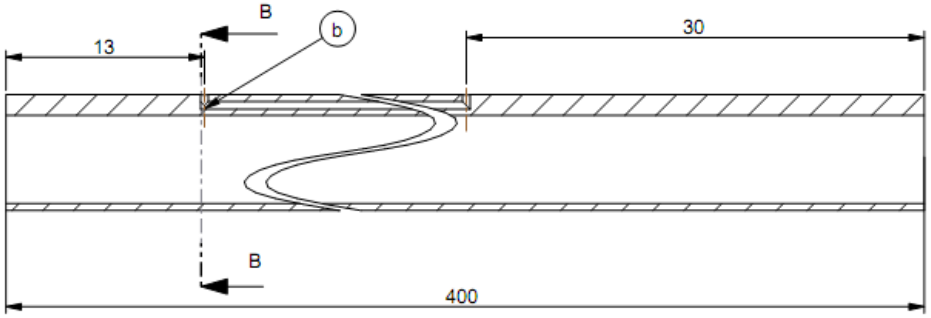
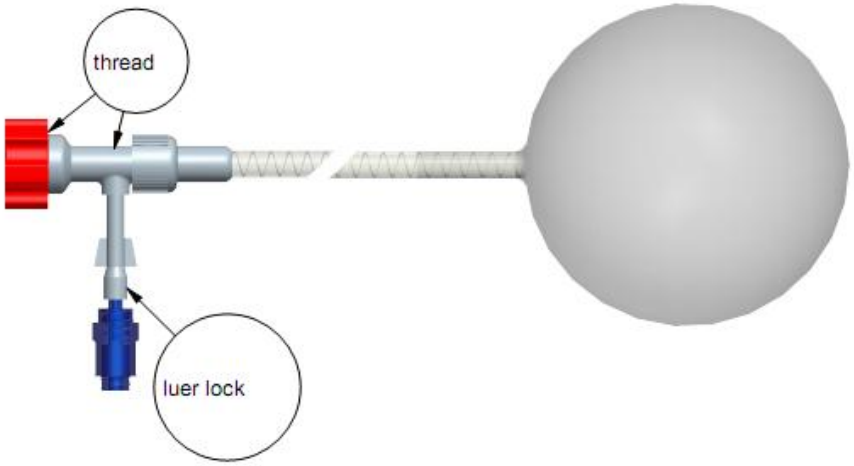


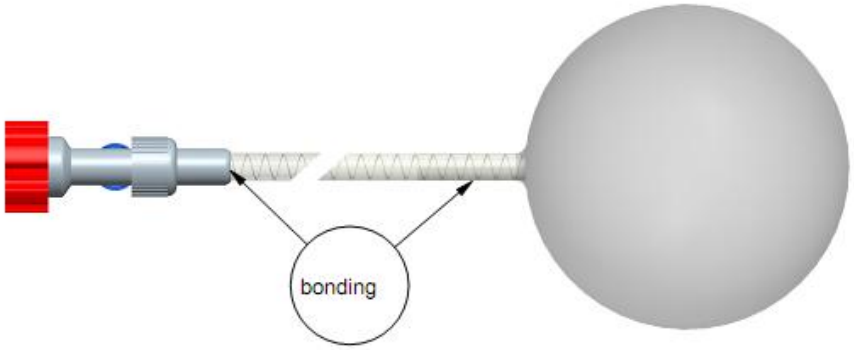
SEZIONE B-B
SCALA 3,500



SEZIONE A-A



SCALA 0,750



17 Annex VIII

FloSeal GI cath. prototypes

Version	Manufactured by	General features	Status
1.0	External subcontractor	See 1.1 Oversheath material more transparent but with morefriction respect to vers.1.1	Existent
1.1 A	External subcontractor	Lenght oversheat: 173cm lenght Cath: 179 cm diam. Est. Oversheat:2.7mm(8fr) diam. Int oversheat 2.1mm thickness 0.3mm diam. Cath 2.0mm diam int. cath. 1.0mm mandrel da 0.4 double until 700mm stopcock	Existent
1.1 B	External subcontractor	Lenght. oversheat: 173cm, lenght. Cath:179 diam. Est. Oversheat:2.7mm(8fr) diam. Int oversheat 2.1mm thickness 0.3mm diam. Cath 2.0mm diam int. cath. 1.0mm mandrel 0.7 corto (per una lenght di 700mm), stopcock	Destroyed
1.1 C	External subcontractor	Lenght oversheat: 173cm lenght Cath:179 diam. Est. Oversheat:2.7mm(8fr) diam. Int oversheat 2.1mm thickness 0.3mm diam. Cath 2.0mm diam int. cath. 1.0mm mandrel da 0.4 double one way valve	Destroyed
1.1 D	External subcontractor	Lenght oversheat: 173cm lenght Cath:179 diam. Est. Oversheat:2.7mm(8fr) diam. Int oversheat 2.1mm thickness 0.3mm diam. Cath 2.0mm diam int. cath. 1.0mm mandrel 0.7 corto one way valve	Destroyed
Baxter	Baxter	Lenght Oversheat :180 cm diam. Est.oversheat:2.45mm diam. Int oversheat: 1.82mm diam. Cath: 1.7mm diam tip cath:1.5mm	Partially modified
1.2	MicroTech (MT)	Uguale a 1.1 con mandrel Ø 0.75mm	Destroyed
1.3	MT	Uguale a 1.1 con mandrel Ø 0.6mm	Destroyed
1.4	MT	as version 1.1 with glued tip of 2 mm in diameter and lenght of 11mm ,soldered mandrel with 2 different diameter(0.8-0.55)	Destroyed
1.5	MT	As version 1.4 1 with glued tip of 1.8 mm in diameter and lenght of 11mm	Existent
2.0	External subcontractor	Lenght oversheat: 173cm lenght Cath:179	Existent

		diam. Est. Oversheat:3.00(+0,-0.05)mm(8fr) diam. Int oversheat: 2.5(+0.03,-0)mm thickness 0.25mm diam. Cath 2.2mm metallic tip insufflation valve	
3.0	MT	As version 1.1 but with different diameter soldered mandrel	Existent
4.0	External subcontractor	Lenght oversheat: 220 cm lenght Cath:227 cm diam. Est. Oversheat: 2.7mm(8fr) diam. Int oversheat: 2.1mm thickness 0.3mm diam. Cath 2.0mm insufflation one way valve spiraled guide wire	CE device-batch 002

18 Annex IX

Floseal GI cath tests

Date: 10/10/2008	Place: ENKI, Concesio Brescia		
People involved in the test session	Bernardo Magnani (MT) Mario Di Cecio (ENKI), Elena Raza (ENKI), Lidia Bonazza (ENKI)		
Vers. Cath.	N. 1.0	Description: lenght 175	N. tested cath.: 2
	N. Baxter	Description: lenght 180	N. tested cath.: 1
Batch Floseal	Not inserted		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results	Test n.: 1	Cath. vers. : 1.0	Result: the catheter works properly
	Test n.: 2	Cath. vers. : 1.0	Result: the catheter works properly
	Test n.: 3	Cath. vers. : Baxter	Result: the catheter works properly
Following actions	Order for the production of 20 catheters with features of version 1.0		
Results of actions	Production of 2 catheters (version named 1.1)		
Test Responsable		Signature	

Date: 01/11/2008	Place: Ospedale del Sacro Cuore, Campobasso		
People involved in the test session	Doc. Gianluca Spera (Ospedale del Sacro Cuore)		
Catheter version	N. 1.1 A		N. tested cath.: 1
	N. 1.1 B		N. tested cath.: 1
	N.1.1 C		N. tested cath.: 1
Batch Floseal	unknown		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results	Test n. 1	N. 1.1 A	the catheter doesn't work, impossible extrusion of Floseal
	Test n. 2	N. 1.1 B	the catheter doesn't work correctly, difficult extrusion
	Test n. 3	N.1.1 C	the catheter doesn't work, impossible extrusion of

			Floseal
General comments Following actions	Doc. Spera was unable to extrude Floseal; the syringe for Floseal crashed and bent (too small); version 1.0 B with a more rigid guide wire was better than the other two; the safety valve was more comfortable than the stopcock: • Choice of one way valve for inflating balloon • Hemostatic valve is ok • preferred transparency of the outer sheath of version 1.0 • the need for more rigid and / or longer metal guidewire • The balloon is good for transparency and volume it is necessary to increase the length of leakage of the catheter compared to the sheath of at least 4.5 cm (lenght of catheter~ 1725mm)		
Results of actions	Planning of additional tests		
Responsabile Test	Doc. Gianluca Spera		Signature

Date: 24/11/2008	Place:MicroTech Peccioli (Pi)			
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT)			
Catheter version	N. 1.1	Description: modified guidewire. Diam. 0.75mm or the entire catheter length		N. tested cath. (same version): 2
	N. 1.3	modified guidewire: diam 0.6 mm for the entire catheter length		N. tested cath. (same version): 1
Batch Floseal	n. HA080515			
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times			
Test results	Test n. 1	Cath. vers. : 1.2	Floseal extruded	
	Test n. 2	Cath. vers. : 1.2	*Phase 1a:* Floseal extruded with a little difficulty; hardly bendable catheter in the distal part	
	Test n. 3	Cath. vers. : 1.3	Floseal extruded with greater difficulty	
	Test n. 4	Cath. vers. : 1.3	*Phase 1bis:* Floseal extruded with greater difficulty hardly bendable catheter in the distal part	
Corrective Actions taken	Evaluation of the length and diameter of the guidewire, evaluation of the procedure. catheter guidewire should be shorter or at least with a smaller diameter in the distal part because of the need to make a 90°curve Correction guidewire diameter			
Results of actions	1. final notch in the distal part of the sheath for better positioning hemostasis valve 2. Guidewire dimensions are important for extrusion 3. In the instructions for use state: • use of gloves to improve grip, • recover drawn product bringing back catheter 4. bring back the catheter to better push Floseal			
Test Responsable			Signature	

Date: 25/11/2008	Place: Ospedale del Sacro Cuore, Campobasso		
People involved in the test session	Bernardo Magnani (MT) Paolo Passi (Baxter) Doc. Gianluca Spera (Ospedale del Sacro Cuore)		
Catheter version	N. 1.2	View the list of prototypes for the features	
	N. 1.3		
	Baxter	"	
Batch Floseal	n. HA080515		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and encountered problems	Test n.: 1	Cath. vers. : 1.2	the catheter doesn't work, impossible extrusion of Floseal
	Test n. 2	Cath. vers. : 1.3	the catheter doesn't work, impossible extrusion of Floseal
	Test n. 3	Cath. vers. : Baxter	the catheter doesn't work correctly, very difficult but possible extrusion of Floseal
Corrective Actions taken	Verify Floseal batch e storage Identification of the cause for no extrudability :the low storage temperature		
Results of actions	The Floseal was actually delivered to the hospital in containers at -20 ° C, which determines the crystallization of the gelatinous matrix and hence the difficulty of extruding the Floseal. Planning further tests		
Test Responsable		Signature	

Date: 28/11/08	Place: ENKI, Concesio Brescia		
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT) Mario di cecio(Enki) Lidia Bonazza(Enki)		
Catheter version	N. 1.2		N. tested cath. (same version): 2
Catheter version	N. Baxter		N. tested cath. (same version):
Batch Floseal	n. HA080515		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and encountered	Test n.:1	Cath. vers. : 1.2	Floseal frozen at -20 °, but thawed after 3 days Lubricated catheter: Floseal extruded but with difficulty

problems	Test n.2	Cath. vers. : Baxter	Floseal frozen at -20 °, but thawed after 3 days Better extrusion of Floseal but not optimal
	Test n.3	Cath. vers. : 1.2	Floseal not frozen, difficoult extrusion
	Test n.4	Cath. vers. : Baxter	Floseal not frozen, difficoult extrusion
	Test n.5	Cath. vers. : 2 precedenti con guaine scambiate	Floseal not frozen, used for the second time Baxter catheter with sheath of Vers. 1.1 is better than 1.1 catheter in Baxter sheath
	Test n.6	Cath. vers. : 1.3	With coating NUSIL-MED 420-12500: Floseal easily extruded
	Test n.7	Cath. vers. : 1.3	lubricated with fluid silicone Floseal easily extruded
	Test n.8	Cath. vers. : 1.2 e Baxter	Both lubricated Floseal easily extruded with Baxter's
Corrective Actions taken	Evaluation of problems encountered in previous tests with bad stored product and search for solutions Rating balloon material Rating balloon / sheath coupling materials Check possibility of using lubricants		
Results of actions	Further tests need to establish the causes of difficult extrusion		
Test Responsable		Signature	

Date: 2-3/12/08	Place: MicroTech Peccioli (Pi)		
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT)		
Catheter version	N. Baxter	Description:	N. tested cath. (same version): 1
	N.1.2 modificato	Description: guidewire 0.75 fino in punta	N. tested cath. (same version): 1
	N. 1.1 con guidewire saldato	Description: welded guidewire,(two different diameters 0.75/0.55 mm on the tip)	N. tested cath. (same version): 1
	N.1.1 D	Description: see annex VI	N. tested cath. (same version): 1
Batch Floseal	n. HA080515		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and encountered problems	Test n.: 1	Cath. vers. : 1.2 modif.	The catheter works enought properly
	Test n.: 2	Cath. vers. : 1.1 D	the catheter doesn't work properly
	Test n.: 3	Cath. vers. : Baxter	the catheter works properly, good extrusion of Floseal
	Test n.: 4	Cath. vers. : 1.1 con guidewire saldato	the catheter works properly, good extrusion of Floseal

Corrective Actions taken	Check the shape and diameter of the Guidewire Finding cause no extrudability	
Results of actions	Welded Guidewire is preferred to the others; so a difference in diameter between the distal and proximal part of the Guidewireis needed , the Guidewire has to reach the distal end of the catheter	
Test Responsable		Signature

Date: 23/01/2009	Place: MicroTech Peccioli (Pi)			
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT)			
Catheter version	N. 1.4		Description:	N. tested cath. (same version): 1
Catheter version	N. 1.5		Description:	N. tested cath. (same version): 1
Catheter version	N. Baxter		Description:	N. tested cath. (same version): 1
Batch Floseal	n.			
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times			
Test results and encountered problems	Test n.: 1	Cath. vers. : 1.4	The catheter works enought properly, extrusion of Floseal	
	Test n. 2	Cath. vers. : 1.5	The catheter works enought properly, extrusion of Floseal but previous version is better	
	Test n. 3	Cath. vers. : Baxter	the catheter doesn't work properly, difficoult but possible extrusion	
Corrective Actions taken	Check Floseal batch Preservation Check possibility of using lubricants Finding cause no extrudability Manufacturing of tips with strict tolerances to avoid excessive lateral leakage of the drug			
Results of actions	The Floseal was actually stored at improper temperature Realization sets of tips to be glued to existing catheters (version 1.1) Planning further tests			
Test Responsable			Signature	
Date: 6/5/09	Place: centro sperimentazione endoscopica Ospedale Gemelli, Roma			
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT) Doc. Gianluca Spera Laura Caliari (Baxter)			
Catheter version	N. 1.4		Description:	N. tested cath. (same version): 1
Catheter version	N.1.5 with teflon sheath		Description:	N. tested cath. (same version): 1
Batch Floseal used	n. HA090407			

Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of 2 cc of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and encountered problems	Test n.: 1	Cath. vers. : 1.4	The catheter works enought properly, extrusion of Floseal
	Test n. 2	Cath. vers. : 1.5 modif.	The catheter doesn't work
Corrective Actions taken	Verify catheter tip shape and diameter Check sheath material Administration of 1cc max		
Results of actions	Leakage almost canceled due to the reduction of the gap between the catheter and sheath. The sheath material impacts on the operation less than the gap		
Test Responsable			Signature

SUMMARY PROGRESS N. 1

It is sometimes difficult to understand how the Floseal extrude properly or it blocks. **Possible causes** are considered to be (in order of importance):

Cause	Degree of concern (1-small, 5-extremely difficult)
1. Storage temperature of Floseal	5
2.dosage of Floseal	5
3. shape of the tip	3
4.dimensions of guide wire	2
5. material of the oversheath	5
6. gap between catheter and oversheath	5

Summary of possible solutions

Solution	Difficulty of solution (1-easy, 5-hard)	Probable effect
Require the proper conservation	3, it is not only a problem in Baxter but also in hospitals	Probably decisive
Reduce the dosage	3, it depends on the surgeons' opinion	Decisive
Reduce the gap between the tip and catheter	4	It can help
Hardening of the guide wire	1	It can help
Use of lubricants	1	It can help, but it would be difficult to prove the complete compatibility with the materials used and in particular with the Floseal
Material change (use of Teflon)	5 (ENKI doesn't use Teflon)	Probably decisive

Undertaken decisions:

- implementation of miniseries (2.0) with steel tip and sleeve micro-striped
- solicitation to Baxter on the verification of the conditions of conservation of Floseal
- request to the clinicians in touch with Baxter on the possibility of extruding a quantity of less than 2 CC of Floseal per time.

NOTE: REQUEST No 3 ACCEPTED, CC introduced a time: 0.5.

Date: 22/06/2008	Place: MicroTech, Peccioli		
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT)		
Catheter version	N. 2.0	Description	N. tested cath. (same version): 1
	N. 3.0	Description:	N. tested cath. (same version): 1
Batch Floseal	n. HA081010		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of **1cc** of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and encountered problems	Test n.: 1	Cath. vers. : 2.0 e 3.0	The catheters work properly; the 2.0 works perfectly well without guidewire
	Test n.: 2	Cath. vers. : 2.0 e 3.0	The catheters work properly
Corrective Actions taken	Verify new prototyping Check old and new prototype with taper guide wire and new dosage of Floseal		
Results of actions	Verification of catheters to be subjected to medical personnel		
Test Responsable		Signature	

Date: 13/07/2008	Place: centro sperimentazione endoscopica Ospedale Gemelli, Rome		
People involved in the test session	Bernardo Magnani (MT) Elena Troia (MT) Prof. Claudio Costamagna (Università Cattolica del Sacro Cuore Roma) Doc. Gianluca Spera (Università Cattolica del Sacro Cuore - Roma) Doc. Rita Conigliaro (Nuovo Ospedale S. Agostino Estense - Modena) Laura Caliari (Baxter) Paolo Passi (Baxter)		
Catheter version	N. 3.0	Description:	N. tested cath. (same version): 3
Batch Floseal	n.		
Test Procedure	Step 1: Block the catheter on the table making an "S", medium radius of curvature of the Beam 30 cm Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of **0.5 cc** of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		

Test results and problems encountered	Test n.: 1	Cath. vers. : 3.0	the catheter is working properly; the oversheath needs to be shortened of 10mm and cutted at the distal end to facilitate the insertion hemostatic valve
	Test n.: 2	Cath. vers. : 3.0	the catheter works properly
	Test n.: 3		
Corrective Actions taken	CE labelling starts Manufacturing of version for the entire GI tract (lenght 2.4m)		
Results of actions	Under development		
Test Responsable		Signature	

Date: 20/10/2009	Place: EETC (European Endoscopy Training Centre) dell'Università Cattolica del Sacro Cuore, Rome		
People involved in the test session	Doc. Gianluca Spera (Università Cattolica del Sacro Cuore - Rome)		
Catheter version	N. 4.0	Description:	N. tested cath. (same version): 2
Batch Floseal	n.		
Test Procedure	Step 1: Block the catheter on an Erlangen model of a suine stomach Step 2: Preparation of Floseal according to IFU Step 3: Assemble the hemostatic valve and introduction of **0.5 cc** of Floseal according to the catheter IFU Step 4: Expulsion of Floseal Step 5: Repeat steps 3 and 4 to 2 times		
Test results and problems encountered	Test n.: 1	Cath. vers. : 4.0	The catheter work properly
	Test n.: 2	Cath. vers. : 4.0	the catheter works properly
	Test n.: 3		the catheter works properly
Corrective Actions taken			
Results of actions	Device ready for the market		
Test Responsable	Spera	Signature	

19 Annex X

ETO Sterization process parameters

Preconditioning period	**14 h min**
Preconditioning temparature	45°C +/- 5°C
Preconditioning relative umidity	45% +/- 5 %
Initial vacuum (-950 +/- 20mbar)	-722 +/- 15 mmHg
Steam immission	23 mmHg (30 mbar)
Steam stabilization time	20 min
Humidity in sterilization chamber	45% +/- 5 %
Sterilization temperature	45°C +/- 5°C
EtO mixture concentration (15% EtO + 85% CO_2)	≥ 235 mg/Lt
Sterilization initial pressure (-20 +/- 13mbar)	-15 +/- 10 mmHg
Sterilization time	≥ 18h
Washings pressure (-800 +/- 26mbar)	-608 +/- 20 mmHg
Number of washing cycles	5