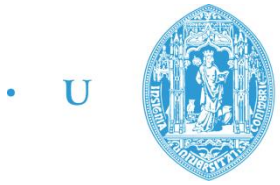

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Filipe André Boiça Costa

The Certification Process of the RDFixer

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2009111136

The Certification Process of the RDFixer

Dissertation presented to the University of Coimbra to meet the requirements needed to achieve the Masters degree in Biomedical Engineering

Advisor: Prof. Dr. João Barreto

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Coimbra, 2014

This work was developed with the collaboration of:

Faculty of Sciences and Technologies of University of Coimbra

Institute of Systems and Robotics of University of Coimbra

Perceive3D S.A.

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To my parents.

Acknowledgements

I would like to thank to my advisor Prof. Dr. João Barreto for allowing me to enter this project. Despite not being always present, he made himself present by helping and criticizing whenever was needed and possible. He is a great person.

I also want to thank to my co-advisor Eng. Ester Soares for guiding me in such an unknown world as medical certification.

I want to mention Peter Pringle and Sandra Balseiro that had a positive interference in my project. By knowing them, I improved more knowledge.

I will never forget Perceive3D team, Prof. João, Rui, Ana, Vitor, Mário, André, Neide, Cristóvão and Carlos. They were so good to me, especially Rui and Ana. Rui because he acted like Prof. João when he was away. He helped me so much and had such patience. Ana worked with me a lot, and she always made suggestions and gave her opinion, sometimes contrary, but always important to my work. I am really grateful.

At some point, I have to thank to Prof. Dr. Miguel Morgado for running the Biomedical Engineering course in such a good tone over these years.

Now, to my friends, I am thankful to all of them. They are part of who I am. Nevertheless, there are some that had a more strong impact this last year. Leonardo was in Groningen this year but almost every day we spoke on the Internet. That is why we are best friends. Fernando, my housemate, taught me so much not only this year, but over the last years we lived together. Ricardo has always been there for me since the start of the course. He has such a unique character but is a very kind person. Gilberto is the funny guy that has some particular similarities with me. So many lunches and football games we had together. Joana is one of my newest friends, and now probably one of the most important. Thank you all for being there with me.

At last, but not the least, to my family specially my parents. Thank you for everything. Thanks you for the opportunity to attend higher education and the support that always motivated me to achieve my goals.

Abstract

During Minimally Invasive Surgery (MIS), many errors occur because the lack of depth perception. Surgeons see their hand-eye coordination affected negatively by one particular optical aberration called radial distortion. Radial distortion cannot be avoided in those small lenses with a wide FOV used in MIS that hinders depth perception and notion of relative distance.

To overcome this need, Perceive 3D S.A. (P3D) created RDFixer. It is a plug-and-play device that intercepts the video feed from any endoscopic equipment and outputs the corrected image signal to the display. It is a software based device that offers new features and brings to the table some benefits in comparison with other devices.

Considered as a medical device, to place it in the market it is required the CE marking under the applicable directive. The Medical Devices Directive (MDD) is 93/42/EEC (EEC stands for European Economic Community), then every device that is developed must be manufactured according to it. By looking at the directive, we identify some aspects very important like the quality management system (product or company), risk management, clinical evaluation, classification, and others.

During this work we can find an introduction to concepts related with the functioning of this particular device, as well as technical and regulation requirements to design new equipments. The main objective is to understand these steps and apply them to the RDFixer towards establishing a clear regulatory path for the product and advance as much as possible with documents to certify the device. In addition, we also investigate the impact that RDFixer can have in different medical endoscopic domains by assessing the amount of distortion present in a collection of 10 scopes of different specialities.

Keywords: medical device, radial distortion, CE marking, endoscopy, Directive 93/42/EEC

Resumo

Durante procedimentos de Cirurgia Minimamente Invasiva, muitos erros ocorrem devido à falta de noção de profundidade. Os cirurgiões vêem a sua coordenação mão+olho afectada negativamente por uma aberração óptica em particular chamada distorção radial. A distorção radial não pode ser evitada em lentes pequenas com um grande campo de visão usadas em MIS, que limita a noção de profundidade e a noção de distância relativa.

Para colmatar esta necessidade, a Perceive3D S.A. (P3D) criou o RDFixer. É um dispositivo plug-and-play que intercepta o sinal de vídeo de qualquer equipamento endoscópico e produz como output o sinal imagem corrigido no monitor. É um dispositivo baseado em software que oferece novas potencialidades e traz para a mesa alguns benefícios comparativamente com outros dispositivos.

Tratando-se de um dispositivo médico, para este entrar no mercado é necessária a marcação CE segundo a directiva aplicável. A directiva para os dispositivos médicos é a 93/42/EEC, assimsendo todos os dispositivos desenvolvidos tem que ser fabricados de acordo com esta. Ao olhar para a directiva, podemos identificar alguns aspectos muito importantes como o sistema de gestão de qualidade (produto ou empresa), gestão de riscos, avaliação clínica, classificação, entre outros.

Ao longo deste trabalho, podemos encontrar uma introdução aos conceitos relacionados com o funcionamento deste dispositivo em particular, bem como requesitos técnicos e de regulação na criação de novos equipamentos. O principal objectivo é compreender estes passos e aplicá-los ao RDFixer com vista a estabelecer um processo regulatório claro para o produto e avançar, quanto possível, com documentação para certificar o dispositivo. Além disso, investigou-se o impacto que o RDFixer pode ter em diferentes domínios da endoscopia médica ao determinar a distorção radial presente num conjunto de 10 lentes de diferentes especialidades.

Palavras-chave: dispositivo médico, distorção radial, marcação CE, endoscopia, directiva 93/42/EEC,

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Acronyms

AIMD - Active Implantable Medical Devices

CE - *Conformité Européene* (European Conformity)

DOF - Depth of Field

EEA - European Economic Area

EEC - European Economic Community

EFTA - European Free Trade Association

EMC - Electromagnetic Compatibility

EMI - Electromagnetic Interference

EN - European Norm

ENT - Ear, Nose and Throat

FDA - Food and Drug Administration

FOV - Field of View

IEC - International Electrotechnical Comission

ISO - International Organization of Standardization

IVDD - In-Vitro Diagnostic Devices

MDD - Medical Device Directive

MIS - Minimally Invasive Surgery

NB - Notified Body

QMS - Quality Management System

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1. Introduction

1.1 Motivation

This project emerges from the need to understand the complex legislation applied to medical devices and use it to run a certification process in a new device that is going to be introduced into the market - the RDFixer.

The regulatory process is a subject where there is limited experience. For that reason, the final goal is to be able to obtain the CE mark by presenting all the necessary documentation.

1.2 Context

Medical interventions using MIS have gained increasing popularity in different clinical specialities, and are currently the standard to perform many of today's diagnosis and surgical procedures. Over time, the MIS industry has been constantly working towards improving the visualization during medical procedures. In the last decade, efforts in visualization have shifted to the depth perception issue. The lack of depth perception during MIS is known to difficult the surgeons hand-eye coordination and contribute to error rates in MIS.

To overcome the current difficulties that are mentioned above, Perceive3D S.A., a company focused in Computer Vision, developed a device called RDFixer. RDFixer is a visualization system for medical endoscopy that improves depth perception of surgeons by removing radial distortion in real-time.

Over the years there was a rise of requirements to new medical devices, since their complexity has also increased. With this increase in complexity, the risk of happening something wrong must be very well controlled. Most of the accidents result from bad use because people don't have enough experience or don't read the required information.

Based on the fact that the product is intended to enter the market, there must be a record of all product characteristics, designs, components and possible failures. Other things such as accessories, safety, usability analysis or features must also be included in the documentation.

Today, the European Commission is more rigid and tough with the manufactures, which require extra caution during the development of new devices. Therefore, the right documentation and the right methods should exist.

1.3 Objectives

There are two main objectives in this project. The first objective is to understand the regulatory process related with new medical devices entering the market. The device is called RDFixer, a software based device. Therefore, there is a need to understand how this software is compliant with all legislation existent both at national and European levels.

It is fundamental to understand the device. To be able to advance for the documentation of the device, we must know its characteristics and its design and understand the software and hardware involved. The documentation is an essential part of the regulatory process related to the device.

This objective included some secondary objectives: interaction with notified bodies and other important entities, study of the market, perform a pilot trial intended to support and test the device, search for relevant documents to understand the certification process, such as directives, norms, guidelines, create a clinical evaluation of the device by compiling all the scientific documentation that supports the device.

By understanding the regulatory process and applying it, some documentation must be produced. This documentation includes a Technical File that resumes and includes all activities related with conception, quality, risk management, and others. Additionally to the Technical File there are also documents such as Quality Plan or a Risk Management File (the Risk Management File is one of the outputs of the risk management).

The other main objective is about knowing more about endoscopy, where the device could bring improvements. This involves studying the optics related with endoscopes, tracking the different type of optics used in each procedure, identification of procedures where the device could be useful and validation of this identification in real tests. To note that the study of the optics includes getting used to the language related with radial distortion and calibration of cameras, as well as the preparation of a small study of several lenses.

All this work is related with a Biomedical Engineer, since he can understand the development steps of any medical device and work in various areas.

1.4 Planning

- First task: Understand the RDFixer
- Second task: Study of documents and directives to understand the regulatory process
- Third task: Define a plan about the work that has to be done (summary of all the work done until this point and further actions)
- Fourth task: Study of optics and surgical procedures where RDFixer could bring some improvements
- Fifth task: Write the thesis

Initial Planning

09/13	10/13	11/13	12/13	01/14	02/14	03/14	04/14	05/14	06/14	07/14
1st										
	2nd									
			3rd							
						4th				
								5th	Presentation	

Final Planning

09/13	10/13	11/13	12/13	01/14	02/14	03/14	04/14	05/14	06/14	07/14	08/14	09/14
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		2nd										
				3rd								
							4th					
									5th			Present.

2. About the RDFixer

2.1 Benefits of MIS

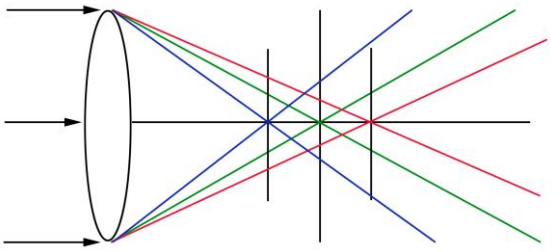
MIS has gained popularity in the last years. Medical interventions using MIS minimize trauma to the patient, which means lower probabilities of facing post-operative problems, faster recovery and consequently shorter permanence periods at the hospital. MIS is currently the "standard" procedure to perform many of today's diagnosis and surgical procedures.

However, not only MIS procedures are considered significantly harder to perform, but also require a longer learning curve than conventional surgery, which contributes to the slower adoption of MIS and limits its penetration.

Most of the specialities using MIS rely on the use of small lens to be inserted in the human body. Small lenses, with a wide FOV, produce an optical aberration called radial distortion that causes a deformation on the images [1].

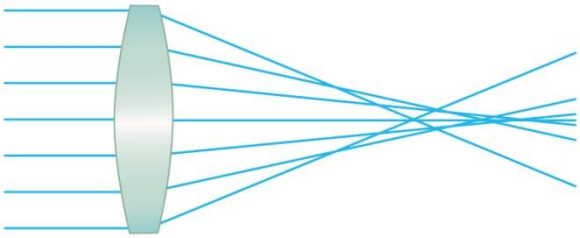
2.2 Optical aberrations

An optical aberration is a deviation of the performance of an optical system from the predictions of paraxial optics. In an imaging system, it occurs when light from one point of an object does not converge into (or does not diverge from) a single point after transmission through the system. Aberrations can occur, not only because the simple paraxial theory is not a completely accurate model of the effect of an optical system on light, but also due to flaws in the optical elements. Aberration leads to blurring of the image produced by an image-forming optical system [2,3].



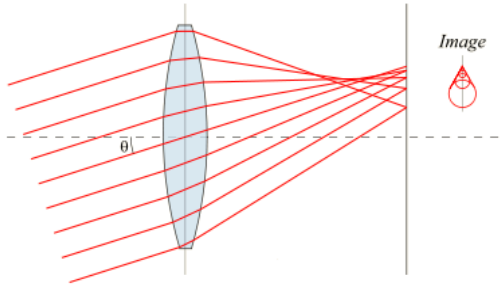
Chromatic Aberration

White light is composed of radiation of many colours. When it passes through a lens, different colours are diffracted by different amounts. Schematically, a blue image is in focus closer to the lens than a red image [2,3].



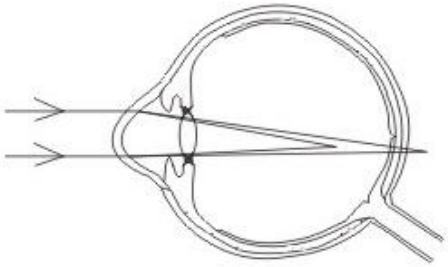
Spherical Aberration

Consider a bright distant object on the optical axis of a lens and its image on the other side. Spherical aberration causes rays passing through the lens far away the optical axis to focus at a different distance from the lens than rays passing through the lens close to the optical axis [2,3].



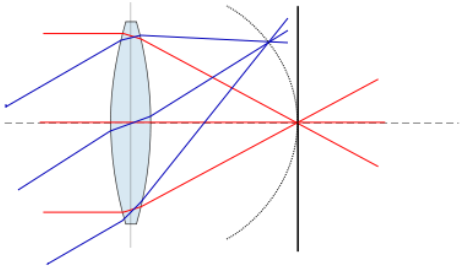
Coma

Similar to spherical aberration, coma affects images of objects not on the optical axis of the lens. In an instrument affected by coma, the image of a bright point is seen as a series of eccentric and diminishing circles or disks, giving the appearance of a comet [2,3].



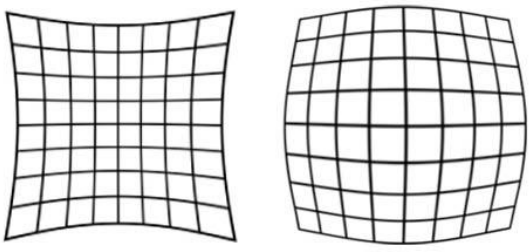
Astigmatism

Causes the image of a sharp point of light to appear as an ellipse away from the focal plane, with the long axis of the ellipse shifting by 90 degrees on opposite sides of the focal plane [2,3].



Curvature of Field

Describes a condition in which the focal plane is a curved surface rather than a true plane [2,3].



Distortion

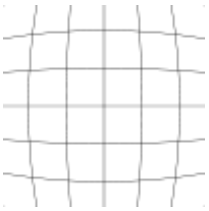
Variations in the focal length of the lens with distance away from the optical axis will produce distortion, which will cause the image of a straight line to bend [4].

A very common effect in spherical aberration when an image is simply out of focus is called defocus. Optically, defocus refers to a translation along the optical axis away from the plane or surface of best focus. In general, defocus reduces the sharpness and contrast of the image. What should be sharp, high-contrast edges in a scene become gradual transitions. Fine detail in the scene is blurred or even becomes invisible.

Nearly all image-forming optical devices incorporate some form of focus adjustment to minimize defocus and maximize image quality. The degree of image blurring for a given amount of focus shift depends inversely on the lens focal length. Lenses with low focal length are very sensitive to defocus and have very shallow depths of focus. Lenses with high focal length are highly tolerant of defocus, and consequently have large depths of focus. The limiting case in focal length is the pinhole camera, in which case all objects are in focus almost regardless of their distance from the pinhole aperture. The penalty for achieving this extreme depth of focus is a very weak illumination at the imaging film or sensor, limited resolution due to diffraction, and very long exposure time, which introduces the potential for image degradation due to motion blur [4].

2.2.1 Radial distortion

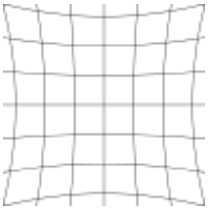
In geometric optics, distortion is a deviation from rectilinear projection, a projection in which straight lines in a scene remain straight in an image. It is a form of optical aberration. Although distortion can be irregular or follow many patterns, the most commonly encountered distortions are radially symmetric, or approximately so, arising from the symmetry of a photographic lens. These radial distortions can usually be classified as either barrel distortions or pincushion distortions [2,3].



Barrel distortion

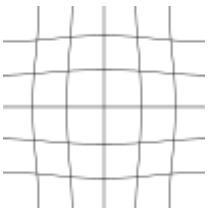
In barrel distortion, image magnification decreases with distance from the optical axis. The apparent effect is that of an image which has been mapped around a sphere (or barrel). Fisheye lenses, which take hemispherical views, use this type of distortion that can be used as a way to map an infinitely wide object plane into a finite image area. We evidence the effect of barrel distortion in the middle of the lens's focal length range and its effect is worst at the wide-angle end of the range (near the boundary) [2,3].

Pincushion distortion



In pincushion distortion, image magnification increases with the distance from the optical axis. The visible effect is that lines that do not go through the centre of the image are bowed inwards, towards the centre of the image, like a pincushion [2,3].

***Mustache* distortion**



A mixture of both types, sometimes referred to as *mustache* distortion (moustache distortion) or complex distortion, is less common but not rare. It starts out as barrel distortion close to the image centre and gradually turns into pincushion distortion towards the image periphery, making horizontal lines in the top half of the frame look like a handlebar moustache [2,3].

In photography, distortion is particularly associated with zoom lenses, particularly large-range zooms, but may also be found in prime lenses, and depends on focal distance. Barrel distortion may be found in wide-angle lenses, while *Mustache* distortion is observed particularly on the wide end of some zooms, with certain retrofocus lenses, and more recently on large-range zooms. A certain amount of pincushion distortion is often found with visual optical instruments, e.g., binoculars, where it serves to eliminate the globe effect [2,3].

In small optics, like the ones used in MIS, the small sizes of the lenses offer good optical quality, but do not avoid unwanted effects, such as radial distortion. To overcome this problem with small lenses, there is RDFixer.

2.3 RDFixer

The RDFixer is a software-based system for improving the visualisation in medical endoscopy by removing the image radial distortion. The radial distortion is an optical aberration that cannot be avoided in small lenses with a wide FOV and that hinders depth perception and notion of relative distance.

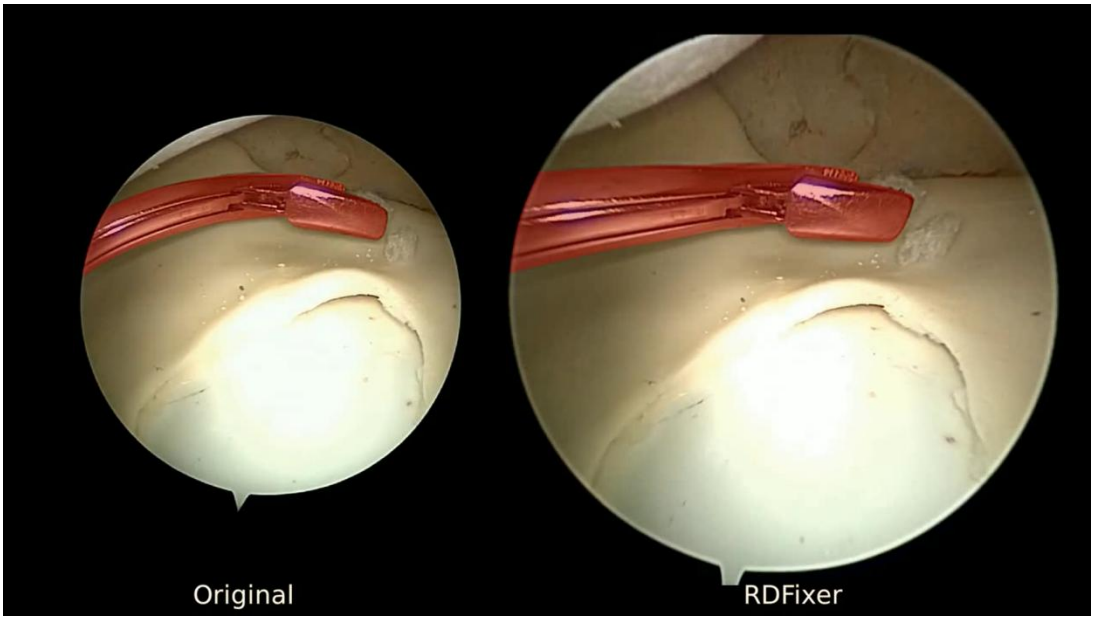


Figure 1: Images evidencing the presence (left) and absence (right) of radial distortion, where the image on the right is bigger just to keep the central region equal (it is not a zoom).

The software runs in a dedicated PC - the RDBox - that is connected in-between the image acquisition system and the display. The system receives as input the original video stream, removes the distortion via image warping, and sends the corrected video to the screen.

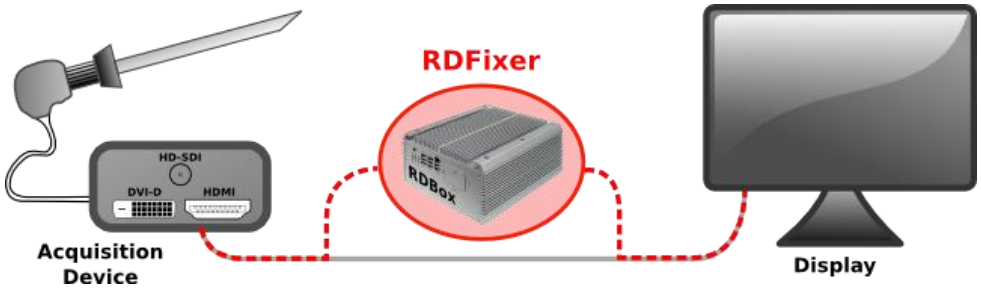


Figure 2: Connection of the RDFixer in-between the image acquisition system and the display.

Consists of a regular workstation (motherboard, RAM, CPU and power source) equipped with a GPU and a frame grabber. The HD video feed is captured through the frame grabber and the image is transferred to the GPU that performs part of the processing. At the end, the resulting corrected image is displayed onto the visualization system through the OpenGL buffer.

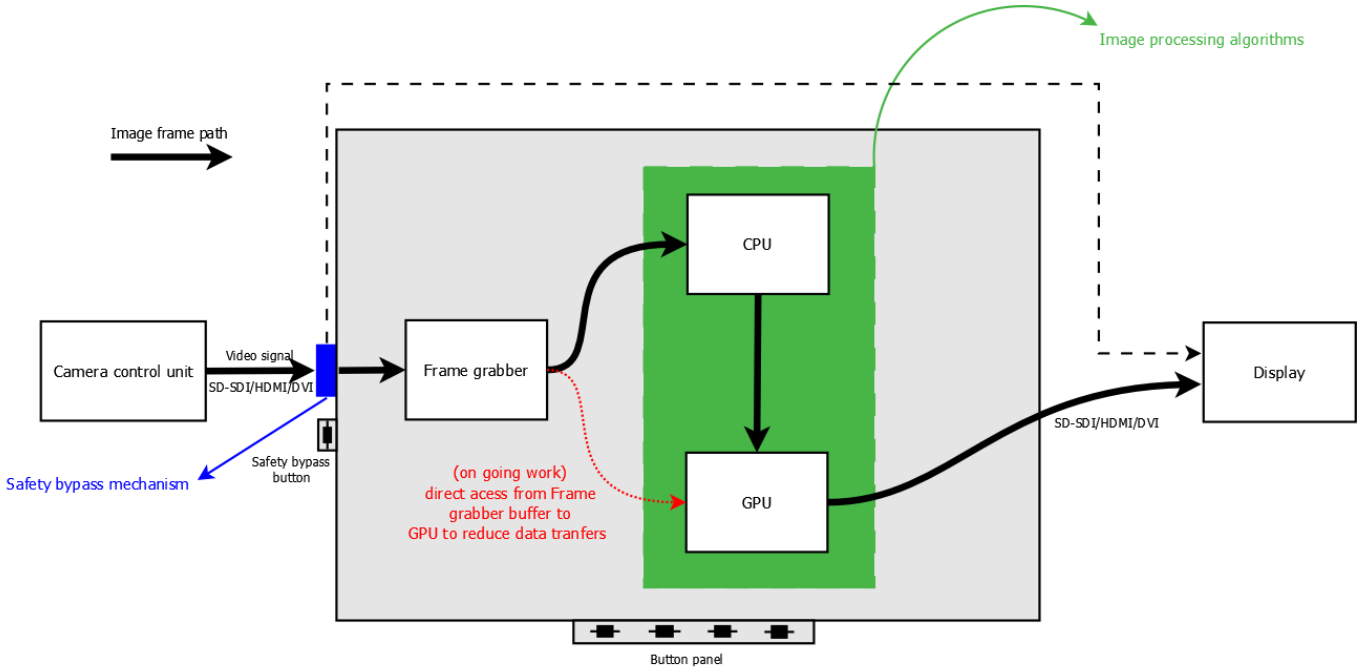


Figure 3: RDFixer architecture.

RDFixer provides free radial distortion images. It is compatible with every endoscopic equipment and/or lens in the market and is transversal with different types of MIS procedures (e.g. arthroscopy, laparoscopy, rhinoscopy, cystoscopy, etc.). RDFixer allows automatic update of camera parameters during operation and runs on COTS hardware (Commercial of-the-shelf hardware), using a multicore architecture. Besides, it doesn't involve changes in the existing surgical routine and have no delays in correcting SD video (legacy equipment) or HD video, including 1080p @ 60Hz.

2.4 Underlying technology

RDFixer main tool is used for calibration and it is called EasyCamCalib. It is a Matlab software for calibrating a camera presenting radial distortion using only one image of a planar calibration grid. The radial distortion is modelled using the so called division model and the method provides a closed form estimation of the intrinsic parameters and distortion coefficient [6].

The software provides a reliable calibration of a camera from a single image. The calibration is performed through the following [7]:

• Boundary Detection (in the case of endoscopic or fish-eye lenses). The boundary between the meaningful region of the arthroscopic image and the background is defined. The boundary information is used to later restrict the automatic corner detection of the chessboard pattern.

• Automatic Corner Detection. The image is searched for plausible corners, which are referenced in the chessboard reference frame. This detection is based in the entropy of the angles and uses geometric metrics to validate and count the corners.

• Initial Calibration. With the automatic corners detected, a first calibration is estimated according with [8]. This calibration will be referred as the *Initial Calibration*.

• New Points Generation. Using the initial calibration estimation, points are generated in the image plane and matched to squares of the calibration grid (chessboard frame).

• Final Calibration. With the new generated points the calibration parameters are recomputed, providing what we will call from now on the *Final Calibration*.

• Calibration Refinement. The calibration parameters are refined using a non linear optimization over the re-projection error. This is the final result of the calibration and will be referred from now on as the *Optimal Calibration*.

For EasyCamCalib to be able to calibrate the camera from a single image, the following requirements must be fulfilled:

• The angle between the optical axis and the normal to the calibration plane should be higher than 15^0, i.e. fronto-parallel configurations (angle=0^0) must be avoided. Highly slanted views contribute to avoid bad automatic corner detections.

• The number of squares present in the image must be enough to calibrate from a single view (at least three squares, which make twelve corners). More points in the image, the better the projection model will be estimated.

• The calibration grid must be in the central part of the image. An optimal situation is when all the image is filled with the calibration grid.

2.5 Market study

2.5.1 Overview

Endoscopy systems have a huge market demand across the globe owing to their wide application areas (orthopaedics, urology, gastroenterology and others), as well as their flexibility in terms of specification of instruments, which fits in with the various requirements of different procedures. The market has seen an extraordinary amount of technological improvements and breakthroughs in the last few years, as companies have focused on developing products that are capable of reducing pain, curtailing the number of sick days, and reducing the overall cost of the treatment. The global endoscopy equipment market was estimated at $28.2 billion in 2013 and is expected to reach $37.9 billion by 2018.

The market for visualization equipment is segmented into endoscopy cameras, video processors, video convertors, camera heads, light sources, wireless displays and monitors, transmitters and receivers, and others. The wireless displays and monitors segment is the fastest-growing segment of the visualization systems market.

Over the years, the demand for endoscopy has increased significantly because of the growing preference for minimally invasive surgical procedures. Apart from being minimally invasive, endoscopic procedures are also cost effective in terms of pre- and post-operation care costs and length of stay at hospitals. The technological advancements and breakthroughs in the field of endoscopy are expected to drive the global market in the coming years. These technological developments have resulted in several advancements, including increased angles in the FOV in endoscopes, incorporation of high-resolution technologies such as 3D systems, capsule endoscopes,

and miniaturized endoscopy systems. The other factors that are driving the growth of the global endoscopy equipment market include the favourable reimbursement scenario from the countries where was investment, growing aging population, and increasing prevalence/incidence of diseases that require endoscopy procedures.

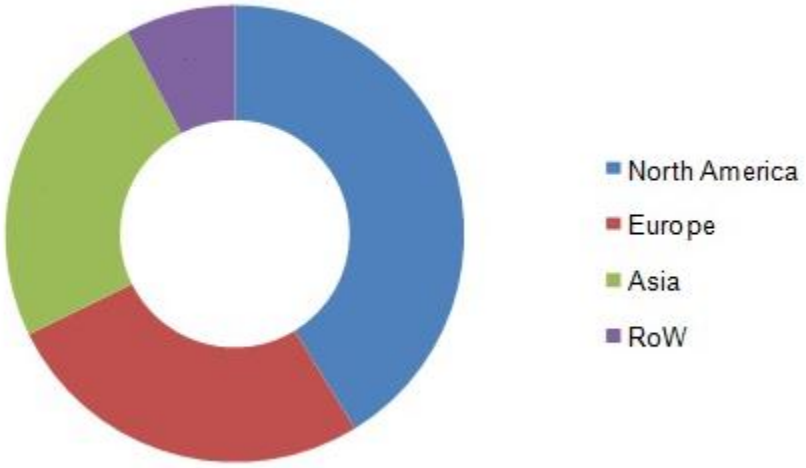


Figure 4**:** Endoscopy equipment market by geography 2013 [9]

The global market is dominated by North America, followed by Europe and Asia. The growth in the endoscopy market is likely to be focused on the fast-growing Asian region owing to increased healthcare spending by the government in China; the increasing number of endoscopic surgeries; the improving endoscopic infrastructure in India; the establishment of training centers for endoscopy in India, China, and Japan; wide support for endoscopy-related research activities in Japan; and increased patient awareness about MIS in Asia. The Rest of World (RoW) region - which includes South America, the Middle East and North Africa, and the Pacific countries - is likely to witness steady growth in the endoscopy market. This is due to the increasing focus of key players on the Middle Eastern countries and Brazil, the increasing number of endoscopy training workshops and investments in Australia, and several government initiatives in New Zealand to develop an efficient workforce for endoscopy services [9,10,11].

2.5.2 Relevant companies

- **Stryker** introduced some years ago the *Idealeyes* lenses with the claim of distortion reduction. However, the compensation is far from being perfect and it

typically involves reducing the FOV. Moreover these features are only available for large diameter scopes and HD systems [1,12,13].

- **Olympus** introduced a few years ago the *TrueView II* lenses claiming, among other features, low distortion images. More recently they developed a powerful optical technology for image improvement called NBI (Narrow Band Imaging) that increases the visibility of blood vessels and other structures. This has been implemented all over their products in different areas. In laparoscopy, Olympus has also a technology for 3D visualization [1,14].

- **Karl Storz** is a privately held global medical device company. It undertakes the the design, manufacture, distribution and sales of endoscopy, laparoscopy, gynecology, urology, proctology, arthroscopy and other surgery related medical devices and instruments. Its wide product range is used in human and veterinary medicine as well as in industrial applications [1,15].

- **Viking Systems** is a designer, manufacturer and marketer of laparoscopic vision systems. The company's flagship product is a three-dimensional (3D) vision system that offers advanced 3D laparoscopic visions with high definition (HD). It also manufactures two dimensional (2D) laparoscopic vision systems and digital cameras. It was considered the only company effectively commercializing 3D systems. It is a subsidiary of Conmed Corporation [1,16,17].

- **Conmed** is an important company in development and manufacture of surgical instruments and devices used for minimally invasive procedures and monitoring. They present HD arthroscopes capable of improve the light transmission and depth perception, and also increase contrast. The company offers a broad range of products, not only in arthroscopy and endoscopic technologies, but also in powered surgical instruments, electrosurgery, cardiac monitoring disposables and endosurgery. Conmed’s products are used by surgeons as well as physicians in various applications [1,17,18].

- **Sometech** has a technology of 3D visualization that, according to the company, improves the depth perception, reduces the duration of medical procedures and the learning curve since the image seen is like the one seen in reality. It can also reduce side effects like nausea or headaches [19].

- **Panasonic** developed medical displays that allow 3D visualization with interesting features. The 3D effect and image quality are indicated for endoscopic procedures. This detailed quality allows a correct reproduction of the colour and a consistent performance that won't be affected by the environment where the procedure is going to be made [20].

- **Sony** stepped in with 3D displays, creating devices capable of improve the depth perception and spatial orientation during complex procedures. They offer other tools of image optimization like ChromaTRU [21].

- **InnerOptics** proposed a stereo technology that partially uses the existing endoscopy system in order to minimize the end-user cost. InnerOptics proposes to sell a dual channel endoscope that can be mounted in the already purchased HD camera. Like in RDBox, a PC is used to intercept the video and render the stereograms to be sent to a 3D display. Although not explicitly said in their brochures, the technical solutions can provide in the best case SD resolution [1,22].

- **Aesculap** is a medical device manufacturer that operates as a subsidiary of B. Braun Melsungen. Its product range includes among other items surgical instruments for open or minimally invasive approaches, implants (e.g. for orthopaedics, neurosurgery and spinal surgery), surgical sutures, sterile container, storage, motor and navigation systems as well as products for cardiology [23,24].

- **NDS** designs and manufactures comprehensive medical imaging and informatics solutions for today’s operative and interventional suites. Their Advanced

Imaging Processing and Digital Signal Processing technologies include new features capable of enhance the visualisation (e.g. Image-Lag Reduction) [25].

- **Zmed** develops medical image processing technology and related devices for endoscopic and MIS markets. The company's flagship product, the Zmed Clarity, is a small dedicated computer system about the size of a set-top box. The device receives a live video stream from the surgical camera, applies image processing algorithms designed to eliminate distortion and improve image clarity, and then transmits the processed image stream to a display monitor in the operating room [26,27].

- **Johnson & Johnson** owns a group called **Ethicon Endo-Surgery, Inc** that develops and markets advanced medical devices for minimally invasive and open surgical procedures. It focuses on procedure-enabling devices for the interventional diagnosis and treatment of conditions in general [28].

- **Richard Wolf** is one of the leading manufacturers of high-quality products for endoscopic diagnostic and therapy in human medicine. They offer all kind of instruments for endoscopic use in the entire field of human medicine. New and innovative products such as Full HD digital video cameras in conjunction with a distinguished Picture Archiving and Communication System (PACS) prevent movies and images in a high quality [24,29].

- **FUJIFILM** is one of world's leading imaging and photographic equipment producers. The company along with its subsidiaries is engaged in the development and production of imaging, information and document solutions. FUJIFILM also offers medical systems, graphic system machinery, life science machinery, optical devices, front panel display materials, inkjet materials and electronic components [30].

- **World Of Medicine (WOM)** is principally engaged in the manufacture and development of medical technical equipments for the treatment of MIS. One of their divisions offer products for visualization and transmission of diagnostic

data and video documentation systems for visualization for MIS. World Of Medicine is now a subsidiary of ATON GmbH [24,31].

- **Pentax** is engaged in the business of manufacture and sale of medical device, cameras and optical equipment. They develop and market video and fiber endoscopy equipment and computer technology and imaging products for diagnostic, therapeutic and research procedures in the GI, ENT and Pulmonary medical areas. The company provides a complete line of endoscopes, accessories, carts, computer hardware and software platforms, video equipment, and computer software for image and data management. Recently, Pentax was merged with Hoya Corporation, to operate as a single entity [32].

- **Medrobotics** is a company that engaged in developing advanced robotic technologies. The company services are applicable in a number of different medical specialist areas which include minimally-invasive cardiac surgery, electrophysiology, laparoscopy, colonoscopy and arthroscopy. The company's technologies find their applications in various markets which include medical, industrial, military, and law enforcement [24,33].

2.5.3 Competition and differentiation

Some manufacturers of endoscopy lenses have tried to gain advantage with respect to the competitors by diminishing the amount of radial distortion through careful optical construction. There is also companies offering, or intending to offer, 3D endoscopy systems aiming at enhance depth perception through stereo imaging. The manufacturers of displays provide from generation to generation new breakthroughs not only on resolution, colour and contrast, but also introducing algorithms capable of improving the way we see the images. Some of the major players in the global endoscopy equipment market include Ethicon (a Johnson & Johnson company), Olympus, Karl Storz, Stryker, Hoya Corporation (Pentax), Fujifilm, Richard Wolf and Conmed [9].

RDFixer offers strong value propositions in terms of newness, accessibility, risk reduction and cost, the two latter being specially relevant to fulfil an increasing concern

all over the world about the costs of healthcare. Both technical advances in 3D endoscopy and advances in optical construction leading to distortion free endoscopy lenses are unlikely to happen soon.

If we consider that endoscopic devices have a lifespan of 5 years and they are sold at an average of 100K every year, we can predict that there are currently 500K equipments in operation worldwide. Therefore, the primarily targets should be the verticals of Arthroscopy, ENT endoscopy and Neuroscopy (26% of the specialities) in Europe (28% of the world endoscopic devices market) [1].

3. Certification Process

3.1 CE Mark

What does the CE mark means? CE stands for *Conformité Européene* which means European Conformity. The CE marking indicates that a product is compliant with some legislation, European Community Directives also known as EC Directives, allowing its free movement throughout the European Economic Area (EEA; 28 member states of the EU plus EFTA countries Iceland, Norway and Liechtenstein), Switzerland (also from the EFTA but not member of the EEA) and Turkey. By affixing the CE mark on a product, a manufacturer assumes all responsibility for guarantee conformity with all of the legal requirements implicated [34,35,36,37]. There are also numerous "Agreements on Mutual Recognition of Conformity Assessment" between the European Union and other countries such as the USA, Japan, Canada, Australia, New Zealand and Israel [38].

Some products don't need CE marking. Only those which Directives are mandatory can hold the CE mark. Directives are legal acts of the European Union, which requires member states to achieve a particular result without dictating the means of achieving that result. It can be distinguished from regulations which are self-executing and do not require any implementing measures [39]. Each Directive has different requirements and conditions to fulfil, which make it match with the different products. Before the product is placed on the market, the CE mark is required and it is the result of a successful conformity assessment procedure completed by the manufacturer as laid down in Community legislation applying to the product in question [34].

There are mechanisms that make sure that the CE marking is put on products correctly. The following list contains the Directives applied to devices [40]:

- AIMD
- Appliances burning gaseous fuels
- Cableway installations designed to carry persons
- Eco-design of energy related products
- Electromagnetic compatibility
- Equipment and protective systems intended for use potentially explosive atmospheres

- Explosives for civil uses
- Hot-water boilers
- IVDD
- Lifts
- Low voltage
- Machinery
- Measuring Instruments
- Medical devices
- Noise emission in the environment
- Non-automatic weighing instruments
- Personal protective equipment
- Pressure equipment
- Pyrotechnics
- Radio and telecommunications terminal equipment
- Recreational craft
- Safety of toys
- Simple pressure vessels

The CE mark is affixed based on the level of risk of the product; if only by the manufacturer (in this case, only a Declaration of Conformity is necessary, stated by the manufacturer that everything is conform), or by an authorized representative, a Notified Body, who decides whether the product meets all the CE marking requirements. Notified bodies are certification organisations notified by the European Commission that, in accordance to all authorized representatives from the member states mentioned before, carry conformity assessment procedures [41]. Forward in this work we will talk more about these organisations.

The certification process, that ends with the CE mark, can be divided among six stages [42,43]:

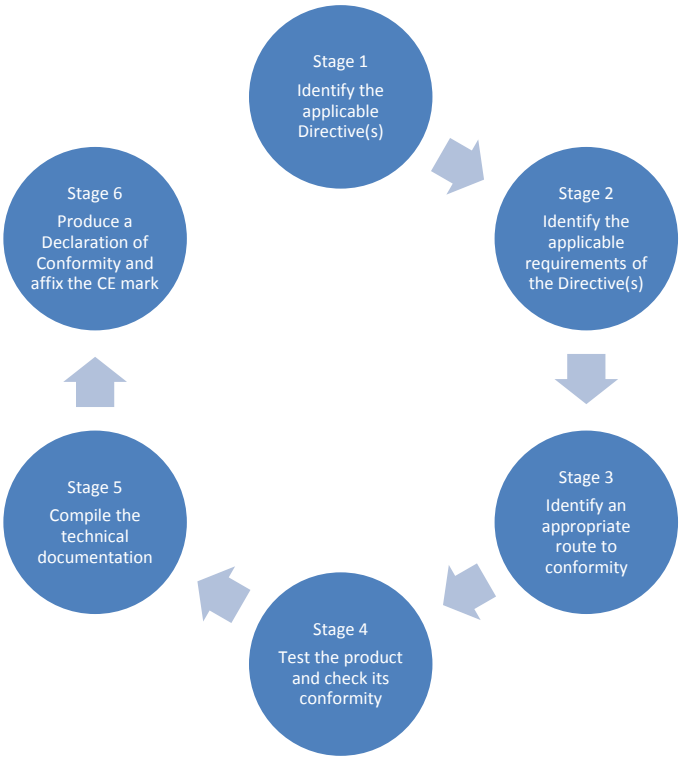


Figure 5: Certification process stages

Stage 1: Identify the applicable Directive(s)

Not all products are required to hold CE marking. Only the products that fall within the scope of at least one of the directives mentioned above. To accomplish this stage, it is required to read the scope of each directive.

Stage 2: Identify the applicable requirements of the Directive(s)

The intended use of the product, as well as its classification, influence the way of demonstrating conformity, because every Directive has different essential requirements that the product has to meet. After defining which Directive, we should go for the applicable "harmonised standards", which offer an assumption of conformity to the essential requirements.

Stage 3: Identify an appropriate route to conformity

It is not obligatory for all products, but it must be considered the involvement of notified bodies on the conformity assessment procedure. It will depend most of times on the Directive covered and classification of the product.

Stage 4: Test the product and check its conformity

After the requirements have been established, the conformity of the product needs to be checked. This usually involves assessment and/or testing at the responsibility of the manufacturer, and may include an evaluation of the conformity of the product to the harmonised standard(s) essential requirements.

Stage 5: Compile the technical documentation

Technical documentation normally referred to as the technical file or technical folder, should cover every aspect relating to conformity and details of the design, development and manufacture of the product. Technical documentation usually includes:

- Technical description (section 4.5)
- Drawings, circuit diagrams and photos
- Specification and, where applicable, Declarations of Conformity for the critical components and materials used
- Test reports and/or assessments
- Clinical Evaluation (section 4.3)
- Risk management (section 4.2)
- User guide, installation manual, quick user guide
- EC Declaration of Conformity (section 4.6)

Stage 6: Produce a Declaration of Conformity and affix the CE mark

When the manufacturer and consequent authorised representative are both satisfied that the product is compliant with the applicable Directive, a Declaration of Conformity must be created. Once this declaration has been completed, the CE mark can be affixed to the product.

By affixing the CE mark and drafting the technical documentation and the EC declaration of conformity, the manufacturer declares on his own responsibility, the conformity of the product to the relevant legislative requirements and confirms that the necessary assessments have been completed. Technical documentation provides the information about the product's conformity to the relevant requirements, as well as for the risk assessment.

While manufacturers have the responsibility of ensure product compliance and affixing the CE mark, importers and distributors also play an important role by making sure that only products which comply with the legislation and hold the CE mark are placed on the market. Not only does this help to reinforce the EU's health, safety and environmental protection requirements, but also supports fair competition with all players holding them under the same rules [34].

3.1.1 CE mark for medical devices

After this introduction to CE mark for any general product, now we will focus on medical devices. Medical devices have a very important role in healthcare. The variety and innovation offered by this sector contribute a lot to improve the quality and effectiveness of healthcare. By covering a wide range of products, the medical devices sector plays a key role in two big areas: (1) diagnosis, prevention, monitoring and treatment of diseases and (2) improvement of the quality of life of people suffering from disabilities.

The EU works at the regulatory framework for devices before entering the market, for international trade relations and regulatory convergence, with the aim of ensuring the highest level of healthcare possible, while still promoting innovation and competitiveness in the sector [44].

One of the three following Directives must be applied and respected in medical devices intended to enter the European market. The Directives are:

- the Medical Devices Directive 93/42/EEC (MDD);

- the Active Implantable Devices Directive 90/385/EEC (AIMD Directive);

- and the In Vitro Devices Directive 98/79/EC (IVDD Directive).

It cannot be forgotten that in first place the right Directive must be picked to guarantee the correct conformity of the product.

The next stage is the fulfilment of the essential requirements, mentioned in the respective Directive applied. To accomplish this stage, most of the times some standards may be used to demonstrate compliance. For example, the EN ISO 13485 is a standard that stands for the quality management system (ISO means International Organization of Standardization, section 3.2.3 has more details related to this standard). When we

talk about this route for medical devices falling under Directive 93/42/EEC, there is a fundamental classification to be determined in accordance with certain rules based essentially in the intended use of the device. For IVDD the same route is determined using lists (contained in annex II of the Directive), and for AIMD is determined without lists or classifications (falling in a high risk category).

After this stage, the conformity assessment procedure must be followed. Depending on the procedure, it could be required a quality management system (QMS) and technical documentation review by a Notified Body (NB) before the product can enter the market. Only after the NB verifies all the requirements the CE mark can be added to the device to demonstrate the compliance.

	I (non-sterile and non-measured)	I (sterile and measured)	IIa	IIb	III
Annex II (+ section 4)					●
Annex II (– section 4)		●	●	●	
Annex III				●	●
Annex IV		●	●	●	●
Annex V		●	●	●	●
Annex VI		●	●	●	
Annex VII	●	●	●		

Figure 6: Table with the different conformity assessments for MDD [45].

If a medical device has the CE mark, allows its free movement throughout any country, as referred in the beginning of this chapter. Nevertheless, many states can request the registration of the medical device and additionally, that part of the documentation must be translated [46].

CE marking is the medical device manufacturer's statement, with full responsibility, that a product meets the essential requirements of all relevant European MDDs and is a legal requirement to place a device on the market in the European Union, which means, apply the CE mark. Take in consideration that the CE marking process can be a "challenge for both smaller companies and global manufacturers", according to BSI Group [47].

Each state has its own national laws that contain the requirements transposed from the three medical Directives. The Competent Authority must be notified about a new device and then proceed for its registration. They shall process the data and inform the Commission of the European Communities and the other States Party to the Agreement on the European Economic Area [48]. After the product registration, the manufacturer or its authorized representative must inform the Competent Authority about any modifications to the registered details. The Competent Authority will also review the records and request updating/confirmation of the registered information regularly [49].

There are documents that work as guidelines, aiming at promoting a common approach by manufacturers and notified bodies involved in the conformity assessment procedures according to the relevant annexes of the Directives, and by the Competent Authorities charged with safeguarding public health - the MEDDEVs.

MEDDEVs have been created through a process of consultation with various interested parties during which intermediate drafts were circulated and comments were taken up in the documents. Therefore, they reveal positions taken in particular by representatives of Competent Authorities and Commission Services, Notified Bodies, industry and other interested parties in the medical devices sector.

The guidelines are not legally binding. It is recognised that under given circumstances, for example, as a result of scientific developments, an alternative approach may be possible or appropriate to comply with the legal requirements.

Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that the guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions. Guidelines are subject of a regular updating process [50].

In the following scheme about medical devices, we can take a closer look at the steps that must happen during the conformity assessment. After that, a list including the certification process focused only on medical devices [51].

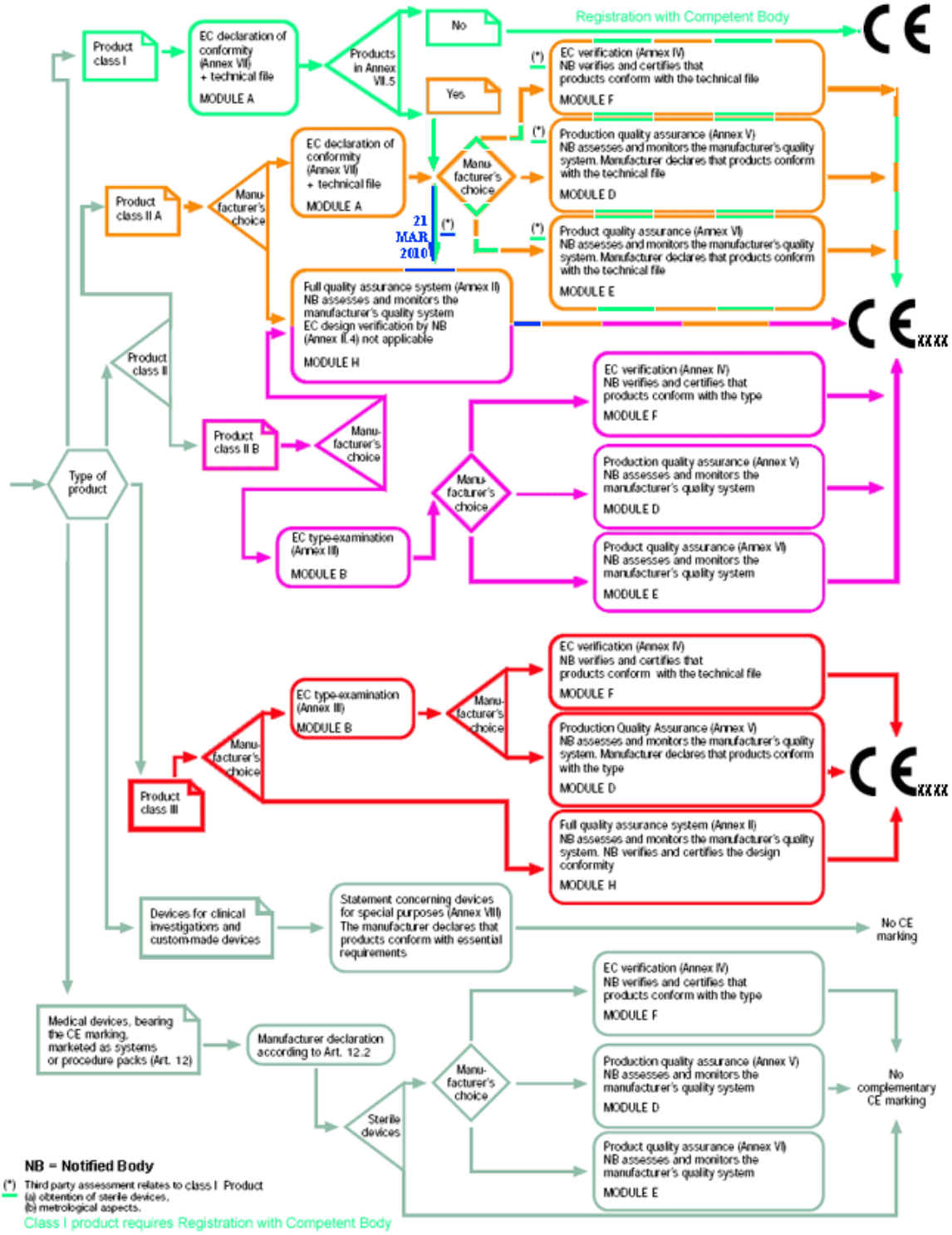


Figure 7: Scheme with different steps to achieve CE mark based on the type of the product [52].

Step 1

Determine which EU MDD applies to your device: 93/42/EEC (MDD), 90/385/EEC (AIMD) or 98/79/EC (IVDD)

Step 2

Determine classification of your device using Annex IX of the MDD: class I (non-sterile, non-measuring), class I (sterile, measuring), class IIa, class IIb or class III/AIMD. AIMD are subject to the same regulatory requirements as class III devices.

Step 3

For all devices except class I (non-sterile, non-measuring), implement QMS in accordance with Annex II or V of the MDD. Most companies apply the ISO 13485 standard to achieve QMS compliance.

Step 4

For Class III/AIMD devices, prepare a Design Dossier. For all other devices, prepare a CE Technical File that provides detailed information on your medical device demonstrating compliance with MDD 93/42/EEC.

Step 5

For all devices except class I (non-sterile, non-measuring), your QMS and Technical File or Design Dossier must be audited by a NB.

Step 6

For all devices except class I (non-sterile, non-measuring), you will be issued a European CE Marking Certificate for your device and an ISO 13485 certificate for your facility following successful completion of your NB audit. CE Marking certificates are typically valid for 3 years. ISO 13485 certification must be renewed every year.

Step 7

All class I devices must be registered with the Competent Authority where your EC REP is based. Most EU member states do not require registration of class IIa, IIb or III devices.

Step 8

Prepare a Declaration of Conformity, a legally binding document prepared by the manufacturer stating that the device is in compliance with the applicable Directive.

3.2 Directives and standards of interest

We always assume that most medical devices on the market were tested and are made according to all rules existing nowadays. But that is not always the case. Most people do not even recognize how significant standards are in the daily life. Almost everything we enter in contact with during our everyday life was subjected to the application of standards - the food we eat, the car or motorbike we drive, or even the bed we sleep on, all were produced according with standards.

There are companies that do not know how to proceed as a good manufacturer (some of those "companies" consist of nothing more than one person). It is easier for these people to make a device at his or her house, with no control over how the product was designed and architectured, no monitoring of customer complaints and no written processes regarding how the product is manufactured, stored or tracked. Fortunately, there are standards, such as European Norm ISO 13485 (EN ISO 13485), that provide "best practices" guidance on how products should be manufactured, distributed and tracked.

It is a good strategy to have standards. Before the beginning of the 20th century, not many documented standards were in place. Let us see an example of how important is the application of standards. The remote control of the TV is without battery and it needs a new one. Regardless of manufacturer, the fact that all batteries from a specific size match with the remote control, is no coincidence.

Standards are regulated and introduced by several national and international organizations. Some of these organizations include the International Organization for Standardization (ISO), American Standards for Testing of Materials and European Committee for Standardization, known by its French acronym, CEN. The Official Journal of the European Union is responsible for publishing a list of harmonized standards for the medical device industry.

Standards can be described as vertical or horizontal, depending on how broad they are. Vertical standards are specific to a device, while horizontal standards apply to a wide range of devices. Examples of common horizontal standards are EN ISO 13485

and EN ISO 14971. An example of a vertical standard is EN 62304, which deals with medical device software [53].

3.2.1 Directive 93/42/EEC

Directive 93/42/EEC regulates the movement, the placing on the market and the use of medical devices. The annex I of the Directive, which is entitled Essential Requirements, is according with the approach of the Directive, since the design and manufacture of medical devices must always consider the protection of the health and safety of patients and users of these devices. Despite this Directive only applies to medical devices and their accessories, as discussed before, for each kind of device there is a respective directive.

The clinical condition or the safety of patients must be in the first place and the Essential Requirements must guarantee that devices respect that. Those same devices must be safer, not presenting any risk to the persons using them, or near persons. They must do what they are intended to do by the manufacturer, and must be planned and architectured in a way that allow a correct storage under specific transport conditions.
This Directive shall be public, making it part of the legislation of each member state. By doing that, countries must check that medical devices are according with the essential safety requirements set out in this Directive and regulate their traceability, their entering in the market and their correct use. In Portugal, the Directive has been transposed to Decree-Law 273/95, from the 23rd of October, and it is Infarmed obligation to make the Directive respected.

This Directive states that all devices must have a conformity assessment procedure. Therefore, member states authorize independent entities (Notified Bodies) to contribute to the application of these kind of procedures for devices, that are different depending on how much risk the device has (different classes).

The Directive also mentions an European database that has the objective of saving the data required by law. This data must be available to the competent authorities and shall include data on registration of manufacturers, data relating to certificates issued, amended, suspended, withdrawn or refused, data obtained in accordance with the vigilance procedure and data on clinical investigations. Consequently, the manufacturer is responsible for informing the competent authorities of any incident causing death or damage to the health of a patient [54].

3.2.2 EN ISO 14971:2012

ISO 14971 is an international horizontal standard that guides the risk management process for medical devices. It is the primary standard for Risk Management for some of the most important regulation entities like the European authorities, United States Food and Drug Administration (FDA), Health Canada, the Australia Therapeutic Goods Administration and other regulators. ISO 14971 enters the life cycle process of medical devices and cannot be dissociated from the quality system. The idea behind ISO 14971 is to establish, document and maintain a risk management process capable of:

- Review the intended use given to the medical device.

- Identify hazards and estimate the probability that harm might occur.

- Estimate the severity of each hazard and evaluate the associated risks.

- Control those risks and monitor the effectiveness of the controls put in place.

Adopt ISO 14971 is not an easy task. Almost every medical device companies consider it challenging. It includes a periodically review of the product's risk assessment to watch for any modifications, from design changes to customer input/feedback, including in post market surveillance. This kind of analysis can be done during management reviews and should also make part of internal audits [52]. Is up to the manufacturer to make judgements about the safety of a medical device, including the acceptability of risks, taking into account the generally accepted state of the art, in order to determine the probable suitability of a medical device to be placed on the market.

When talking about medical devices, there are always risks associated. The idea of risk can be divided in two parts: the probability of the occurrence of harm and the consequences of that harm. The acceptability of a risk by someone responsible and qualified for this matter is influenced by those parts and by the person’s perception of the risk. Experience, insight and judgment are just some applied concepts to manage the risks. Risk Management is a complex subject because of this. Each person places a different value on the probability of harm occurring and on the detriment that might be suffered on exposure to a hazard.

Previously to any decision to go with a clinical procedure using a medical device, the residual risks shall be balanced against the anticipated benefits of the procedure. These thoughts should take into account the intended use, performance and risks that follow the medical device, plus the risks and benefits associated with the clinical procedure [55].

3.2.3 EN ISO 13485:2012

ISO 13485 is an horizontal standard that provides requirements for a QMS, specifically for medical companies, that include on one hand the design and development, production, installation and servicing of medical devices, and on the other hand the design, development, and provision of related services.

It is similar to ISO 9001, but there are differences in process control, design control, retention of records, accountability, traceability, and others, which make ISO 9001 more focused on the customer. Based on these differences, companies that want to implement a QMS conform to ISO 13485 cannot declare conformity to ISO 9001. The conformity to ISO 9001 demands the conformity with all requirements of this standard.

Implementing ISO 13485 is voluntary for manufacturers in Europe. Most companies go for this standard to demonstrate compliance with the Directive 93/42/EEC [56]. Generally, it is the chosen path for medical devices to meet the QMS requirements, not only across Europe, but also in some other countries outside Europe like Canada, Australia and Japan. FDA does not recognize ISO 13485. The FDA follows its own system, the system of Good Manufacturing Practices, making the development of ISO 13485 not applicable. Let's just not forget that both quality systems have a lot in common, with many overlap points [57].

About this standard, it also must be noted that:

- It can be used as guidance by internal and external parties that include certification bodies, to assess the organization’s ability to meet some requirements, both regulatory and customer.

- the QMS requirements specified in this standard are complementary to technical requirements for products.

- some of the particular requirements of this standard only apply to named groups of medical devices.

- the decision of implementing the QMS should be well planned by the company. The design and implementation of an organization's QMS is influenced by varying needs, particular objectives, the products provided, the processes employed and the size and structure of the organization [58].

3.2.4 EN 60601

Commonly known as IEC 60601 (IEC means International Electrotechnical Comission), EN 60601 is a series of technical standards that allows the control of the safety and the effectiveness of the use of medical electrical equipment.

The primary standard, EN 60601-1 (Medical Electrical Equipment - Part 1: General requirements for basic safety and essential performance), is all about the medical device design. Often, when many companies want to enter the market with some of their products, it is required that the compliance with this standard has been one of the requirements.

Despite some products may appear uncomplicated and with a nice design, many of them are very difficult and sophisticated, with circuits and software that the user do not see but have to be regulated. EN 60601-1 becomes important because it is intimately involved not only with the performance test and verification, but also with the product development process.

When creating a new product, based on its complexity, the number of potential test cases can be very high, as well as permutations and combinations, both on normal and non-normal operating modes. The standard provides the guide to assess all this tests during the development of the device, a task that cannot be done only at the end. It provides also information about the risk management, a vital part, a multistep process that must be taken in consideration during all development [59,60].

3.2.5 EN 62304

Being another standard adopted from IEC, EN 62304 is similar to EN 60601 since they are both technical. This standard is focused on the development and maintenance of software for a medical purpose. Its content includes both software embedded in medical devices and software as a medical device.

We find more often software that is part of a medical device technology. To run a certification process around this standard, it requires knowledge of what the software is intended to do. Moreover, to establish the proper safety and the effectiveness of the

medical device it must be demonstrated that the use of the software fulfils those intentions without causing any unacceptable risks according with risk management.

With these objectives, the standard provides a guide of life cycle processes with activities and tasks necessary for the safe design and maintenance of software, in particular medical device software. A manufacturer of a medical device software system is required to assign a software safety class (A, B, or C) according to the possible effects on the patient, operator, or other people resulting from a hazard to which the software system contributes, described in greater detail in the standard. The software safety classes are assigned based on severity as follows:

– **Class A:** no injury or damage to health is possible;

– **Class B:** non-serious injury is possible;

– **Class C:** death or serious injury is possible.

Sometimes, to make the software development process a little bit simpler, the system and the software design can be merged, which make it easier. Also EN 60601 identifies IEC 62304 as part of the software procedures for software incorporated in a medical device [61].

It is mainly divided among six phases [62]:

- Specifications (System and software Requirements Analysis),
- Design (Architecture, Interfaces and Detailed Design),
- Coding,
- Tests (Unit tests, integration tests, verification tests),
- Delivery and
- Validation.

3.2.6 EN 62366

As for the two previous standards, this standard is also adopted from IEC. EN 62366 is a standard focused on usability. It describes an usability engineering process, and provides comprehensive guidance on implementation of the process, in order to reduce the risk of use error in medical devices.

Most of the times it can be confusing what are the usability tests and how different are they from clinical investigations. Despite there isn't any detail both on

usability standards or the MDD, these subjects must be studied separately and information from the two shall exist.

Usually, one way to obtain usability data is to collect data during a premarket clinical investigation. This way we can obtain data that is part of the device validation, both from safety and performance, using a method very efficient and cost-effective. This approach helps to reduce the number of studies needed. Since it occurs during a very early stage of the project, it also helps to avoid potential problems, in terms of determining ethical and regulatory requirements applicable in this particular situation [63].

4.3 Electrical compliance

Nowadays, the society is dependent of electric and electronic equipments not only to give a better life quality but also to a better health safety assurance.

With the technologic evolution have appeared in the market medical devices more advanced, turning the medicine area much more dependent on electronics. With the technological advances of medical devices has been verified an increase of technologies of communications. As a result of these developments we have assisted to problems related with the interaction between equipments that emit and produce electromagnetic energy and the medical devices. Medical devices also emit electromagnetic energy that interferes with other equipments.

This subject is important not only by the fact of involving the safety of patients in case of a bad operation of the equipment, but also by presenting other implications as the increase of maintenance costs, the non-availability of the equipment and resulting stop of the medical service, as well as the loss of confidence in information provided by the equipment.

One of the most effective ways of avoiding problems of Electromagnetic Interference (EMI) is to develop equipments with features that turn them to be compatible with each other in specific conditions. To achieve this, rules of construction and protocols of operating have been described as standards of Electromagnetic Compatibility (EMC).

At an international level, EMC for medical electrical devices or equipments of technologies and communications used in medical applications must be compliant with the requirements of the standard EN 60601-1-2 (General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility -

Requirements and tests). The reason for the publication of this standard is the effect of EMC on the work of different systems and guarantee a good practice of EMC to reduce the possibility of occurring EMI. The circumstances in which the equipments and/or the systems are inserted are constantly changing and these must be projected in a way that won't be necessary a frequent adjustment by the user. the standard presents tested levels of immunity and transmission of electromagnetic interference that represent the scale of levels of interferences expected for devices operating.

The interaction between medical equipments and the electromagnetic environment is a bigger challenge each day to everyone who is related with the equipment. To guarantee the EMC is necessary that be given responsibilities from the start of the project until the start of the use of the equipment.

The supplier is the starting point to guarantee that a equipment work in EMC, since he is responsible for make sure that the equipment respects the limits of emissions and immunity levels. There are limits for emissions a medical device can produce and also limit values which the device must be immune. Is also responsibility of the supplier guarantee that the equipment respects all requirements of the current legislation, supply necessary information about the specifications of the equipment and inform the environment conditions under which the device works.

The responsibility of knowing about EMC falls into the following groups [60,64,65,66]:

- anyone who gives maintenance or does reparations during the lifetime of the equipment, allowing them to implement the demands present in the documentation that go along with the equipment.

- the users of the equipment, allowing them to recognize problems with EMI, making easier to identify and present difficulties to the supplier or the maintenance.

- the hospital administration that must nominate someone responsible with knowledge about EMC and capable of maintain the EMC all over the environment. This person must be capable, for example, to identify areas where mobile phones can be used or also give training in EMC to personnel in the hospital.

5.4 Usability

Briefly stated, however, the usability engineering process includes the following steps:

- Development of the medical device application specification, which identifies the most important characteristics related to the use of the device, based upon the intended medical indication, intended patient population, intended part of the body or type of tissue with which the device interacts, intended user profile, intended conditions of use and operating principles. The application specification lays the foundation for defining the usability specification.

- Determination of frequently used functions that involve user interaction with the medical device. This is an important step in the process because inadequate usability of frequently used functions can adversely affect safety by increasing the probability of use error.

- An identification of hazards and hazardous situations related to usability, which includes the identification of characteristics related to safety and of known or foreseeable hazards and hazardous situations. These activities are part of risk analysis and are to be conducted according to EN ISO 14971.

- Determination of the primary operating functions with input from frequently used and medical device safety functions.

- Development of the usability specification, which will provide testable requirements for usability verification, and testable requirements for usability of the primary operating functions, including criteria for determining the adequacy of risk control achieved by the usability engineering process.

- Preparation and maintenance of the usability validation plan, which specifies the methods and success criteria for the validation of the usability of primary operating functions and specifies the involvement of representative intended users; it must also address frequent-use scenarios and reasonably foreseeable worst case use scenarios.

- Design and implementation of the user interface as described in the usability specification employing, as appropriate, usability engineering methods and techniques.

- Verification of the medical device user interface design against the requirements of the usability specification.

- Validation of the usability of the medical device according to the usability validation plan.

Most of the document consists of informative annexes, which include: general guidance and rationale for various provisions of the standard; categories of user action; examples of use errors, abnormal use and possible causes; guidance on the usability engineering process; questions that can be used to identify medical device characteristics associated with usability that could impact safety; examples of possible usability-related hazardous situations; and usability goals, using an illustrative example for a home parenteral infusion pump.

Clause 5 of EN 62366, Usability Engineering Process, describes the steps in the process. As the standard points out in Clause 4.3, Scaling of the usability engineering effort, they can vary in form and extent, depending on the nature of the medical device, its intended user and its intended use. In addition, the standard advises that, because of the iterative nature of the usability engineering process, the activities described in Clause 5 can be performed in any convenient order [63,67,68,69].

4. RDFixer certification

4.1 Intended use and classification

The RDFixer is intended to improve the visualization in medical endoscopy by performing software-based correction of the image radial distortion introduced by the camera optics. The system receives as input the original video stream, removes the radial distortion in real-time, and sends to the display the geometric correct video as if it would have been acquired by a camera without lens distortion. The device makes no interpretation of the image visual contents for the purpose of diagnosis.

The main objective of the classification of a device is to evaluate how much risk does the use of the device cause, which will influence the pathway taken by the manufacturer to achieve conformity with the MDD [70,71].

According with MDD there are four medical devices classes (see figure below).

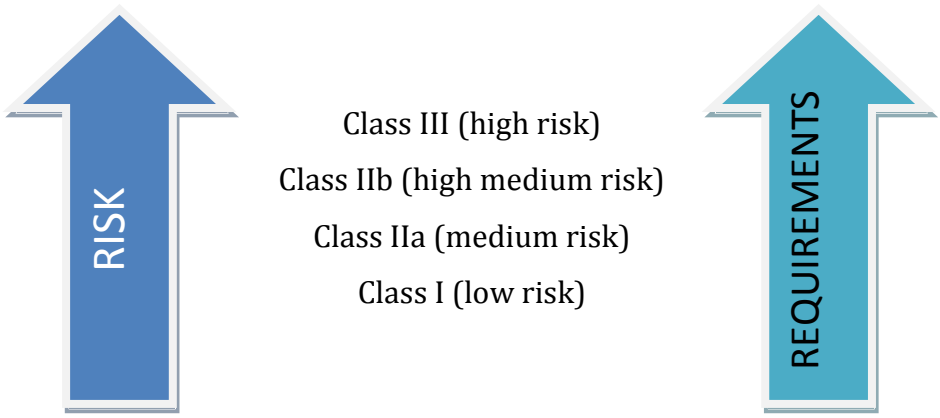


Figure 8: Scheme with the different existent classes

The classification of a medical device is made according with the rules in Annex IX of MDD. Basically, the rules are according the following criteria:

- exposure time with the human body, which can be short, long or temporarily;

- invasiveness of the body (invasive or non-invasive);

- part of the body affected (heart, arms,...);

- potential risks based on the conception and manufacture of the device.

These rules are general and shall be applied according the functioning of a particular device and its characteristics. The characteristic that refers to the highest risk

rule dictates which class is the device. As in a device, the accessories also follow the same rules.

● From Directive 93/42/EEC, Annex IX, Section I - 1.4: Active medical device - Any medical device 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. Stand alone software is considered to be an active medical device.
→ Stand-alone software is considered to be an active medical device. Therefore RDFixer is considered to be an active medical device.

● From Directive 93/42/EEC, Annex IX, Section I - 1.6: 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.
→ Despite not being a device intended for use in diagnosis, it supplies different information from the endoscope working alone.

As an active medical device, RDFixer is classified Risk Class IIa, based on the table that follows below.

Rule	**Applicability**
Directive 93/42/EEC, Annex IX, Section III - 3.2, Rule 10: Active devices intended for diagnosis are in Class IIa - if they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which case they are in Class IIb.	Since it is considered an active device and despite not being a device intended for use in diagnosis, RDFixer enhances the images seen in the medical display

MEDDEV 2.4/1 - rev. 8, Section 3.2: Standalone software, e.g. software which is used for image enhancement is regarded as driving or influencing the use of a device and so falls automatically into the same class. Other standalone software, which is not regarded as driving or influencing the use of a device, is classified in its own right.	Since RDFixer is stand-alone software and influences the use of the endoscope, it will fall at a similar class of the endoscope. Nevertheless, not all endoscopes have the same class and RDFixer works with all brands which doesn't make it the same class as endoscopes

Something that shall be retained about classification:

- It is not viable economically nor justifiable in practice to subject all medical devices to the most rigorous conformity assessment procedures available because the devices have different purposes and different amount of risk for the patients, which implies different costs also.

- In order to ensure that conformity assessment under the MDD functions effectively, manufacturers should be able to determine the classification of their product as early as possible in device development.

- The classification of medical devices is a "risk based" system derived from the vulnerability of the human body taking account of the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways in order to determine classification, e.g. duration of contact with the body, degree of invasiveness and local vs. systemic effect. These criteria can then be applied to a vast range of different medical devices and technologies.

- Although the existing rules will adequately classify the vast majority of existing devices, a small number of products may be more difficult to classify (borderline cases between two different classes of medical devices or even devices that cannot be classified by the existing rules because of their unusual nature or situations). RDFixer is one of those devices where is difficult to determine: 1) if it is medical device or not and 2) which class does it fall [45,72].

4.2 Risk management

The risk management is perhaps one of the most elaborated phases of the certification of a product. Risk management, according to ISO 14971 from 2012, is the

"systematic application of management policies, procedures and practices to the task of analyzing, evaluating, controlling and monitoring risk". Its overall purpose is to reduce risks associated with the use of a medical device to acceptable levels.

We can find different information to help us to understand more about this subject. According with a Product Safety Law (Sweden - SFS 2004:451) and a general product safety directive (2001/95/EG):

- Products placed on the market shall be safe;
- A product is safe if it does not present any risk or only the minimum risks compatible with the product's use;
- The risk must be acceptable and consistent with a high level of protection for the safety and health of persons.

Along with the different standards we can find important information related to risks. Looking at the MDD, we can find that "…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"; in ISO 13485, "The organization shall establish documented requirements for risk management throughout product realization"; in IEC 60601-1 and IEC 62304, "A risk management process complying with ISO 14971 shall be performed".

Absolute safety does not exist. There are only acceptable risks. Safety can be properly understood as "Freedom from unacceptable risk" according with ISO 14971.

There are important definitions that must be retained:

Harm → Physical injury or damage to the health of people, or damage to property or the environment;

Hazard → Potential source of harm;

Hazardous situation → Circumstance in which people, property, or the environment are exposed to one or more hazards;

Risk → Combination of the probability of occurrence of harm and the severity of that harm;

Residual risk → Risk remaining after risk control measures have been taken;

At the end, the manufacturer must:

- Establish a risk management process;
- Establish acceptable levels of risk;
- Demonstrate that the residual risk is acceptable (in accordance with the policy for determining acceptable risk);

All collected hazards, hazardous situations, risks and risk control measures shall be addressed. Not only those addressed by specific requirements in a particular standard. The following list contains the mains steps of the risk management that makes possible to manage all information collected in terms of safety [55].

0. Qualification of personnel

•Persons performing risk management tasks shall have the knowledge and experience appropriate to the tasks assigned to them. These shall include, where appropriate, knowledge and experience of the particular medical device (or similar medical devices) and its use, the technologies involved or risk management techniques. Appropriate qualification records shall

1. Management responsibilities

•provide evidence of the commitment to the risk management process by ensuring the provision of adequate resources and the assignment of qualified personnel for risk management.

•define the policy for determining acceptable risk;

•ensure the provision of adequate resources and the assignment of trained personnel for management, performance of work and assessment activities;

•review the results of risk management activities at defined intervals.

2. Elaboration of a risk management plan

•scope of the planned risk management activities, verification activities, requirements for review of risk management activities, assignment of responsibilities and authorities

•criteria for risk acceptability and activities related to collection;

•review of relevant production and post-production.

3. Risk management process

•The manufacturer shall establish, document and maintain throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls.

4. Elaborate a risk management file

•It provides traceability for each identified hazard to the risk analysis, risk evaluation, implementation and verification of the risk control measures and assessment of the acceptability of any residual risk(s)

4.2.1 Risk management process

Risk management process is the most important step in risk management. It begins with risk assessment, which itself is composed of risk analysis (identification of hazards and estimation of the effect of each hazard) and then proceeds to risk evaluation. Standard techniques such as fault-tree analysis are among those used, but the assessment is not limited to that approach. After the assessment phase, the risk management process moves on to risk control. Here, options for managing the risk are evaluated, any risk-control measures are implemented, and the residual risk is assessed (some risks cannot be eliminated by design changes). There is also risk/benefit analysis, as well as examination of the critical issue of any new risks that may result from the risk-control steps themselves.

The process concludes with an overall evaluation of the total original risk versus the remaining risk, determination if this is acceptable, and a formal risk-management report. After having the risk management report, the phase of production and post-production of information can be entered to collect all risk managements activities [73].

The risk management process can be seen in more detail in the steps below.

Risk analysis

1. Risk analysis process

- description and identification of the medical device that was analyzed;
- identification of the person(s) and organization who carried out the risk analysis (include qualifications);
- scope and date of the risk analysis.

2. Intended use and identification of characteristics related to the safety of the medical device

3. Identification of known and foreseeable hazards in both normal and fault conditions.

4. Estimation of the risk(s) for each hazardous situation (see figure 10)

Risk evaluation

For each identified hazardous situation, using the criteria defined in the risk management plan, determine if risk reduction is required.

Risk control

1. Risk reduction (when required)

2. Risk control option analysis

- Identify risk control measure(s) (one or more) that are appropriate for reducing the risk(s) to an acceptable level.
- Risk control options (in priority order):
  - inherent safety by design;
  - protective measures in the medical device itself or in the manufacturing process;
  - information for safety.

3. Implementation of risk control measure(s) in risk control option analysis (and their verification)

4. Residual risk evaluation

After the risk control measures are applied, any residual risk shall be evaluated using the criteria defined in the risk management plan.

5. Risk/benefit analysis

6. Risk arising from risk control measures

- by introduction of new hazards or hazardous situations
- whether the estimated risks for previously identified hazardous situations are affected by the introduction of the risk control measures.

7. Completeness of risk control by assuring that the risk(s) from all identified hazardous situations have been considered.

Evaluation of overall residual risk acceptability

Must be decided if the overall residual risk posed by the medical device is acceptable using the criteria defined in the risk management plan

Risk management report

Before the release for commercial distribution of the medical device, carry out a review of the risk management process. It ensures that:

- the risk management plan has been appropriately implemented
- the overall residual risk is acceptable;
- appropriate methods are in place to obtain relevant production and post/production information.

Production and post-production information

Establish, document and maintain a system to collect and review information generated by the operator, the user, or those accountable for the installation, use and maintenance of the medical device or similar devices in the production and post-production phases.

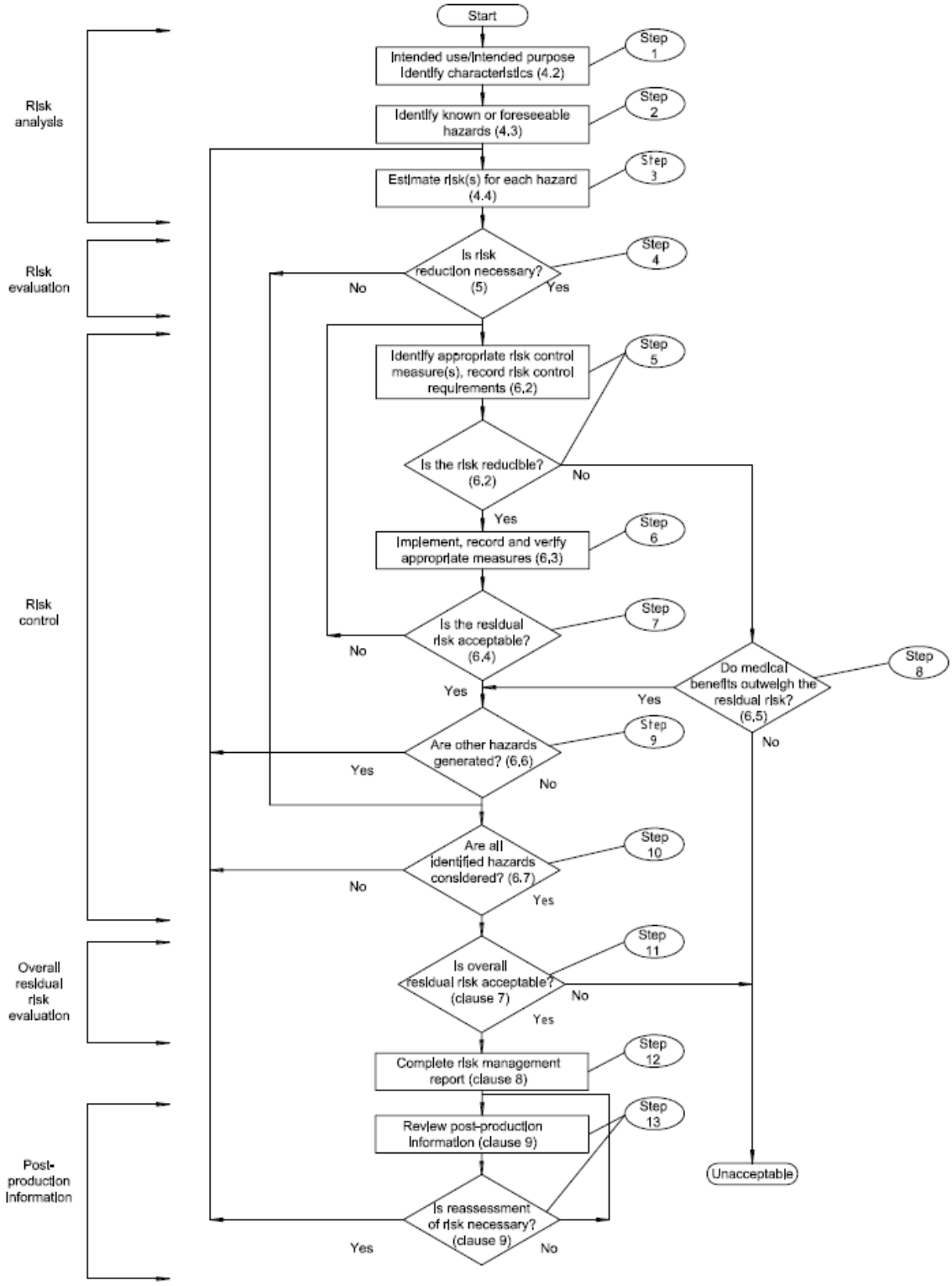


Figure 9: Overview of risk management activities as applied to medical devices [55]

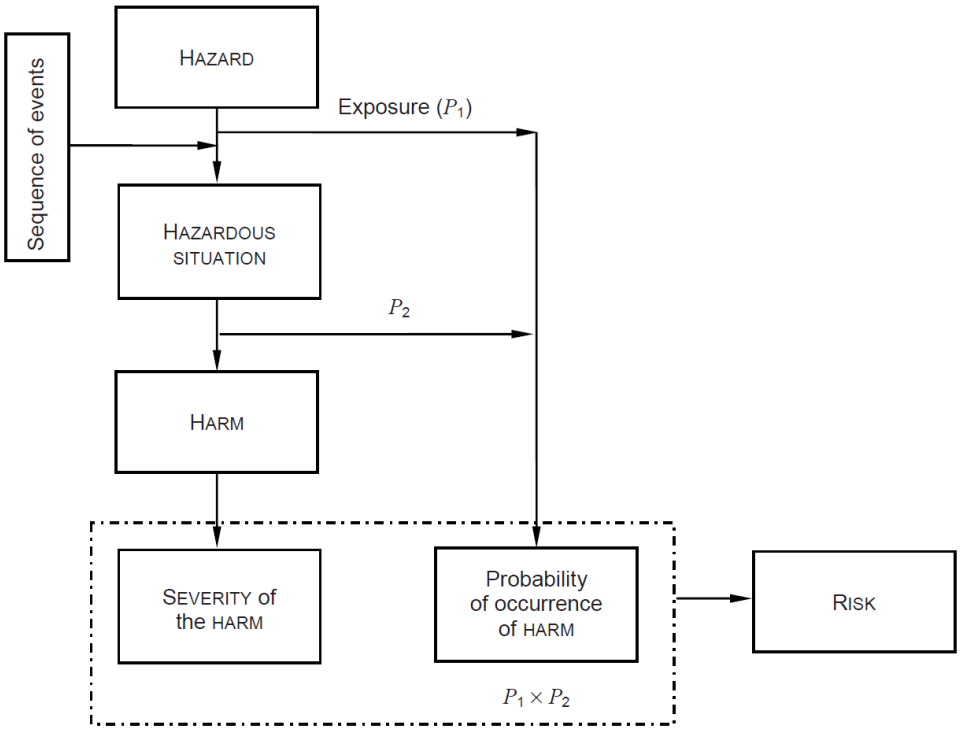


Figure 10: Summary of the relations between concepts important for risk management [55]

It is important to remember that all the risk management activities are performed and are responsibility of a person qualified for this work. Some of the risk management process stages can be translated to a matrix that contains the identified hazards, probability of occurrence, as other important aspects. The document created with this information is in annex 2 and provides another point of view of the device.

4.3 Clinical Evaluation

Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. As an important component of the CE marking process, "clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device" according to MEDDEV 2.7.1.

In this part, it is expected that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use and that the known and foreseeable risks, and any adverse events, are minimised and acceptable when weighed against the benefits of the intended performance, and that any claims made about the device's performance and safety (e.g. product labelling and instructions for use) are supported by suitable evidence.

The depth and extent of clinical evaluations should be flexible, not unduly burdensome, and appropriate to the nature, classification, intended use, manufacturer's claims and risks of the device in question.

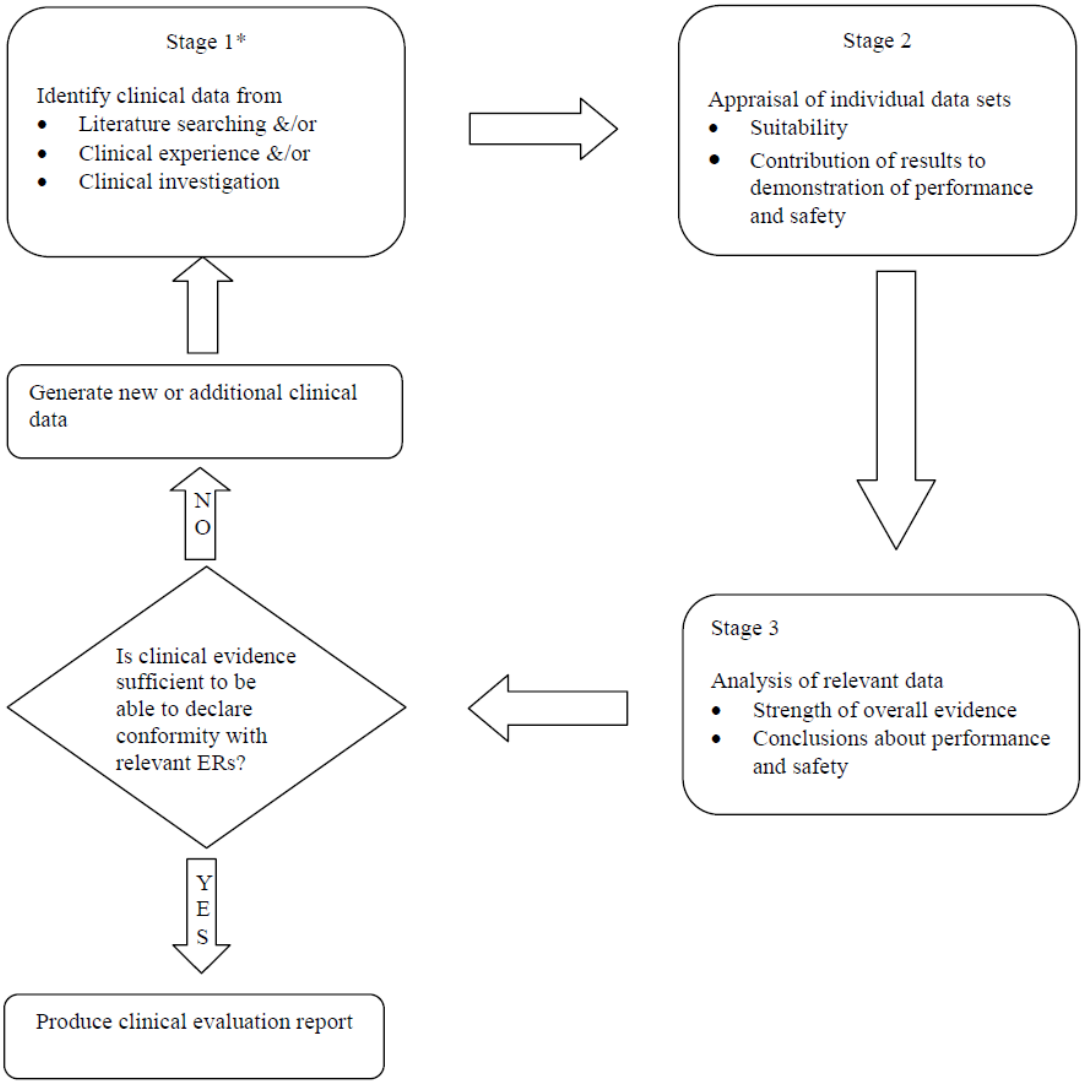


Figure11: Stages of clinical evaluation (* Conformity to harmonized performance standards may be sufficient to demonstrate compliance to relevant Essential Requirements (ERs)) [74]

The MDD 93/42/EEC has an amendment by the name European Directive 2007/47/EC that places greater emphasis on clinical data and a Clinical Evaluation Report. In the current Directive 2007/47/EC, clinical data, even for Class I devices will generally be required. Also, Annex I, Essential Requirements now states that "demonstration of conformity with the Essential Requirements must include a clinical evaluation in accordance with Annex X." [74].

Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated [75].

RDFixer clinical evaluation, as a necessary part of the Technical File, can be consulted in annex 1.

4.4 Pilot Trials

For many years, pilot trials have been used as a tool to guide clinical and translational research. Pilot trials are studies limited in size and scope that give insight into the actions, effectiveness, and safety of a drug or device but cannot provide definitive support for specific mechanistic or therapeutic claims.

Different from pivotal trials (i.e., the trial that will be used to make specific claims about effectiveness and safety), pilot trials are not typically designed to test a critical hypothesis required for drug or device approval; rather, the data obtained from the pilot study are used to optimize the design of subsequent pivotal trials.

The objectives of a clinical pilot trial typically include accessing feasibility (e.g., preliminary device performance), exploring eligibility criteria and their practical application for the pivotal randomized controlled trial, ascertaining potential harm (preliminary safety evaluations), studying drug mechanism, validating a method for determining an outcome measure, using a defined drug mechanism to validate a surrogate outcome measure, and evaluating the logistics of pivotal trial performance. The advantages of performing a clinical pilot trial follow from these objectives. Pilot trials can be used to predict the feasibility and operational acceptability of a protocol design planned for a pivotal trial and can achieve this end with comparatively few patients. Thus, the results of a pilot trial can help to guide the effective use of limited (financial and nonfinancial) resources essential for a successfully performed pivotal

trial. Two other advantages include their use in identifying unpredicted harm early in the course of drug or device development and assessing the utility of a surrogate end point in the pivotal trial.

Even though these rational objectives and advantages of pilot clinical trials, their use is also associated with clear disadvantages. Complex pilot trials can be expensive relative to the information they provide. Owing to their size that is typically comparatively small and to the average frequency of clinical end points expected for most pivotal trials in the current era, they are unlikely to provide reliable estimates of sample size requirements for the definitive trial. Similarly, pilot trials are rarely powered adequately to detect harm with respect to clinically important end points, and, by their very design, they are underpowered to provide reliable estimates of benefit.

A major problem with clinical pilot trials is that their results are often overinterpreted, misleading and misguiding investigators and interested readers to consider potential benefit or potential harm when the statistical power to do so is woefully inadequate. The statistical basis for this conclusion can be illustrated by first considering the implications of small-sized studies in which an outcome of interest does not occur. With small sample sizes, the likelihood of observing even comparatively common occurrences is low [76].

The following study is a pilot trial performed over the last year. This study was based on several papers and had the primary objective of comparing the performance of people using the new visualization and the old one. It consists in practice a particular task in a facility of the Coimbra University Hospital.

Procedure

Population: 19 subjects (10 arthopaedic interns + 9 medical students) divided into two groups (group A and group B).

Metrics: Time to completion the task; number of errors; questionnaires evaluating their experience with both visual modalities; number of movements, speed and distance made by the tool and the tool tip.

Task

- Group A performs the task under the original visualization and after 2 weeks the same task but under the corrected (with RDFixer) visualization. Group B performs the opposite.
- Touch a defined set of points located randomly in a surface inside a box. The subject is asked to touch each mark with a palpation hook in a defined order. It is repeated three times each session.

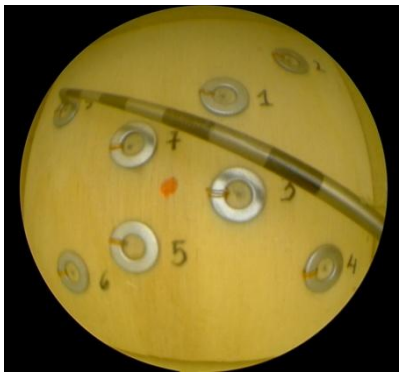


Figure 12: Original Image seen during the pilot

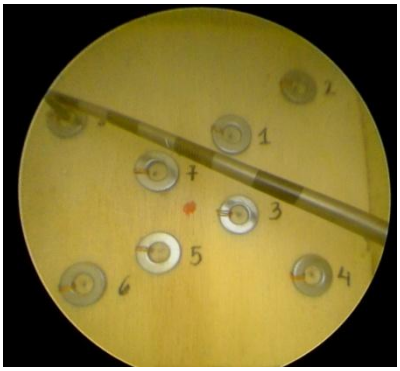
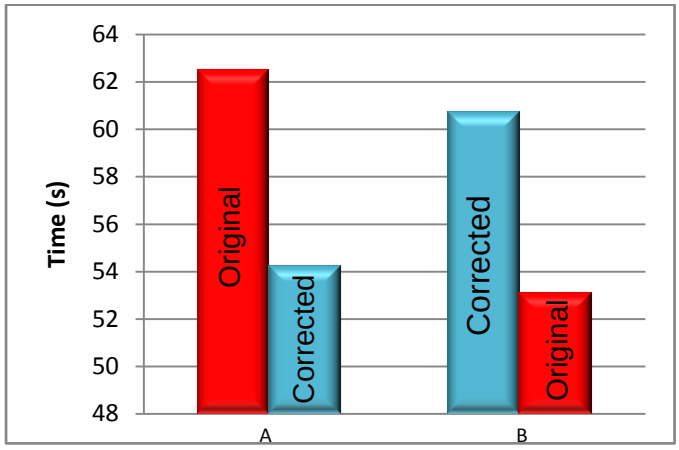


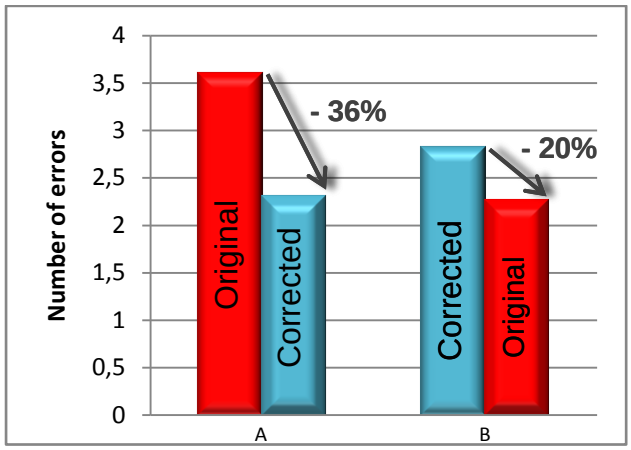
Figure 13: Corrected Image (with RDFixer) seen during the pilot

Results

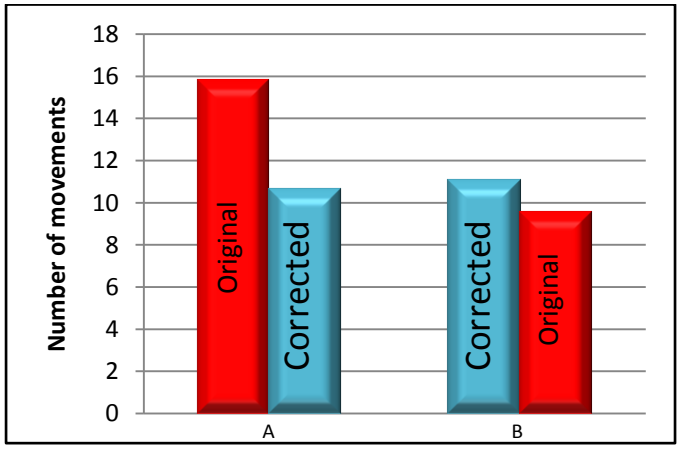
Average Time



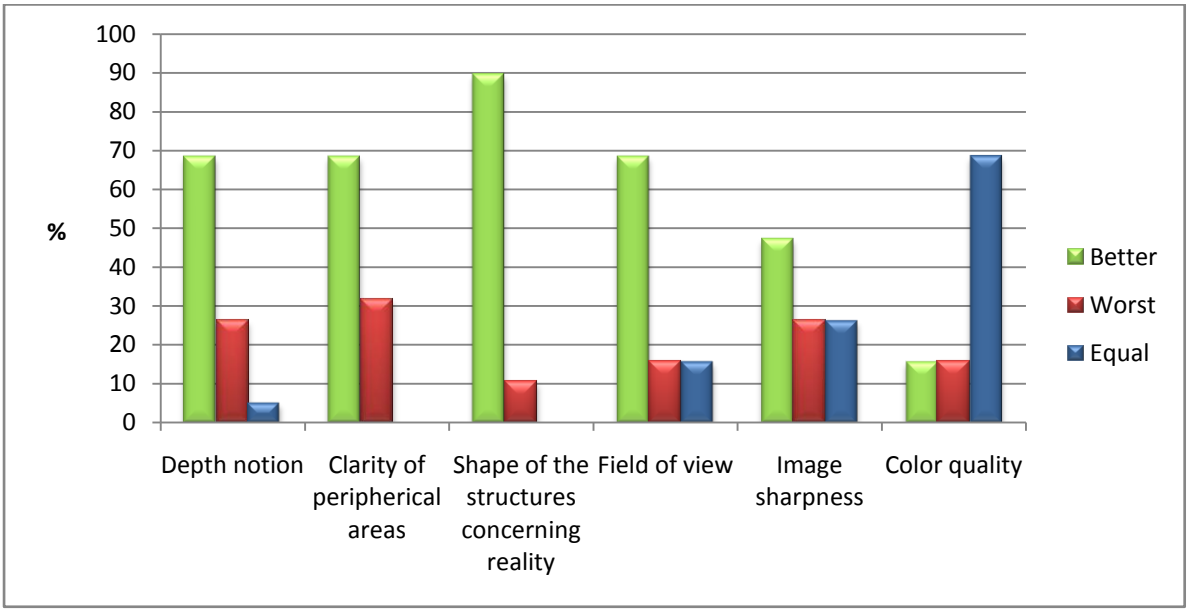
Average Number of errors



Average Number of movements with the tool tip



Questionnaires: Corrected vs. Original



4.5 Description of the Technical Folder

Union harmonisation legislation obligates the manufacturer to draw up technical documentation containing information to demonstrate the conformity of the product to the applicable requirements. This documentation may be part of the quality system documentation and must be available when the product is placed on the market, whatever its geographical origin or location.

The technical documentation of medical devices must be kept for five years from the date of placing the product on the market, unless the applicable Union harmonisation legislation expressly provides for any other duration.

The contents of the technical documentation are laid down, in each Union harmonisation act, in accordance with the products concerned. As a rule, the documentation has to include a description of the product and of its intended use and cover the design, manufacture and operation of the product. The details included in the documentation depend on the nature of the product and on what is considered as necessary, from the technical point of view, for demonstrating the conformity of the product to the essential requirements of the relevant Union harmonisation legislation or, if the harmonised standards have been applied, to these by indicating the essential requirements covered by the standards. The requirements in Annex II of Decision No 768/2008/EC refer to the contents of the technical documentation that are relevant for proving the conformity of the product with the applicable harmonisation legislation.

Furthermore, the requirement for an "adequate analysis and assessment of the risk(s)" does not oblige the manufacturer to conduct an additional risk assessment or to draw up additional documentation when he has applied harmonised standards, the development of which is based on an assessment of the relevant risk(s). Manufacturers may base their assessment on harmonised standards, which already include the risk analysis, but only as far as the risks are covered by that standard.

In the case where a product has been subject to re-designs and re-assessment of the conformity, the technical documentation must reflect all versions of the product; describing the changes made, how the various versions of the product can be identified and information on the various conformity assessment. This is to avoid situations where during the whole life of a product, a market surveillance authority is faced with previous versions of the product for which the version of the technical documentation it is presented with, is not applicable [77,78,79].

The following information presents the general structure that a Technical File should have. RDFixer Technical File can be consulted in annex 1.

Revision history

- Revision
- Version
- Date
- Description
- Author)

Introduction

Objectives - purpose of the document

Manufacturer - introduction of the company

Perceive3D research & development - partners (what they do, what they are searching and investigating)

References - Directives applied, harmonized standards, national laws and guidelines

Device description

Product description - shall describe the function, any different versions and their differences and shall be understandable for a non-medical professional

Intended use - the intended use is vital part because it is upon this and the other factors relating to function, energy, duration of use, method of application, etc., that will affect the classification of the product

Risk classification - a description of the device with focus on intended use and application; the description shall be so detailed and comprehensive that the NB, without contacting an expert in the current medical field, is able to decide if the correct rule and product class have been stated

Supported configurations - e.g. those scenarios where the user may change or select a different configuration, other than the default one

Accessories - every part of hardware that is needed to RDFixer work properly

General architecture description - shall include the minimal requirements of the product, a navigation workflow and a high level view of the components

Product description

List of features - The manufacturer should define the technical requirements/specifications which must be satisfied in order to ensure that each of the applicable directive requirements are met. Illustrations of the device should be contained in the technical document along with a more detailed description of the parts of the equipment (e.g. parts lists, circuit diagrams, block diagrams, flow-diagrams, etc.)

Advantages - what does the product offer that makes it useful?

Labelling and packaging

Device and packaging labelling - this should contain the device description, the model number, the legal manufacturer symbol and the full name and address of the manufacturer, shows the electrical specification and the CE mark and NB number; it should show the serial number of the device and uses symbols for warning, read instructions for use and WEEE disposal; other labels are warning labels and shock warning labels along with the software label which identifies the version, and a date of manufacture label

Instructions for use - appropriate font sizes of text, quality of translations and understand ability of texts and graphics, especially when proper/safe use comprises subsequent steps or procedures or where devices are used with accessories or other devices or products; the needs and abilities of intended users have to be taken into

account; appropriate checks should be performed by the manufacturer on suitable samples of target users whether IFUs are really readable and assure proper and safe use of the device

Package description - what should be included when we sell the product

Transport - conditions of transport of the product (humidity, temperature, maximum distance covered and others)

Countries of commercialization - those markets we are going to enter

Design and development information

Product design - description of how the product has evolved and been produced

Product development process - shall include the detailed software development applied to the development of the product is in accordance with QMS requirements and reflect the activities performed in each life cycle phase of the development.

Essential requirements checklist - the manufacturer is required to demonstrate how each of the applicable essential requirements and any derived technical requirements/specifications for the particular device concerned have been met; note that references must be made to documentation demonstrating compliance with the requirements.

Risk analysis and control summary - A documented risk analysis shall be part of the documentation. It shall cover all risks related to the device and its use. It shall include a conclusion, with appropriate evidence, that the overall remaining risks are acceptable when weighed against the intended benefits to the patient.

Product verification and validation

Algorithm validation - accordance with IEC 62304 and the other norms

Software validation - This includes results from all verifications and/or validations performed to establish conformity with established requirements. Such testing shall be performed according to predetermined conditions. These test reports may be maintained according to special document control procedures in the manufacturer's quality system. The documentation necessary for the review shall at least include a list with clear references to this documentation providing sufficient traceability to each test report.

Clinical evaluation - title, author and importance of the paper for all the work

Annexes

Declaration of conformity - as discussed in the next section of this work, the declaration of conformity is where the manufacturer assumes responsibility for the compliance of the product

Existing technologies and products - market study and business strategies

Pilot trials - clinical evaluation

4.6 Declaration of conformity

Upon completion of all other steps required for conformity assessment, the manufacturer is expected to provide a written declaration that the device(s) concerned meet the provisions of the Directive which apply to them, regardless of whether or not a NB is involved in the conformity assessment. By drawing up and signing the EU Declaration of Conformity, the manufacturer assumes responsibility for the compliance of the product.

The declaration must be the final step in the relevant conformity assessment procedure. It would not be possible for example, for the manufacturer to issue a final declaration under MDD Annex II until the NB had approved the quality system, and additionally for class III devices approved the design. It may be helpful however for the manufacturer to prepare a draft declaration of conformity for NB review.

Just as it is the case for the technical documentation, the EU Declaration of Conformity must be kept for ten years from the date of placing the product on the market, unless the legislation provides for any other duration (for medical devices is about 5 years).

The declaration shall include:

- document title,

- under what Directive(s) and Annex(es) it is made (mention the standards),

- identification of the product(s) to which it relates (name, type, description),

- the name and address of the manufacturer,

- name and address of authorized representative (if applicable),

- statement of compliance under the sole responsibility of the manufacturer to the national legislation,

- GMDN Number (Global Medical Device Nomenclature),

- number identifying the product (it does not need to be unique to each product, since it could refer to a product batch, type or a serial number),

- date, name and title of the authorized approver (the date could be any after the completion of the conformity assessment).

Note that this document must be translated into the language or languages required by the Member State in which the product is placed or made available on the market [43,77,80,81].

4.7 Interaction with Notified Bodies and National Competent Authorities

Notified bodies are certification organizations notified by the European Commission that carry conformity assessment procedures, according to all authorized representatives from the member states mentioned before. Their activities include full quality assurance, examination of the design, type examination, verification and production and product quality assurance. In the presence of medical devices, it is mandatory a NB in case of a device class I with measure function, class IIa, class IIb and class III [41].

Figure 14: Objectives of Competent Authorities [61].

How the Authorities achieve these objectives? How can they act over the companies and National Authorities?

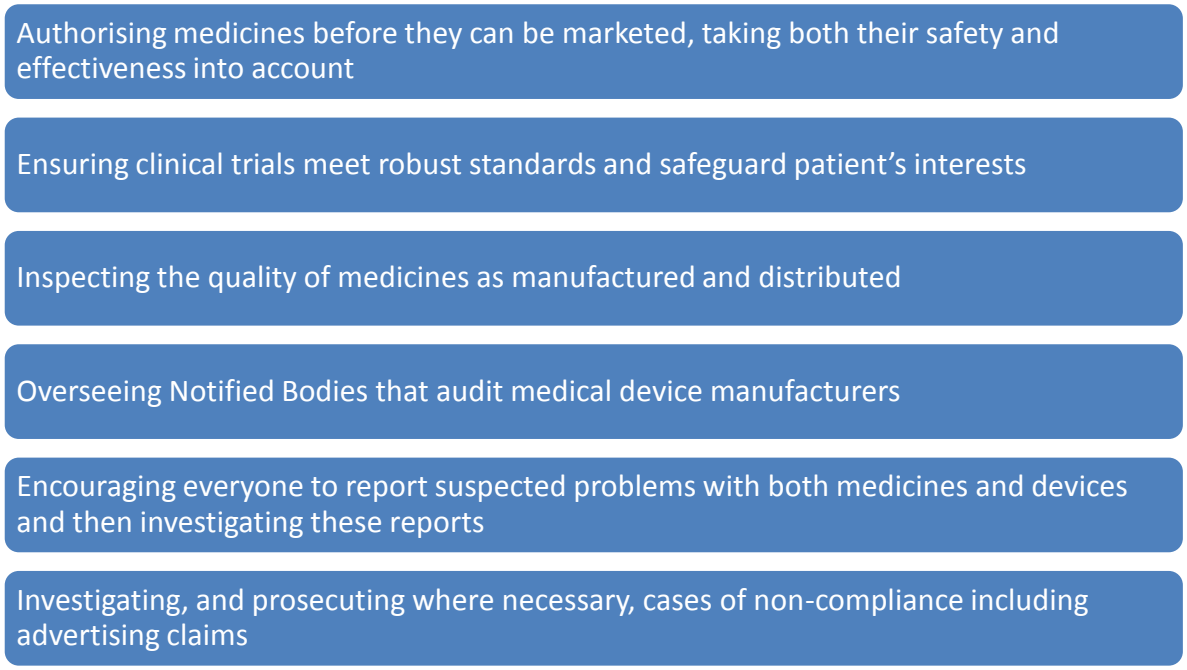


Figure 15: Competent Authorities actions [82].

There is a list of notified bodies on the Internet, in the European Commission official page. There is information about all the applied directives to the different products, plus it can be selected one of them to find a list of Notified Bodies across Europe that work with that kind of products.

With regards to the interaction of Perceive3D with NB and consultants, please consult annex 3, which contains important information about the stages and documentation of the certification process. The more interactions with different entities you make, the better it is. It allows compiling different opinions and always new perspectives, since certification is a questioning subject.

4.8 Implementation of ISO 13485 and other future work

When a company wants to contact a client or a partner, most of times they are questioned about the stage of certification. For that reason, having a company with a QMS implemented and fully recognized by a NB is very important and significant.

Perceive3D is a company focused in medical software. They considered the possibility of implementing ISO 13485, with the intent of turning the company rightfully

qualified for the conception, development and production of software. Since ISO 13485 is a horizontal standard and its chapter seven is related with conception, development and production, EN 62304 is also required because it is a standard more specific.

There are documents under development about EN 62304, hoping to be able to describe the processes to be included in the software development life-cycle for the development of safe medical device software.

Besides ISO 13485 and EN 62304, documentation related with usability of the RDFixer should be compiled (EN 62366). Usability has already been mentioned in this work and it is necessary, based on the fact that there is an interaction of the interface of the RDFixer with the user.

5. Impact of RDFixer in different medical procedures

5.1 Important definitions

- One important concept, vital for the intended use of the device, is depth of field (DOF). It refers to the distance between the nearest and farthest objects in a scene that appear acceptably sharp in an image. Although a lens can precisely focus at only one distance at a time, the decrease in sharpness is gradual on each side of the focused distance, so that within the DOF, the unsharpness is imperceptible under normal viewing conditions [83,84].

- The aspect ratio of an image describes the proportional relationship between its width and its height. It is commonly expressed as a ratio of two numbers [83,84].

- The focal distance of an optical system (f) is a measure of how strongly the system converges or diverges light. For an optical system in air, it is the distance over which initially collimated rays are brought to a focus. A system with a shorter focal length has greater optical power than one with a long focal length; that is, it bends the rays more strongly, bringing them to a focus in a shorter distance [83,84].

- The skew is a measure of the intensity of those rays that does not propagate in a plane that contains both the object point and the optical axis. Such rays do not cross the optical axis anywhere, and are not parallel to it [83,84].

- The FOV is the extent of the observable world that is seen at any given moment. In case of optical instruments or sensors it is a solid angle through which a detector is sensitive to electromagnetic radiation [83,84].

- Qsi quantifies the amount of image deformation, according with the division model already mentioned before. It is related with η and focal length by equation 3.

- The reprojection error is a geometric error corresponding to the image distance between a projected point and a measured one. It is used to quantify how closely an estimate of a 3D point $\hat{X}$ recreates the point's true projection X [83,84].

5.2 Method used to identify procedures

As mentioned earlier, the final objective of this work was a study of different lenses to determine where RDFixer could add value.

Using a database of different lenses, we elaborated two lists, one commercial and one technical. The commercial list contains information related with the procedures and areas of practice of the lenses, as well as the amount of radial distortion they offer, both in dry and wet medium. There are procedures commonly practiced in dry medium, but there are others in a wet medium, so is important to have this comparison. In this list, there is also the FOV of the lenses that is an important concept when comparing them.

Besides the commercial list, there is also a technical list. This list contains information about the parameters of calibration of each lens, plus some physical specifications and image characteristics.

Both these two lists are important in commercial and certification terms, since it allows determining the areas where RDFixer could add value and some limitations of RDFixer. During a certification process, having more detailed information about the device, is always useful to corroborate features and clinical evaluation.

5.3 FOV and radial distortion in water medium

When a camera is in a water medium, there is a variation of the focal length, which implies a decrease of the solid angle of view. As a result, even without any distortion, the image must be magnified by a factor, that corresponds to the water refractive index (1,333).

Let f be focal length of the lens and f' the focal length of the same lens in water. Let's consider u to be the distorted image of a point in the air medium and du the distortion correction to obtain the perfect perspective projection. If in the same way u' is the distorted image of a point in the water medium and du' the new distortion correction, we have [85]

$$1{,}333(u + du) = u^{'} + du^{'} (1)$$

or, comparing the focal lengths,

$$1{,}333f = f^{'} (2)$$

By having a different focal length, the new η' is

$$\eta^{'} = \frac{f'}{\sqrt{-\xi}} (3)$$

The original and corrected images in water medium will both be different from dry medium, because focal distance is different, and consequently eta will also be different, as we can see in figure 16.

As for the calculus of FOV, looking at figure 16, let's consider a, b, c and d to be the distance from point A, B, C and D to the centre, respectively. The equation used was

$$FOV = \tan^{-1}\left(\frac{a}{f}\right) + \tan^{-1}\left(\frac{b}{f}\right) (4)$$

Since there are two FOVs, one horizontal and one vertical, the equation 4 takes the form of

$$FOV\ vertical = \tan^{-1}\left(\frac{a}{f}\right) + \tan^{-1}\left(\frac{b}{f}\right) (5)$$

$$FOV\ horizontal = \tan^{-1}\left(\frac{c}{f}\right) + \tan^{-1}\left(\frac{d}{f}\right) (6)$$

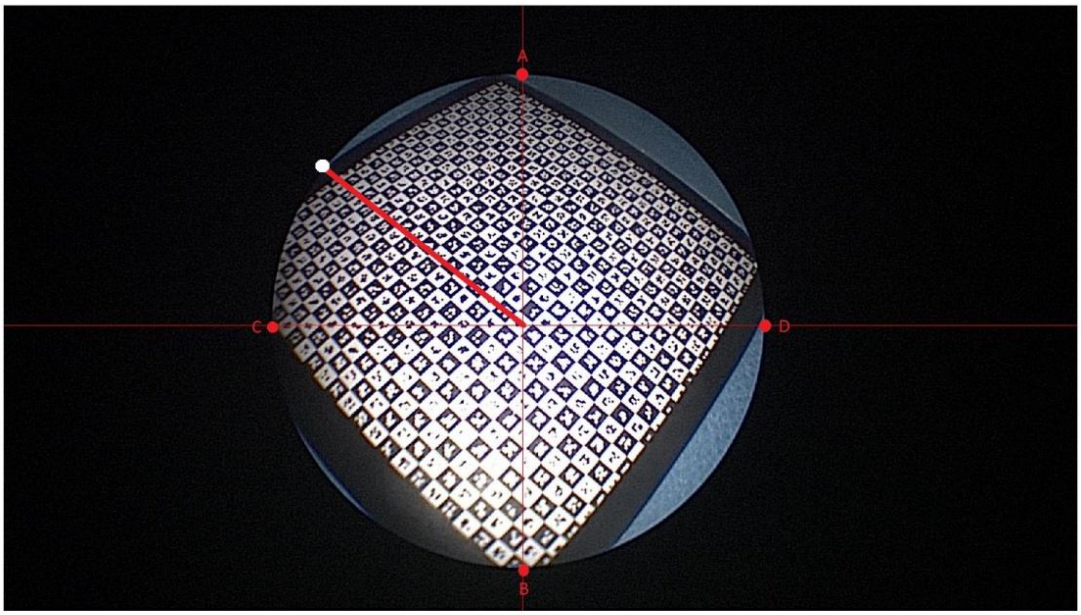


Figure 16: Example of an image of the database, with all important points showed in red and white.

The radial distortion percentage can be calculated using the distance from the farthest point of the centre (white point in figure 14) to the centre (let's call this distance r_{max}) according to

$$\%\ radial\ distortion = -\eta \times {r_{max}}^2 \times 100$$

5.4 Lists with results

5.4.1 Commercial list

Identifier	Practice Area	Procedure	Description					
			FOV in Degrees (Dry)		FOV in Degrees (Wet)		% Radial Distortion (Dry)	% Radial Distortion (Wet)
			Horizontal	Vertical	Horizontal	Vertical		
K01	Urology	Cystoscopy	80	80	58	58	24,7	13,9
K02	Urology	Ureteroscopy	78	78	57	57	26,7	14,5
K03	Neurosurgery, Cardiovascular Surgery, Ginecology, Urology, Orthopaedics, Sports Medicine	Laparascopy, Arthroscopy, Thorax, Neuro-Endoscopy	75	75	59	59	6,6	3,7
K04	Surgery, Ginecology, Urology	Laparascopy	70	70	52	52	14,2	8,0
K05	Ear, Nose and Throat (ENT)	Bronchoscopy, Esophagoscopy, Thorax	71	71	53	53	17,2	9,7
K06	Neurosurgery, Cardiovascular Surgery, Ginecology, Urology, Orthopaedics, Proctology, Gastroenterology, Pediatric Surgery, Sports Medicine	Laparascopy, Arthroscopy, Thorax, Neuro-Endoscopy	75	75	59	58	6,6	3,7
K07	Surgery, Ginecology, Urology	Laparascopy	72	72	56	56	5,1	2,9
K08	Urology	-	63	68	46	50	32,7	18,4
K09	-	-	101	101	74	74	33,3	18,7
K10	-	-	101	75	74	55	59,2	33,3

NOTE: Lenses K08, K09 and K10 miss some information in columns Practice Area and Procedure since they were incorrectly identified, making it impossible to reach which lenses they are referred to.

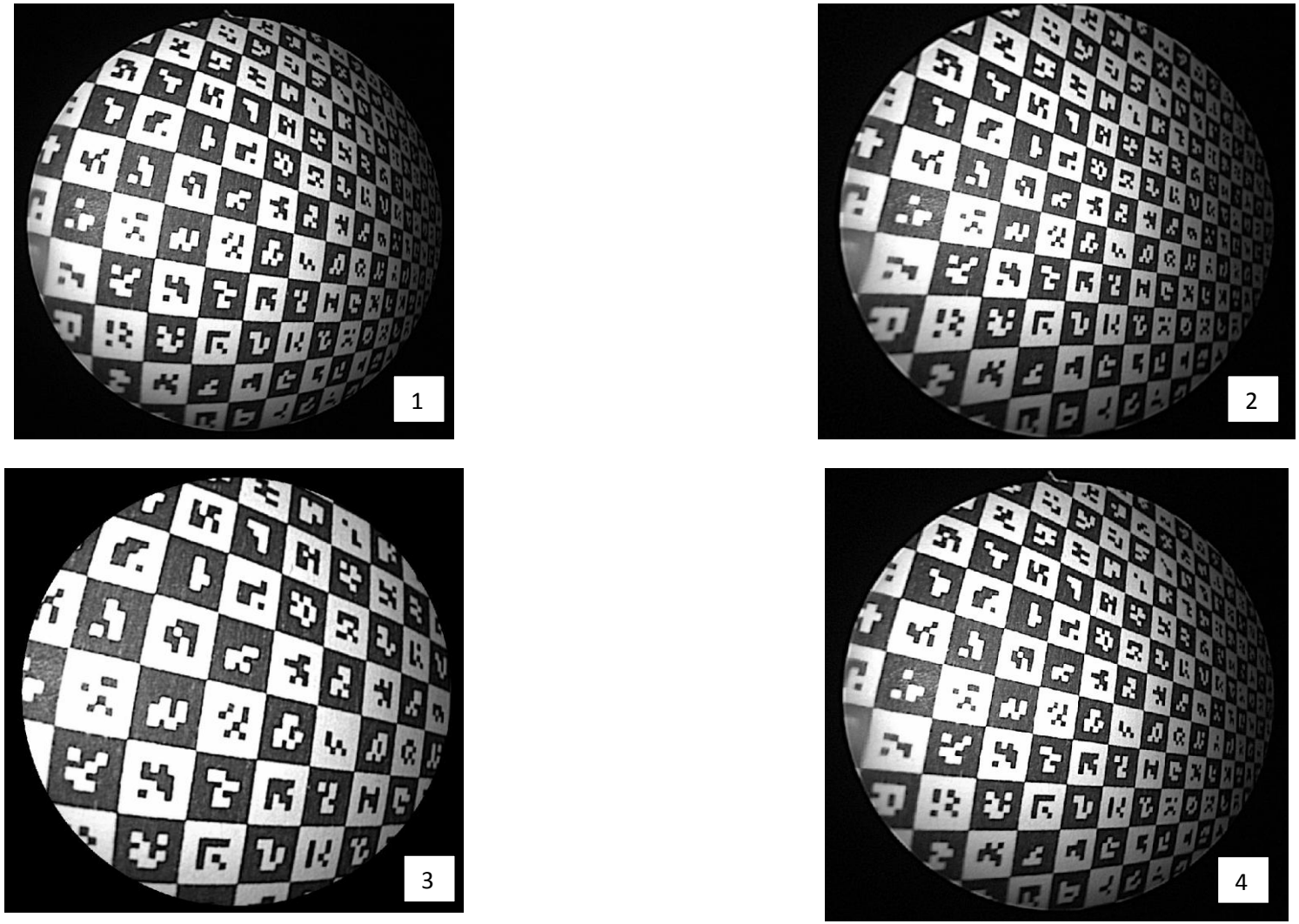


Figure 17: Differences between original and corrected images, both in dry and wet medium. Image 1 corresponds to the original image taken from the database. Image 2 corresponds to the correction of image 1, assuming both of these two images are in dry medium. Image 3 corresponds to the original image considering it is in a wet medium. At last, image 4 corresponds to the correction of image 3.

5.4.2 Technical list

Identifier	Physical Specifications			Number of Images	Image Parameters					
	Diameter (mm)	Working Length (cm)	Cut (Degrees)		Resolution	Boundary Type	Radius	A	B	Φ
K01	4	30	70	19	1920x1080	Circle	495,52	495,80	495,24	0,34
K02	2,8	45	0	9	1920x1080	Circle	540,00	-	-	0,00
K03	10	31	30	18	1920x1080	Circle	654,44	655,92	652,95	-1,24
K04	5,5	50	30	20	1920x1080	Circle	442,46	442,94	441,99	1,19
K05	5,5	50	90	20	1920x1080	Circle	434,71	434,87	434,56	1,42
K06	10	31	0	17	1920x1080	Circle	649,30	650,02	648,59	-0,05
K07	10	42	45	20	1920x1080	Circle	651,49	651,98	651,00	0,54
K08	3,7	-	6	20	1920x1080	Circle	445,60	446,39	444,81	1,48
K09	-	-	-	19	1920x1080	Circle	519,71	519,88	519,54	0,46
K10	-	-	-	22	1920x1080	Rectangle	-	-	-	-

NOTE: Part 1 of the technical list. The number of images corresponds to how many images there were in the database from that lens. A, B and ϕ are the parameters from the ellipse created, although, since these ellipses are almost circular, the radius becomes the mean value between value A and B and the boundary type is considered to be a circle. Lenses K08, K09 and K10 miss some information from the same reason as mentioned in the note from the commercial list.

Calibration Parameters Optimized							
Identifier	Focal distance	Qsi	Center (x,y)		Skew	Aspect Ratio	Reprojection Error in Pixeis (mean)
K01	762,16	-0,53	930,86	564,70	-5,41E-05	1,00	2,44
K02	378,99	-0,48	969,22	526,65	-7,78E-04	1,00	1,51
K03	901,64	-0,11	937,20	569,17	-2,36E-04	1,00	1,76
K04	731,90	-0,37	929,28	570,95	-4,23E-05	1,00	1,12
K05	711,54	-0,40	959,64	537,67	1,71E-04	1,00	1,20
K06	899,19	-0,12	915,82	599,56	-8,76E-04	1,00	2,02
K07	946,90	-0,10	948,00	583,24	-1,20E-03	1,00	2,41
K08	782,43	-0,49	1009,84	734,40	1,69E-04	1,00	1,96
K09	632,09	-0,47	971,75	567,70	4,25E-04	1,00	2,54
K10	875,92	-0,51	936,03	495,69	-2,67E-05	1,00	1,94

NOTE: Part 2 of the technical list. In this part, the final calibration parameters were returned from EasyCamCalib for each lens.

Identifier	Calibration Parameters 1by1													
	Focal distance	σ	Qsi	σ	Center (x,y)				Skew	σ	Aspect Ratio	σ	Reprojection Error in Pixeis (mean)	σ
					X	σ	Y	σ						
K01	768,36	35,84	-0,54	0,06	931,59	9,52	564,68	7,97	-5,78E-05	5,24E-04	1,00	2,49E-04	1,61	0,35
K02	374,07	1,41	-0,50	0,02	968,00	8,77	544,90	38,78	-6,94E-04	1,30E-03	1,00	6,27E-04	0,50	0,15
K03	893,75	112,30	-0,11	0,02	936,30	16,07	565,85	58,32	-7,20E-04	2,10E-03	1,00	8,37E-04	1,91	0,49
K04	734,25	14,65	-0,37	0,01	928,67	7,80	568,45	19,86	-5,74E-06	5,22E-04	1,00	1,85E-04	1,37	0,41
K05	710,61	11,61	-0,40	0,03	960,94	18,96	537,25	14,08	2,11E-04	5,92E-04	1,00	4,16E-04	1,33	0,35
K06	895,83	94,26	-0,11	0,02	915,53	20,92	589,91	97,58	-4,22E-04	3,20E-03	1,00	1,00E-03	2,03	0,46
K07	1069,56	156,69	-0,13	0,03	975,03	39,98	527,82	89,41	-2,10E-03	2,50E-03	1,00	1,10E-03	2,16	0,39
K08	770,51	38,67	-0,47	0,07	1017,21	30,04	735,64	22,48	4,65E-04	1,10E-03	1,00	4,63E-04	1,73	2,00
K09	644,96	40,00	-0,49	0,07	971,65	8,08	565,74	11,90	4,97E-04	3,94E-04	1,00	2,77E-04	1,82	0,54
K10	871,23	22,11	-0,50	0,03	935,30	13,24	495,61	12,18	-2,74E-05	3,96E-04	1,00	3,69E-04	2,05	0,35

NOTE: Part 3 of the technical list. In this part, also with the help of EasyCamCalib, the calibration parameters were calculated for each image of the same lens, and then, the final calibration parameters of the lens were calculated by applying the mean to the values from each image (plus standard deviation).

5.5 Discussion and conclusions

By looking at the information taken from the lenses, it can be identified possible areas, and subsequently procedures, where RDFixer could bring improvements.

RDFixer works in images both with high or low distortion, but only those that present some radial distortion can evidence the enhancement of the image. After knowing this, we took into account that there are procedures made in a wet medium, like Uretroscopies, while others are made in a dry medium, just like Bronchoscopy.

For instance, lens K08 is used in Urology, which includes procedures done in wet medium. This lens has a radial distortion around 18% in wet, which is a considerably high value. RDFixer can add value by increasing the visualization in those procedures practiced in this area with this kind of lenses. Another example is ENT, which is an area that deals most of times with dry conditions. Almost 18% of radial distortion in dry conditions indicates that RDFixer can bring high improvements here.

Concluding, RDFixer improves all areas, but there are just some that evidence more improvement than others. We must look at the amount of distortion in both dry and wet mediums. Considering the obtained values in the commercial list (the ones with shade), Urology, ENT and Orthopaedics are some of the areas worth to investigate further.

6. Conclusion

Medical devices can only be useful if their use do not bring any excessive risks for the patients and users, because safety is the primary concern about medical devices. To make that happen it is necessary to take preventive measures based on possible risks that any equipment may present.

This was pretty much a research work based on read and study of different type of documents. This work intended to contribute for the minimization, and removable if possible, of any risks involved in the development, conception and production of medical devices by Perceive3D.

To achieve this objective, I studied some theory about optics and legislation, and then I ran some comparisons between lenses to understand a bit more about endoscopy. I also participated and helped with pilot trials performed to the product.

During this last year, I had improved my autonomy, based on the fact that I had no background about how to apply the CE mark to a medical device. It helped me to interact with other environments and other people capable of giving me new information and making me suggestions of good practices to have.

According with MDD, the device is classified as class IIa, as a result of having low risk. This process is hard to please and time consuming, even with many similar technologies already available in the market.

The certification process of medical devices is not a common practice in Portugal yet. Despite already being included in Portuguese legislation, many medical devices developed have their entry in the market prolonged, and sometimes blocked, because sometimes there is not that initial concern of knowing the legislation applied to the device since its development stage, which means start collecting documentation from the beginning. For example, the standard ISO 14971:2007 – Application of risk management to medical devices was analyzed and implemented at the risk analysis, and the clinical evaluation was compiled using guides from the European Commission.

At a regulatory level, even after the entrance of the medical device in the market, it is important to collect as much information as possible. An efficient gather of information helps to improve the quality of the devices placed in the market.

According with the objectives proposed, all necessary regulatory requirements have been brought together for the development and certification of this device. However, there is still documentation not finished, the pilot trial are still in progress, the

device can have some modifications, that contribute for the objectives of this work have only been partially accomplished. Nevertheless, the work done can be used as a basis on other devices developed by the company and other documentation needed.

As for future work, besides the documentation that has to be created and finished, the company should consider to finish the QMS that is an add value whenever they reach a client. As for future devices of the company intended to enter the market, many of the documents will be similar, and the ones that are not similar or are new, will be produced easily.

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Annexes

Annex 1: Technical File

Annex 2: Identified Risks and Hazard-Harm Matrix

Annex 3: Interaction with Notify Bodies and other Entities

Annex 4: Repeatability Study