Faculdade de Ciências e Tecnologia da Universidade de Coimbra

Departamento de Física

Launch of the Application Retmarker

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To my family …

Abstract

Currently, the increase of the population suffering from diabetes is one problem that most concerns the authorities responsible for public health. A large majority of these patients will develop, among other complications, diabetic retinopathy, which, in a very advanced state, can lead to blindness. The effects of this disease, as is known, are reversible at an early stage and is aiming an earlier detection of symptoms that Critical Health launches new software, the Retmarker.

Taking advantage on recent technology (image co-registration) and based on studies developed by AIBILI, that reveals the discovery of a new biomarker for the progression from an early stage of Diabetic Retinopathy to a Clinically Signicant Macular Edema (CSME), the microaneurysm turnover, Retmarker, as a tool to help diagnosis, gives us indicators very accurate of the possible evolution of the disease.

The challenge of this project was to understand the product and all steps after its development until it enters the market. Then, Oftaltec using his vast market knowledge disclose it and try to place it in the domestic market.

This thesis provides a description of the necessary steps to allow the product sale and the business strategy to do it.

Resumo

Actualmente, o aumento da população que sofre de diabetes é um dos problemas que mais preocupa as entidades responsáveis pela saúde pública. A grande maioria destes doentes irá desenvolver, entre outras complicações, retinopatia diabética, que, num estado muito avançado, pode levar até à cegueira. Os efeitos desta doença, como é sabido, são reversíveis numa fase inicial e é com o objectivo de uma detecção mais precoce dos sintomas que a Critical Health lança no mercado um novo software, o Retmarker.

Tirando partido de uma tecnologia recente (co-registo de imagens) e baseado em estudos do AIBILI, relativamente à descoberta de um novo biomarcador para a progressão de um estágio inicial da Retinopatia Diabética para um Edema Macular, o turnover de Microaneurismas, o Retmarker, como ferramenta de auxilio ao diagnóstico, dá-nos indicadores muito precisos de uma possível evolução da doença.

O desafio deste projecto foi conhecer o produto e todas as etapas seguintes ao seu desenvolvimento até à sua entrada no mercado. Aí, a Oftaltec, tirando partido do seu vasto conhecimento do mercado, tentará divulgá-lo e introduzi-lo no mercado nacional.

Esta tese fornece uma descrição dos passos necessários para que o produto possa ser vendido e a estratégia comercial.

Acknowledgments

Acknowledgments are only a small part of the long road that I have done, sometimes difficult and painful, so these words are few and to not achieve the happiness and relief felt by the end of this journey.

So, first of all, I want to thank with my parents. Thank you for the opportunity to go further. Then I want to thank my brother, Tiago, for being always on my side.

A special thank to Professor José Paulo Domingues and Dr. Afonso Martinho for being always present when I needed.

Also a special mention to Professor Miguel Morgado for being the “father” of all Biomedical Engineering students of Coimbra.

I want also to thank to all the people that work in Oftaltec for the good environment, friendship and support. The same is valid for Critical Health people during the short time I was there.

To my friends Rui, João, André, Portulez, Rita, Neuza for the support.

And last but not least, I would like to thank my girlfriend for the support she gave me whenever I needed and the encouragement in the moments I were frustrated, sad and disappointed.

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1. Introduction

1.1. Motivation

Diabetic Retinopathy is one of the main causes of blindness in the industrialized countries. About 90% of the diabetic patients develop retinopathy[1].

To enable better and early diagnosis of some retinal diseases, Critical Health developed a new software, Retmarker.

For now, exist the Retmarker C (retinal changes) and the Retmarker DR (Diabetic Retinopathy) and they both aim to make a more accurate, and automatic detection of the retinal changes. Retmarker DR besides highlighting the differences, it also, and mainly, provides the possibility of detect the microaneurysms, which presence is an important biomarker for the retinopathy.

Thus, Retmarker pretends to be a tool that provides ophthalmologists more information to support diagnosis. Our main motivation is to improve the management of the diseases.

1.2. Objectives

The main intention of this project was to put Retmarker on the market, and to achieve that, the project was divided in two different parts: one was to know the software, to study it, to know what it was capable to do and suggest some possible changes. The second part was to follow all the process of putting it into the market (Technical presentation and demonstrations, legal and commercial aspects and strategies, etc…). Being in company environment would also bring as an objective to take contact with the area of retina diseases and diagnosis devices.

1.3. Scope

This project was developed in the scope of the Master integrated in Course of Biomedical Engineering, taught on the Physics Department of the University of Coimbra. This project was realized in partnership with Oftaltec and Critical Health.

1.4. Audience

This project is addressed to the supervisors and jury members, and possible future students that may continue this project and general readers interested in retinal diseases and diagnosis.

1.5. Document Structure and Organization

This document is divided in nine chapters.

The aim of the present chapter is to introduce the reader to the project motivation and objectives.

The next one, Project Management, provides information about the project organization, such as project members and their functions. It also provides a brief summary about Oftaltec and Critical Health.

On the third chapter is described the scientific background that supports the software.

The fouth chapter provides the reader with an overview about the the state of art in retinal diseases dignosis.

On the fifth chapter we talk a little about the studies performed in AIBILI related with Retmarker.

Chapter 6 – How does Retmarker works? – is the description in detail of the software.

Chapter 7 is about some tests validation tests and market studies carried out by Critical Health.

In chapter 8 are described the steps to achieve the CE marking.

Chapter 9 is where is explained the strategy to sell Retmarker, and in the tenth we refer the awards won by Retmarker.

In the last chapter, the conclusion, is drawn a brief appreciation about the project and the possible future works.

2. Project Management

2.1. Project Members

The project was developed by a Biomedical Engineering student of the Faculty of Sciences and Technology, University of Coimbra and their supervisors.

The student was responsible for all the study related to Retmarker. The supervisors accompanied the project evolution and individual development of the student, being responsible for the orientation and coordination of his work.

The elements that composed the team are presented in the table.

Table 1. Project Members

Name	Contribution	Contact
Carlos André Neves	Student	andrecneves@hotmail.com
Professor José Paulo Domingues	Coordinator	jpd@fis.uc.pt
Dr. Afonso Martinho	Coordinator	afonsomartinho@oftaltec.pt
Eng. Frederico Teles	Supervisor	ft-santos@critical-health.com
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Eng. João Pinto	Supervisor	jp-pinto@critical-health.com

2.2. Project Supervising

The project was supervised by two entities, Oftaltec, and Critical Heath.

2.2.1. Supervising at OFTALTEC

It stands out for the highly sophisticated equipment that sells, which are developed based on the most advanced technologies. It has market leadership in some business areas, for example in refractive surgery. Oftaltec represents exclusively several manufacturers such as Heidelberg Engineering or Technolas.

The company has a commercial department, a clinical application department and a technical department. The technical department is composed by three technicians with specific training given by the manufacturers.

2.2.2. Supervising at CRITICAL HEALTH

Critical Health is a spin-off of Critical Software created in 2008 to continue the healthcare activities started in 2006. Critical Software is specialized is real-time systems for defense, aerospace and telecommunications.

Since it was created, Critical Health has tried to create solutions capable of reducing healthcare spending and accessible to everyone.

The company objectives are:

To develop solutions to help to prevent Loss Vision of Mobility and Cognitive skills for diabetics and people with more than 65 years old and to build Technological Partnerships with Internationally Institutions

Critical Health works in two different business areas:

- **Vision**

In this department the gold is to develop solutions for retinal diseases like Diabetic Retinopathy, Age-related Macular Degeneration or Glaucoma.

Retmarker was the first to be concluded and it is useful to monitor the progression of Diabetic Retinopathy. Analyzing fundus photos, it provides additional information that helps the doctor in his diagnose.

- **Health Monitoring**

In this division Critical Health is developing software to monitor patients ECG, fall detection and their location. The patients wear necklaces or bracelets and the device quickly alerts the caregivers. The system is being developed directly with customers.

3. Scientific background

3.1. The human eye

The human eye is an almost spherical structure with a diameter about 24mm. It is divided in three layers: the outer layer composed by sclera and cornea (*tunica fibrosa*); choroids, ciliar body and iris are the middle layer (*tunica vasculosa*) and the inner layer is composed by the retina and the retinal pigment epithelium.

Figure 1. Human eye

The external coat of the eye is the sclera and it occupies about 80% of the surface of the human eye. Sclera function is to maintain the spherical shape of the eye, besides the protection of the inner structures. Cornea acts as the

eye's outermost lens. Its function is to control and focus the entry of light into the eye.

In the *tunica vasculosa,* the major part of the layer is occupied by the Choroid. It is a thin black membrane of blood vessels (so avoids the light reflection) whose main is to provide blood.

The other constituents of the midlle layer are the Ciliary body and the iris. The Ciliary body goes from the Choroid to the Iris.

The lens is transparent structure whose main purpose is to focus light rays onto the retina. To do that correctly, the shape of the lens has to be changed depending on the object's distance. The change is done by the ciliary muscles. Iris is the visible colored part of the eye. It is a muscular contractile structure that surrounds the Pupil. Pupil is the dark center opening in the center of the iris. It changes size to adjust for the amount of light available.

The retina is the inner layer of the eye and it is divided in photoreceptive part and non receptive one: the non-sensory (non-receptive), the posterior part of the retina has a retinal pigmented epithelium which transports metabolic wastes from photoreceptors to the choroids. The photoreceptor cells can be of two types: rods or cones and the distribution of each of these types it's not the same all over the retina. Cones are responsible for color vision while rods are responsible for the vision with reduced light. Macula lutea is an area in the retina that contains special light-sensitive cells, cones. They allow us to see fine details clearly in the center of our visual field.

As we move away from the center of the retina the cones decrease. The optic disk is a region in the retina where occurs the insertion of the optic nerve, a bundle of more than a million nerve fibers that carries visual messages from the retina to the brain. Here does not exist any type of photoreceptor cells, thus the optic disk location is usually called the blind spot,[1], [2].

3.1.1. How eye works

The eye is a very complex organ and in the visual processing all its parts play an essential role.

If a person is looking at a car the light rays are reflected off it and enter the eye through the cornea (transparent outer coating of the eye).

The cornea refracts the rays and they pass through the pupil. The colored part that surrounds the pupil, the iris, regulates the amount of the light that passes through. In bright light, iris reduces pupil's size to prevent too much light from entering. In dim light, the pupil enlarges to receive more light.

After this, the rays light reach the crystalline lens. The lens is important because they refract the rays and focus them in the retina. The ciliary muscles of the eye can contract and relax to change lens shape. If the object is close, the muscles contract and the lens become rounder. If it is distant, the muscles relax and the lens flattens. This feature of the lens allows a perfect vision at different distances.

In the back of the eye there is the retina. It occupies two-thirds of the eye wall and is responsible for the wide field of vision. If light rays focus directly on the retina we get a perfect vision. If light focuses in front of or behind the retina, the result is blurry vision.

The retina function is to transform light rays into electrical signals and transmit them to the brain through the optic nerve. This is achieved by the millions of photoreceptor cells called rods and cones. Rod cells (110 – 125 millions) allow mesopic and scotopic vision (twilight and night vision) and the six or seven million cones respond to bright light and enable to see in color.

The major part of the cones is in the macula. The central part of the macula, fovea, has the highest concentration. The outer portion is the primary location of rods.

The signals are transmitted from the cones and the rods to the brain by the optic nerve. The signals transmitted by each eye correspond to a slightly different image. Once they reach the brain, they are and combined to form just one image. [3].

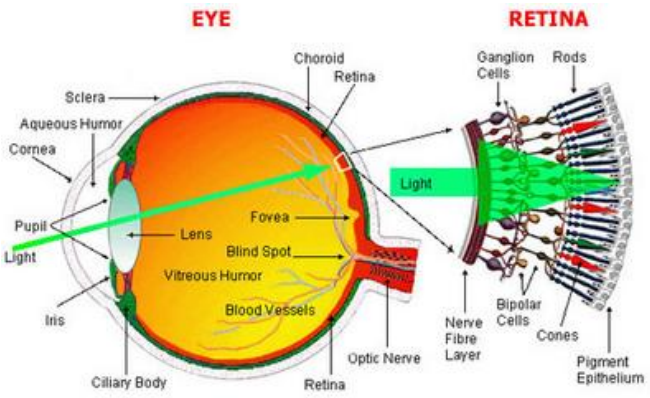


Figure 2. Schematic section through the human eye

3.2. Retina

The retina is the innermost of three layers of the globe. It is a very thin and transparent membrane and is divided in two different parts: photoreceptive part and non receptive one,[4].

The photoreceptive part consists of nine layers:

1. Internal limiting membrane (glial cell fibers separating the retina from the vitreous body)
2. Nerve fiber layer (axons of the third neuron)
3. Ganglion cell layer (cell nuclei of the multipolar ganglion cells of the third neuron; “ data acquisition system”)
4. Inner plexiform layer (synapses between the axons of the second neuron and dendrites of the third neuron)
5. Inner nuclear layer (cell nuclei of the bipolar nerve cells of the second, horizontal cells, and amacrine cells)
6. Outer plexiform layer (synapses between the axons of the first neuron and dendrites of the second neuron)
7. Outer nuclear layer (cell nuclei of the rods and cones= first neuron)
8. Outer limiting membrane (sieve-like plate of processes of glial cells through which rods and cones project)

9. Layer of rods and cones (the actual photoreceptors)

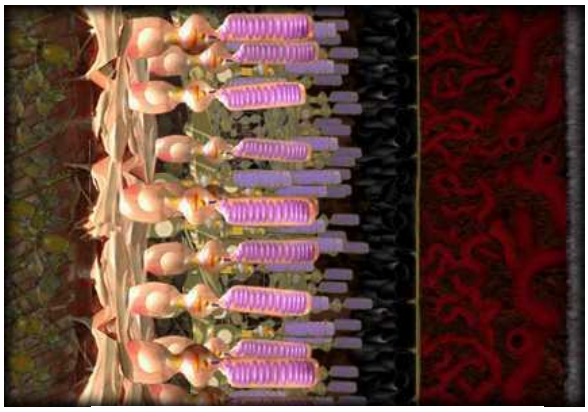


Figure 3. Photoreceptive layer

The non receptive part consists of two layers:

1. Retinal pigment epithelium (a single cubic layer of heavily pigmented epithelial cells)
2. Bruch's membrane (basal membrane of the choroid separating the retina from the choroid)

3.3. Retinal diseases

Retina can suffer from a lot of diseases but the ones that we are more interested in are those which symptoms we can diagnose using retinographies. And the retinal changes that we can observe in a retinography are among others: haemorrhages, hard exudates, drusen and microaneurysms.

These changes are symptoms of retinal diseases such as Age-related Macular Degeneration, and Diabetic Retinopathy,[5].

3.3.1. Diabetic Retinopathy

Diabetic Retinopathy is the disease that we are going to pay more attention.

It is one of the main causes of blindness in industrialized countries and after 15 years of suffering from diabetes, approximately 2% of the people become blind, and about 10% develop severe visual damages.

Diabetes is a disease that damages retina blood vessels because of the high levels of glucose. The walls become thicker but also weaker, which leads to deformation and leakage, so a good blood sugar control is very important to control the disease. In general, the retinopathy is not developed until at least 10 years after the onset of disease.

Diabetic retinopathy appears in patients with type 1 and type 2diabetes but in different ways.

In patients with type 1 diabetes the vision loss is due to the formation of new vessels (proliferative retinopathy), while in type 2 diabetes vision losses are most commonly due to macular edema and proliferative retinopathy is relatively rare.

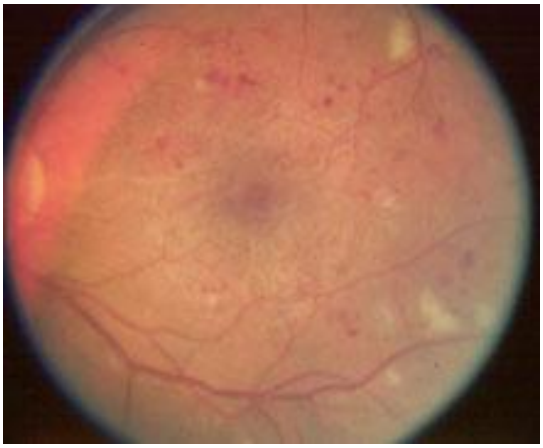


Figure 4. Non proliferative retinopathy

Diabetic retinopathy is characterized by specific alterations in the appearance of the retina. The first change that can be seen is the microaneurysm. Besides this, retinal blot hemorrhages, hard-exudates, cotton-wool spots and intraretinal microvascular abnormalities are some of other lesions that can be found in non proliferative phase of diabetic retinopathy.

In diseases' early stages, it doesn't cause blindness. The hemorrhages can distort parts of visual field or, blur the vision if they are near the macula.

In non-proliferative retinopathy, retina can thicken and if it occurs in the macula we are in the presence of a progression to a Clinically Significant Macular Edema (CSME). The nervous tissue can't work properly due to this thickening and cause vision damages.

In the proliferative retinopathy, the growth of new vessels may seem beneficial, but is not. These new vessels are weaker and grow abnormally. In some cases they can cause a retinal detachment. Proliferative retinopathy is the most dangerous and can cause serious damages like near total blindness and in extreme cases even total blindness.

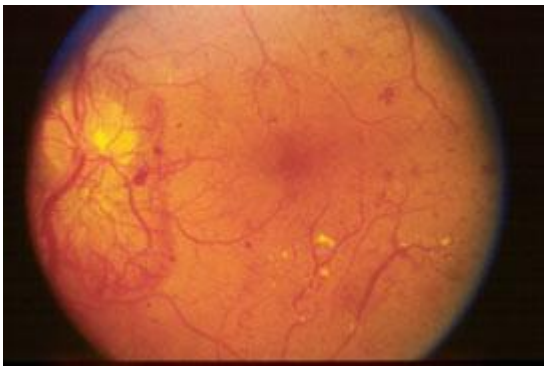


Figure 5. Proliferative Retinopathy

Table 2. Retinal Changes in Diabetic Retinopathy, adapted from Lang, g., *Ophthalmology*. A pocket textbook atlas. 2004

Stage of retinopathy	Retinal changes
Non-proliferative diabetic retinopathy	
1. Mild	• At least one microaneurysm, retinal hemorrhages, hard exudates
2. Moderate	• Mild intraretinal microvascular abnormalities (IRMA) in four quadrantes of the retina • Moderate hemorrhages in two or three quadrants • Venous hemorrhages in four quadrants

3. Severe	• Moderate hemorrhages in four quadrants • Venous beading in two quadrants • Moderate IRMA in one quadrant
Proliferative diabetic retinopathy	
1. Mild	• New vessels elsewhere (NVE) ‹ 0.5 of the disc area in one or more quadrants
2. Moderate	• NVE ≥ 0.5 of the disc area in one or more quandrants • New vessels on the disc (NVD) < 0.3 – 0.25 of the disc area
3. High risk	• NVD ≥ 0.3 – 0.25 of the disc area • Vitreous hemorrhage with any new vessels

Treatment

Does not exist a definitive treatment to diabetic retinopathy. The most common solution is the surgery but it is not a cure. Even after surgery, it is required a close monitoring and some times more treatments may be also needed.

The choice of the treatment depends on the stage and on the type of diabetic retinopathy that the patient had developed.

Early diabetic retinopathy

Usually in an early stage of non proliferative diabetic retinopathy the patient does not receive immediate treatment. In these stages a good sugar control is enough to slow the progression.

Advanced diabetic retinopathy

When the disease is in an advanced stage, the solution is surgical treatment as soon as possible. Depending on the specific problem the surgery performed can be:

- **Focal laser treatment.** This laser treatment, also called photocoagulation, can stop or slow the leakage of blood and fluid in the eye. During the procedure, leaks from abnormal blood vessels are treated with laser burns.

- **Scatter laser treatment.** This laser treatment, also known as panretinal photocoagulation, can shrink the abnormal blood vessels. During the procedure, the areas of the retina away from the macula are treated with scattered laser burns. The burns make the abnormal new blood vessels shrink and scar.

- **Vitrectomy**. This treatment can be used to remove blood from the middle of the eye as well as any scar tissue that's tugging on the retina. Scar tissue and blood in the eye are removed and replaced by a salt solution, which helps to maintain eye's normal shape. Vitrectomy may be followed or accompanied by laser treatment.

Besides treatments, researchers are trying to develop medications to prevent the abnormal blood vessels formation in the eye. This medication can be directly injected in the eye,[6],[7] .

Figure 6. Normal Vision

Figure 7. Vision with Diabetic Retinopathy

3.3.1.1. Relevant symptom in Diabetic Retinopathy: Microaneurysm

It is widely accepted that the earliest clinically recognizable sign of diabetic retinopathy is the microaneurysm (MA). These are small round dark red dots on the retinal surface that are less than the diameter of the major optic veins as they cross the optic disc.

Increasing numbers of microaneurysms are associated with capillary occlusion leading to retinal ischemia (lack of oxygen) and progression of retinopathy[8].

3.3.2. CSME

CSME (Clinically Significant Macular Edema) was defined according to the Early Treatment Diabetic Retinopathy Study classification protocol as the presence of retinal thickening at or within 500μm of the center of the macula or hard exudates at or within 500μm of the center of the macular if associated with thickening of the adjacent retina and/or zones of retinal thickening 1 disc area in size, at least part of which being within 1 disc diameter of the center. An early diagnosis is extremely important to avoid the disease progression to this stage.

Laser treatment is normally the solution when the disease is in an advanced stage,[9].

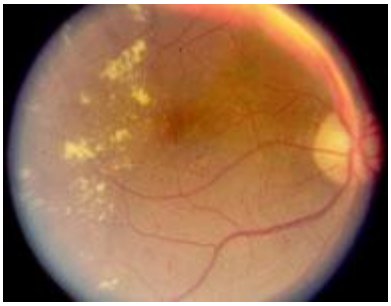


Figure 8. Eye with CSME

4. State of art

Actually, two of the most important exams using retinal images are the angiographies and the retinographies. They are different and complementary for some diseases.

4.1. Angiographies of the retina

Retinal angiography is a diagnostic procedure that photographs the retinal *fundus.* Normally it is performed when the ophthalmologist pretends to identify blood vessels that may be damaged. This diagnostic procedure consists in the injection of a small amount of dye in the circulatory system through a vein in the arm and posterior analysis of the image when the dye reaches the retinal vessels.

After the injection, it is possible to photograph the retinal fundus and easily observe the vessels filled with the tracer. It enables a more detailed analysis of the distribution of the dye and obviously of the evolution of the retinal vessels.

If the dye used is fluorescein it is called a fluorescein angiography. If the dye used is indocyanine it is called an indocyanine green angiography.

In the performance with fluorescein, the eye is illuminated with blue light and that allows a maximum excitation of the tracer. When excited, the fluorescein fluoresces in the yellow-green wavelengths. The light emitted is then filtered and only the yellow-green light reaches the camera. The images acquired are grey scaled images. When the dye reaches the vessels of the retina, it becomes possible to identify some white regions that are the vessels where the dye circulates.

Diabetic retinopathy, between others diseases, affects the retinal circulation and the fluorescein angiography is essential to diagnose it. In other eye disorders, such as age-related macular degeneration, it is mandatory to do an indocyanine green angiography because leakages are in the choroidal blood vessels.

The two dyes have the same purpose but for different parts of the retina. The indocyanine green reaches its maximum excitation when it is illuminated by infrared light and fluoresces with infrared light too. Thus, this allows that the infrared light emitted from the choroids vessels reaches the camera. The infrared light is not visible, so are used high-sensitivity digital cameras in infrared spectrum,[10].

4.1.1. Spectralis HRA

A step ahead of the commom angiographies cameras is the Spectralis. It is a device manufactured by Heidelberg Engineering (German company) and sold by Oftaltec. There are 3 different Spectralis: the HRA, the OCT and the HRA+OCT.

All the devices from the Spectralis line are diagnostic tools and produce various types of retinal images of the human eye. They support the evaluationand treatment of different diseases of the posterior segment, such as

related macular degeneration with age, diabetic retinopathy and glaucoma. We are going to describe a little bit the Spectralis HRA (Heidelberg retina angiograph)[11],[12].

4.1.1.1. Description

Confocal scanning laser is replacing digital cameras because they add motion, depth, and clarity to fundus imaging. Instead of difficulties to control random white light from a flash, lasers enable exact location and ideal wavelength selection.

The detail and perspective that laser imaging with the HRA provide are far away better than in photography, whether digital or film. This is achieved because of the in the properties of confocal scanning laser technology which enable wavelength-selective imaging and fast scanning speeds enabling 16-frame-per-second motion images.

So, this equipment is an ophthalmoscope confocal scanning laser used in angiographic exams of the retina and is able to do the diagnosis by detecting reflected light. it allows use the following imaging techniques:

- Fluorescein or fluorescein angiography (FA)
- Indocyanine green angiography (ICGA)
- Reflectance infrared (IR = "infrared")
- Reflectance without the red or blue (RF = "redfree)
- fundus autofluorescence (AF)
- Simultaneously FA and ICGA
- Simultaneously FA and IR
- Simultaneously ICGA and IR
- Simultaneously AF and IR

With each of the imaging techniques mentioned above , can be picked up and saved individual images or image sequences.

4.1.1.2. Light sources

The dyes are excited with the bands wavelengths relatively narrow. The use of laser is the most efficient excitation, since all power is concentrated in a particular wavelength, and not in a relatively broad continuum, as is the case of conventional flash photography. The laser light sources of the Spectralis emit three different wave lengths:

- For the excitation of fluorescein, it uses a solid-state blue laser (Wavelength equal to 488nm). A filter band eliminator separating the 500nm excitation light of fluorescent light emitted. The same wavelength is also used (no filter eliminator) to generate images by blue reflectance. Furthermore, they can acquire with the Spectralis HRA auto fluorescence images (488nm) of high quality.
- For the excitation of indocyanine green, it uses a laser diode with a wavelength of 790nm, equipped with an 830nm filter eliminator separation of the exciting light of fluorescent light emitted.
- A second laser diode with a wavelength of 820nm is for imaging by infrared reflectance (IR).

Table 3. Light Sources

Fluorescein angiography	488 nm solid state laser	Invasive
Indocyanine green angiography	790 nm diode laser	
Blue reflectance	488 nm solid state laser	Non-invasive
Infrared reflectance	820 nm diode laser	
Autofluorescence	488 nm solid state laser	

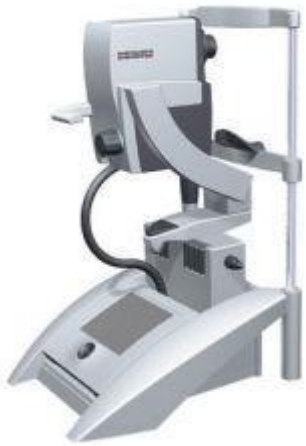


Figure 9. Spectralis HRA

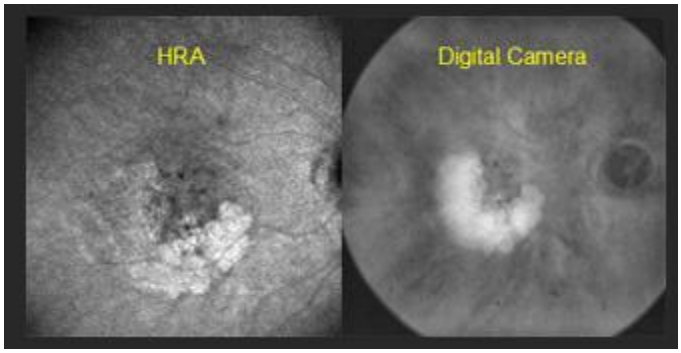


Figure 10. Quality different between images from a Spectralis HRA and a normal digital camera

4.1.1.2. Confocal Scanning Laser Ophthalmoscope

The confocal ophthalmoscope is a device that allows visualization of the retinal fundus.

To illuminate it the light source used is a laser. The laser is targeted to the retina's part you want to analyze. The light reflected off the retina is then divided from the incident light and a beam splitter deflects it to a detector. This allows the measurement of only the light reflected at different points.

In a confocal optical system a small diaphragm is placed in front of the detector where its position is optically coupled with the focal plane of the lighting system. The confocal hole is important to focus the light reflected off the eye. The confocal hole only focus the light reflected directly to it and this way only a part of the light is detect by the photodetector. Thus, with a confocal scanning system can be observed images with very good resolution.

In what concerns to Diabetic Retinopathy, the angiographies are the gold standard exam due to the ease to detect microaneurysms (hallmark of the disease). But angiographies are an invasive exam and are not tolerated by all the patients. Thus, AIBILI developed some studies (will be detailed later) and

achieved a new Biomarker for Diabetic Retinopathy that can be found with the same reliability using retinographies.

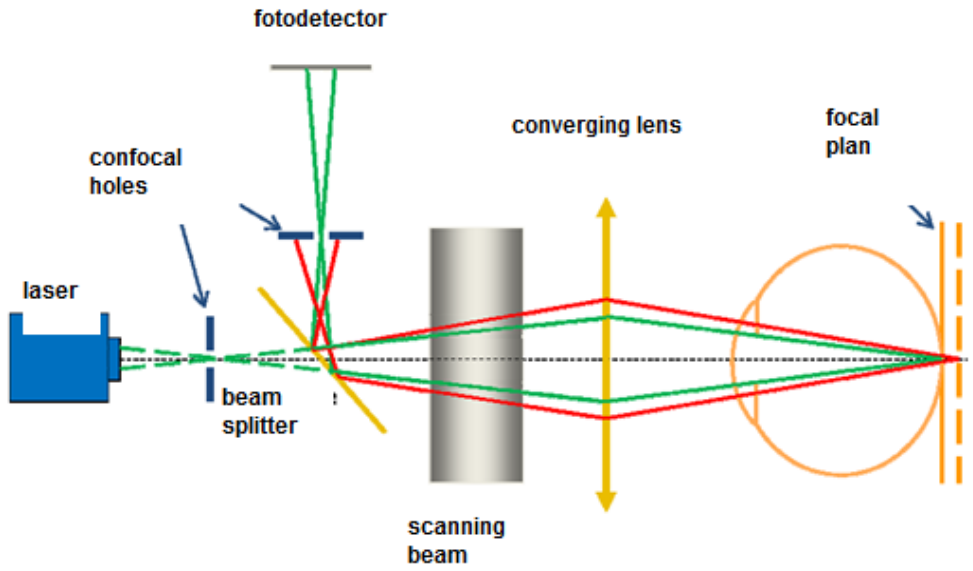


Figure 11. Schematic Confocal Scanning Laser Ophthalmoscope

4.2. Retinographies

Retinography is an exam performed by ophthalmologists and consists in the acquisition of color photographs of the retinal *fundus* and it is done with a fundus camera.

The patient's eye is illuminated with white light and photographed.
It is also possible to illuminate the eye with green light, instead of white one. It's called a red-free retinography. These images are almost completely dark images with the vessels in darker colors than the retina surface and the optic disk region is near white colored. This type of retinography provides better contrast between the vessels and the retina surface than the color colored one.

Retinographies are normally used to see the evolution of diseases like diabetic retinopathy, macular degeneration and ocular tumors because thought these images we are able to identify symptoms such as haemorrhages, hard exudates situations, vasodilatation, drusen and microaneurysms,6].

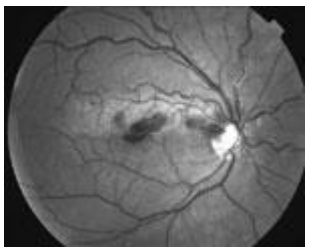


Figure 12. Red-free Retinography

4.2.1. Color fundus camera

All the fundus cameras operate in a similar way. Either the viewing bulb or the electronic flash, pass through several beam splitters, mirrors and lenses before passing through the cornea until reach the retina.

The light paths of incident and reflected light are independent, so, there are minimal reflections of the light source captured in the image.

The image forming rays directs to the telescopic eyepiece. When the picture is taken, a mirror cuts the path of the illumination system and allows the light from the flash bulb to pass into the eye. Simultaneously, another a mirror redirects the light onto the capturing medium, whether it is film or a digital CCD.

The quality of the image achieved through the fundus camera is great, allowing a clear vision of the retina. Usually, cameras have a power of magnification of 2.5X and the image angle is about 30°.

It allows several exams, such as: color and red-free photographs and angiographies,[13],[14].

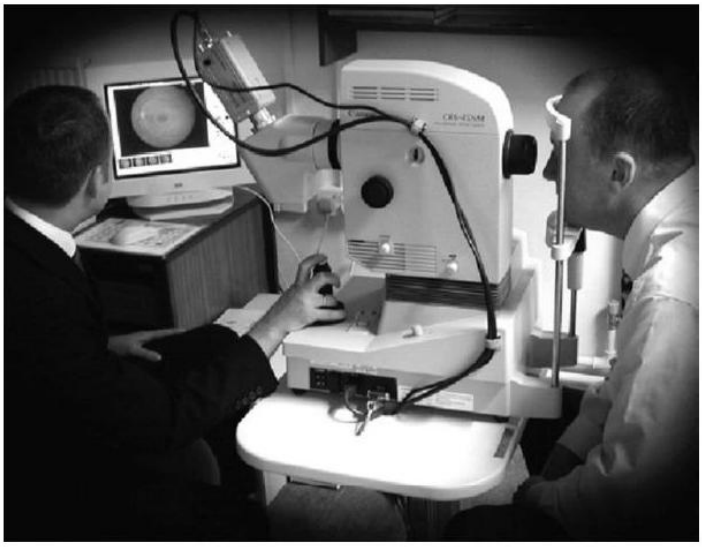


Figure 13. Screening for Diabetic Retinopahty using a digital fundus camera

5. Studies carried out AIBILI

This research institute has been developing an amazing work in the early prediction of the diabetic retinopathy.

They have done several studies that confirm the new biomarker that supports Retmarker DR: the microaneurysm turnover.

In a paper published in 2009 they present an innovative method that is able to perform reproducible and meaningful assessmentof microaneurysm turnover by mapping the specific location of each microaneurysm, registering its exact coordinates in the ocular fundus.

In the study were included 47 patients with type 2 diabetes and mild non proliferative diabetic retinopathy from 43 to 70 years old. They were followed up every 6month over a 2 year period. In each of the visits were performed color fundus photograph and fluorescein angiography (the gold standard exam for microneurysm detection).

The essential tool of this study is the MA – Tracker. It is an algorithm that enables the manually microaneurysm earmarking.

First it processes the images to extract the Region of Interest (ROI) and to enhance the images to make easier the microaneurysm detection. The step is the image co-registration. The images are overlapped in relation to the first visit.

Last, in both type of examinations the microaneurysms are marked manually. The co-registration of the images enables to mark the microaneurysms in the baseline image and to identify the visit in which it appeared.

Analyzed the results, was verified that the microaneurysm turnover was more reliable than the simple count. It was shown that the microaneurysms no not remain stable between visits. Since the number of microaneurysm didn't vary that much between the visits, the simple count could suggest that the disease was stable. The microaneurysm turnover showed that microaneurysms do not remain stable from one visit to another. The number of microaneurysms could be similar but the formation and disapearence rates were much higher, which shows that the disease is progressing more rapidly.

Another important conclusion was that although fewer microaneurysms were found in the fundus photograph in comparison to the angiographies, there was an agreement in the turnover between both exams.

Therefore, this study shows that increased formation rates of microaneurysms appeared to be more reliable then the count for the diabetic retinopathy progression and that this can be obtained from color fundus photograph[15].

In the same year, another study, using retinographies and the MA – tracker they could prove that, for patients with the same problem, the microaneurysm turnover was a reliable indication for aggravation of the disease to a CSME.

This was a 10-year follow-up study. Using the MA – tracker were analyzed data from 113 patients with mild-to-moderate non proliferative Diabetic Retinopathy during the first 2 years to observe the Microaneurysm turnover. In the last 8 years was monitored the occurrence of Clinically Significant Macular Edema (CSME).

Thanks to the MA – tracker, the microaneurysm turnover can the computed and was found that a formation rate of at least 2 microaneurysms/year indicates that these patients require closer monitoring because they have a higher risk of progression to CSME.

From the 17 patients that developed CSME, 12 of them had a microaneurysm turnover of at least 2 microaneurysms per year which is a significant result[16].

So, this study shows that microaneurysm turnover in color fundus photography is a good biomarker of diabetic retinopathy progression.

6. How does Retmarker works?

Retmarker uses color retinographies, which are a widespread tool for diagnosis of retinal diseases; it uses a proprietary co-registration algorithm which automatically overlaps the images.

Retmarker has two modules: the Differences Analysis and the Microaneurysm Analysis. We are going to focus on Retmarker DR because it has the Differences Analysis module that exists in Retmarker C and also does the microaneurysm detection.

6.1. What are the inputs?

As it was said before, Retmarker works only with retinographies. They are cheap and in comparison with angiographies they are advantageous because they are non-invasive.

These should be 45° or 50° retinographies, centered on the posterior pole (field 2). Retmarker was extensively tested with Mydriatic images. Retmarker also works with Non-Mydriatic exams but it requires some additional care when choosing the images to analyze.

Every fundus camera's software allows exportation of the exams' images in different formats. Retmarker was tested with images from KOWA, Canon, Zeiss and Topcon fundus cameras with TIF and JPEG formats; others formats may also work. The minimum size accepted is 768px x 578px.

Additionally, the retinographies should have been taken with the same fundus camera device.

6.2. What's the procedure?

Retmarker is a very simple and intuitive software.

When we initiate the software you immediately see an authentication system which is very useful if you for example have a server license.

Then we have a panel where we can select to see all the patients listed, add another, search one by name and also a select a dashboard with the analysis that were performed but not seen yet.

When we make the registration of a patient, besides all the identity and contacts data it is possible to make a full clinical history; previous surgeries, laser treatments, if he suffers from myopia, tumors, etc.

The next thing to do is create the image database. Click on “add images” and we can import them easily. OD (*oculus dexter*) to right eye retinographies, OS (*oculus sinister*) to the left.

The images must be from the same patient, same eye and same angle definition, otherwise, Retmarker can’t complete the analysis.

6.2.1. Differences Analysis

To perform a difference analysis, we need obviously at least two retinographies. Even if we have more, all the images are compared against the baseline one. We can choose which image we want for baseline. With the differences highlighted, we can see the evolution of the eye over time.

This way it makes possible to the doctor to focus on the areas where the differences are marked. It identifies details that are difficult to the human eye to observe. Retmarker only shows the differences; it doesn’t classify them as a symptom.

Figure 14. Comparison side-by-side of the images in the differences analysis

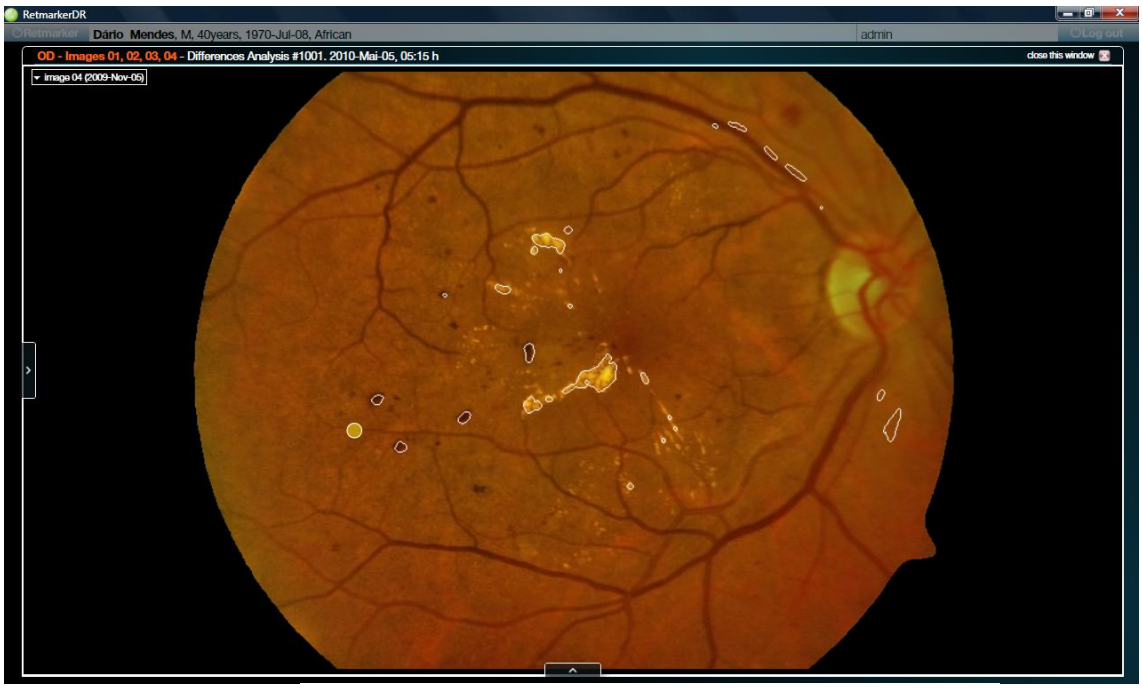


Figure 15. Retinography with the changes marked

6.2.2. Microaneurysm Analysis

In the early stages, diabetic retinopathy lesions are reversible but it is hard to detect the disease because it remains asymptomatic for a long time.

Regarding the studies develop by Aibili the Microaneurysm (MA) turnover is a new and even more reliable Biomarker for the Retinopathy progression to CSME than the simple count.

And it is the microaneurysm detection and posterior calculation of the MA turnover that makes Retmarker DR innovative. It is capable of detecting each microaneurysm as a single entity in a specific position allowing to calculate the turnover (formation and disappearance) ratios.

Considering the reliability of the MA turnover, Retmarker DR should be used in early stages – ETDRS level < 35.

Table 4. The ETDRS scale and severity of retinopathy

ETDRS retinopathy level	Severity of retinopathy
10	None
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53a-d	Severe NPDR
53e	Very severe NPDR
61	Mild PDR
65	Moderate PDR
71,75	High-risk PDR
81,85	Advanced PDR

To perform a Microaneurysm Analysis, we need at least 3 images. In this case, the comparison is made with the previous image. The prediction of diabetic retinopathy progression using MA turnover as biomarker, has a very good accuracy for a follow-up every 6 months over 1-2 years.

The software detects every microaneurysm as a single entity in a specific location. This way it can tell us if the microaneurysm has disappeared (marked with a yellow circle), if it is new (red circle) or if it is already existed (green circle).At the same time it calculates the MA formation and disappearance rates. As it is said in the study carried out by Aibili, a patient with a formation rate superior to 2 microaneurysms per year needs a closer monitoring because it is likely that the disease progresses to a CSME.

Figure 16. Evolution of the microaneurysms over time

Besides these two types of analysis, Retmarker also enables to store clinical information about the patients and has links to practice guidelines.

Figure 17. Formation and disappearance rates

As we can see, in both analyses, it is possible to perform a side-by-side comparison up to 4 images.

6.3. Which are the advantages?

Retmarker brings a lot of benefits, both clinical and in business.

- Clinical Benefits:

  1) Automatic detection of retinal changes

  2) Is a powerful tool in the early diagnosis of the diabetic retinopathy.

- Business Benefits:

  1) Improves care quality because the results that it gives are very precise

  2) Improves care delivery because the results are fast and effortless

  3) Provides a digital imaging archive

7. Validation tests and Market studies

Validation tests

To ensure that the results given were reliable Retmarker, were carried out several tests.

Images co-registration: validation performed based on the KPI (key performance indicator) analysis of the overlapping factor of vessels from the various fundus photographies

Differences Detection: comparing of the results obtained by the algorithm and a *ground-truth* designed by AIBILI experts

Microaneurysms detection: comparison of the results against a *ground-truth* of AIBILI experts

Microaneurysms Turnover Concept: based on the comparison between the results achieve by the software and the scientific studies made by AIBILI and confirming that the results were in line with the results of those studies, more specifically, the microaneurysms detection and the calculation of the Formation Rate.

Market Studies*:

Two market researches were made by the company IMS Health.

The first one, in 2007 aimed to collect information on the use of retinographic equipment and its different types (type of photo, camera characteristics, parameters for the export of image,…) in several European countries.

The second one, more recently, was a *conjoint analysis*, that based on *focus groups*, qualitative and quantitative interviews, had has purpose to define the *pricing policy* of the product, taking in account the policy/ objectives of Critical Health and in consideration the value given by the users in the various segments of potential clients. This work was developed in Portugal, United Kingdom and Germany.

8. CE Marking

After all the development of the software, there is still a lot of work to do: put it in the market. And the first step is to get the certification according to the Medical Devices Directive and consequently the CE marking.

When a company develops a product and pretends to sell it in the European Union it needs the CE marking mandatorily.

CE is a french acronym that means *Conformité Européeneé* and indicates that the product respects all the directives defined by the European Union and

his way it can be commercialized in all the European Economic Area composed by 30 countries.

Figure 19. CE Marking

Usually the medical devices use the CE marking plus 4 digits “CExxxx”. The 4 digits correspond to the Notified Body once is required a conformity assessment performed by this Notified Body.

So, to be certified, the product has to fulfill the European Union directives. The one that regulates medical devices is the 93/42/CEE.

The free movement of goods is one of the single market freedoms of the European Union. Since January 1993, were suppressed checks of the traffic of goods on the domestic market and since then, the EU emerged as a single territory, without borders.

So, there was the necessity of standardize the directives from each country to a single one.

The medical devices directive 93/42/CEE was created back there and posteriorly has been updated.

The last amendment was the directive 2007/47/EC and became mandatory on 21 March 2010.

The first thing to do in order to obtain the CE marking is to check if the product is a medical device is to confirm that it fits in the new definition.

This way, according to Directive 2007/47/EC Medical Device means: “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its

manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

,and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means".

After the conclusion that it fits within the medical device definition the next step is to classify the software.

Medical devices are divided in Class **I** (**Is** and **Im**), Class **IIa**, **IIb** and **III**. The higher the classification the greater the level of assessment required and the risk associated.

The rules to classify medical devices are explained in Annex IX of the directive 93/42/EEC. The classification of a medical device depends on some factors such as:

- how long the device is intended to be in continuous use
- if it is or not invasive or surgically invasive
- if the device is implantable or active
- if it contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device

Retmarker was considered a Class 2a Medical Device.

In order to obtain the device compliance as a class IIa there are some steps that are needed:

1. Classification: ensure the device is a Class IIa medical device.
2. Choose Conformity Assessment Route.
3. Compile the Technical File.
4. Obtain certification from a Notified Body
5. Declaration of Conformity.
6. Vigilance and Post Market Surveillance. (affix CE marking & market the products)

Class IIa Medical Devices: Conformity Assessment Routes

Class IIa devices manufacturer's besides the declaration of conformity with the provisions of the Directive and Regulations that ensures that his products comply with relevant Essential Requirements, they need to back up this declaration with conformity assessment by Notified Body. The manufacturer can choose which assessment he wants:

1. follow the procedure related to the EC declaration of conformity set out in Annex II (full quality assurance)

or

2. follow the procedure related to the EC declaration of conformity set out in Annex VII, coupled with either:

- the procedure related to the EC verification established in Annex IV;

  or

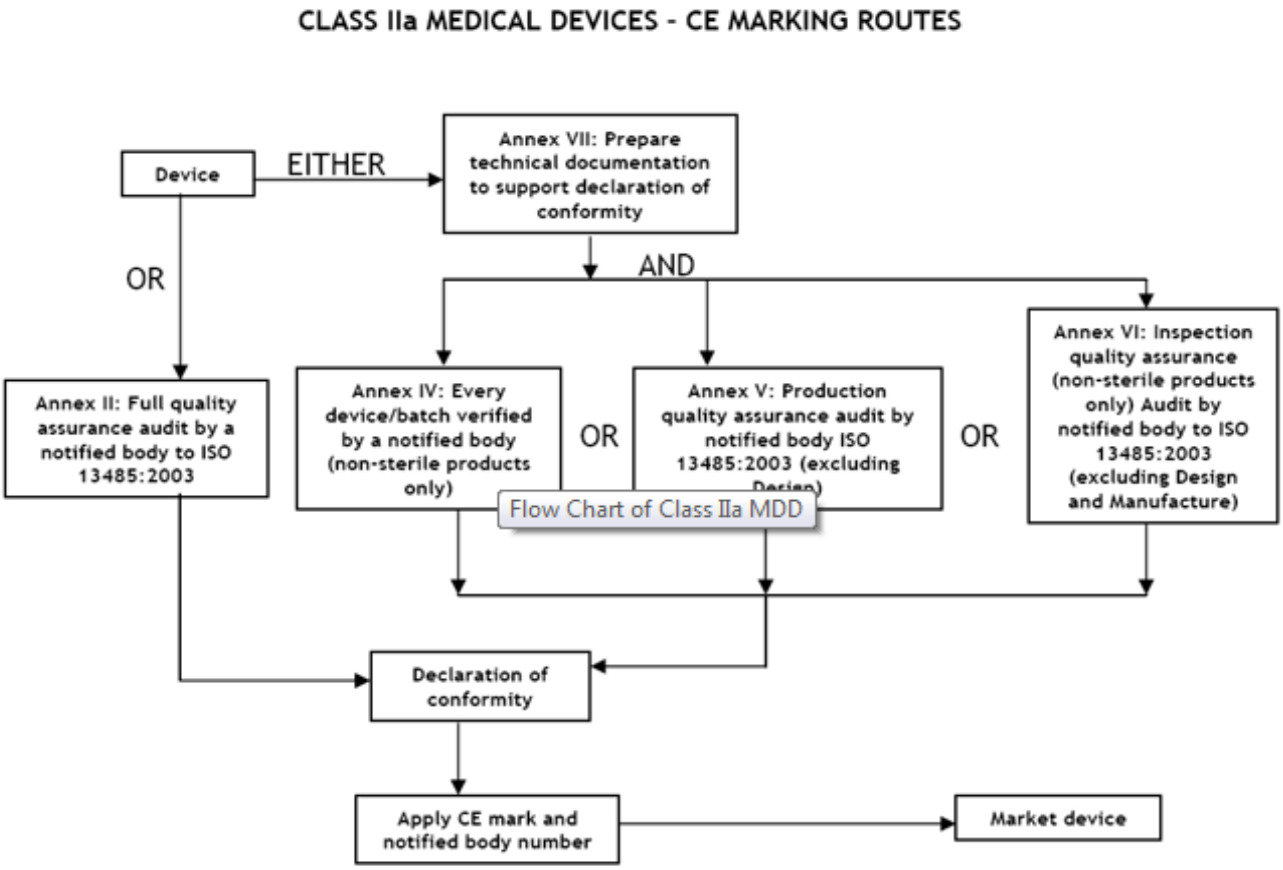
- the procedure related to the EC declaration of conformity established in Annex V;

  or

- the procedure related to the EC declaration of conformity established in Annex VI.

The manufacturer can CE mark his product and sell it after the Notified Body gives him the certification.

The notified Body that made all the certification was Tüv Rheinland. It was made according the annex II (procedure 1). After the audition to the system, all was according to the standards required (ISO 13485) and ,finally, Retmarker received the CE marking “CE0197”,[17],[18-19].



9. Versions available and Strategies to sell it

Retmarker is available in the following options:

Table 5. Retmarker versions

Retmarker C	Individual	250 analysis package
		Desktop License (unl. use)
	Corporate	Server License (unl. use)
Retmarker DR	Individual	250 analysis package
		Desktop License (unl. use)
	Corporate	Server License (unl. use)

There were 868 Ophthalmologists in Portugal in 2009 and among those few are retina specialists, [20].

The Retmarker is a tool that will support mainly the non retina specialists. Those are our main market and particularly the ones that have a color fundus camera in their practice.

This way, whenever they are confronted with a retinopathy, they can send the patient to a specialist in retina with some information.

The commercial activities will be focused on those doctors and will be supported by demonstrations, offer of Retmarker free trial periods and on-line demonstrations on the site WWW.RETMARKER.COM.

Another market are the retina specialists ophthalmologists.

After taking contact with the product and its advantages, as Key Opinion Leaders, KOL, they will help us to consolidate the sales growth.

The commercial department has already initiated the product presentation to our clients.

10. Awards**

Retmarker has already won some prizes which is leaving us even more hopeful in a good reception from the market.

Coimbra, 4th of March, 2010 – Critical Health S.A. is proud to announce that it has won an **award in the European IT Excellence Awards**, an event which gathered in London the leading organizations in this area. Critical Health won in the category for Information Management, with one of its Retmarker product (www.retmarker.com). The European Excellence Awards are organized by IT Europa, aimed at recognizing the crucial part that ISVs (Independent Software Vendors) and Solution Providers play in the resolution of their clients' real problems. Entities from 26 countries competed for this prize.

Coimbra, Portugal, 2nd of June, 2010 - Critical Health was distinguished yesterday with an **Honourable Mention in the COTEC-UNICER Award for Innovation Products**, an award attributed by the Entrepreneurial Association for Innovation (Associação Empresarial para a Inovação - COTEC) and UNICER, and supported by the Expresso Newspaper. This award aims to recognize the Retmarker product, a Medical Device for decision support in the ophthalmology domain from Critical Health, a holding of Critical SGPS devoted to the development of groundbreaking technological solutions to prevent loss of mobility and vision. This award was presented by Carlos Moreira da Silva, Chairman at COTEC, and António Pires de Lima, UNICER's President of the Executive Board, during the 7th COTEC National Innovation Encounter, which

this year was dedicated to the theme “The Innovator’s DNA”, and was held in Estoril’s Congress Centre and had the presence of His Excellency the President of the Portuguese Republic, Professor Aníbal Cavaco Silva.

11. Conclusion

As it became expressed in all the work, Retmarker is a software that can bring major improvements in the diagnosis of retinal diseases. It is a recentproduct based in a recent study (a new biomarker for Diabetic Retinopathy) and only now has begun its commercialization. The cooperation between Critical Health and Oftaltec can be an important asset to be well succeed in the market.

The project was designed thinking that Retmarker would be able to analyze images of the Oftaltec equipment Spectralis. For now, such analysis is not possible (not to say that will not be in the future). Beyond this setback, there were still delays in the commercialization due to the time it took to obtain the CE marking (6months). The project then underwent some alterations and the last plan was completed.

Concluding, and taking in account all the difficulties encountered during this year, the final result surpasses the student’s expectations.

11.1 Future Work

Regarding the future work Critical Health has under development the Retmarker AMD Research,a new software solution which enables computer-assisted marking of digital images from patients with Age-related Macular Edema (AMD), the main cause of blindness in people over 50 years old in developed countries.

Another challenging task would be the integration with the camera fundus software, so that the export of the images from the software of the device to Retmarker is automatic.

This year they thought I could do it but unfortunately, I do not have the skills required for such a huge task.

11.2. Final Appreciation

Despite the fact that this wasn't my first project choice, I am very satisfied with the way it ran.

Although the thesis had been about Retmarker I was able to do other tasks. For example, accompany the technical team of Oftaltec in the maintenance of laser equipment.

The work for the thesis, unlike what was expected, was essentially bibliographic research and that helped me to develop autonomy skills.

Another great opportunity was the possibility to understand the business environment in two companies so distinct. This will help me for the next stage of my life, which passes through the entry in the work market.

*confidential studies, not revealed by Critical Health

**from Critical Health Website

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Annexes

Annex A – Full quality assurance System

COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

ANNEX II

EC DECLARATION OF CONFORMITY (Full quality assurance system)

1. The manufacturer must ensure application of the quality system approved for the design, manufacture and final inspection of the products concerned, as specified in Section 3 and is subject to audit as laid down in Sections 3.3 and 4 and to Community surveillance as specified in Section 5.

2. The declaration of conformity is the procedure whereby the manufacturer who fulfils the obligations imposed by Section 1 ensures and declares that the products concerned meet the provisions of this Directive which apply to them.

The manufacturer must affix the CE marking in accordance with Article 17 and draw up a written declaration of conformity. This declaration must cover a given number of the products manufactured and be kept by the manufacturer.

3. Quality system

3.1. The manufacturer must lodge an application for assessment of his quality system with a notified body.

The application must include:

- the name and address of the manufacturer and any additional manufacturing site covered by the quality system,

- all the relevant information on the product or product category covered by the procedure,

- a written declaration that no application has been lodged with any other notified body for the same product-related quality system,

- the documentation on the quality system,

- an undertaking by the manufacturer to fulfil the obligations imposed by the quality system approved,

- an undertaking by the manufacturer to keep the approved quality system adequate and efficacious,

- an undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device leading for the reasons referred to in subparagraph (i) to systematic recall of devices of the same type by the manufacturer.

3.2. Application of the quality system must ensure that the products conform to the provisions of this Directive which apply to them at every stage, from design to final inspection. All the elements, requirements and provisions adopted by the manufacturer for his quality system must be documented in a systematic and orderly manner in the form of written policies and procedures such as quality programmes, quality plans, quality manuals and quality records.

It shall include in particular an adequate description of:

(a) the manufacturer's quality objectives;

(b) the organization of the business and in particular:

- the organizational structures, the responsibilities of the managerial staff and their organizational authority where quality of design and manufacture of the products is concerned,

- the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality of design and of product, including control of products which fail to conform;

(c) the procedures for monitoring and verifying the design of the products and in particular:

- a general description of the product, including any variants planned,

- the design specifications, including the standards which will be applied and the results of the risk analysis, and also a description of the solutions adopted to fulfil the essential requirements which apply to the products if the standards referred to in Article 5 are not applied in full,

- the techniques used to control and verify the design and the processes and systematic measures which will be used when the products are being designed,

- if the device is to be connected to other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when connected to any such device(s) having the characteristics specified by the manufacturer,

- a statement indicating whether or not the device incorporates, as an integral part, a substance as referred to in Section 7.4 of Annex I and data on the tests conducted in this connection,

- the clinical data referred to in Annex X,

- the draft label and, where appropriate, instructions for use;

(d) the inspection and quality assurance techniques at the manufacturing stage and in particular:

- the processes and procedures which will be used, particularly as regards sterilization, purchasing and the relevant documents,

- the product identification procedures drawn up and kept up to date from drawings, specifications or other relevant documents at every stage of manufacture;

(e) the appropriate tests and trials which will be carried out before, during and after manufacture, the frequency with which they will take place, and the test equipment used; it must be possible to trace back the calibration of the test equipment adequately.

3.3. The notified body must audit the quality system to determine whether it meets the requirements referred to in Section 3.2. It must presume that quality systems which implement the relevant harmonized standards conform to these requirements.

The assessment team must include at least one number with past experience of assessments of the technology concerned. The assessment procedure must include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.

The decision is notified to the manufacturer. It must contain the conclusions of the inspection and a reasoned assessment.

3.4. The manufacturer must inform the notified body which approved the quality system of any plan for substantial changes to the quality system or the product-range covered. The notified body must assess the changes proposed and verify whether after these changes the quality

system still meets the requirements referred to in Section 3.2. It must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment.

4. Examination of the design of the product

4.1. In addition to the obligations imposed by Section 3, the manufacturer must lodge with the notified body an application for examination of the design dossier relating to the product which he plans to manufacture and which falls into the category referred to in Section 3.1.

4.2. The application must describe the design, manufacture and performances of the product in question. It must include the documents needed to assess whether the product conforms to the requirements of this Directive, as referred to in Section 3.2 (c).

4.3. The notified body must examine the application and, if the product conforms to the relevant provisions of this Directive, issue the application with an EC design-examination certificate. The notified body may require the application to be completed by further tests or proof to allow assessment of conformity with the requirements of the Directive. The certificate must contain the conclusions of the examination, the conditions of validity, the data needed for identification of the approved design, where appropriate, a description of the intended purpose of the product.

In the case of devices referred to in Annex I, paragraph 7.4, the notified body shall, in view of the aspects addressed in that paragraph, consult one of the competent bodies established by the Member States in accordance with Directive 65/65/EEC before taking a decision.

The notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the competent body concerned.

4.4. Changes to the approved design must receive further approval from the notified body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements of the Directive or with the conditions prescribed for use of the product. The applicant shall inform the notified body which issued the EC design-examination certificate of any such changes made to the approved design. This additional approval must take the form of a supplement to the EC design-examination certificate.

5. Surveillance

5.1. The aim of surveillance is to ensure that the manufacturer duly fulfils the obligations imposed by the approved quality system.

5.2. The manufacturer must authorize the notified body to carry out all the necessary inspections and supply it with all relevant information, in particular:

- the documentation on the quality system,

- the data stipulated in the part of the quality system relating to design, such as the results of analyses, calculation tests, etc.,

- the data stipulated in the part of the quality system relating to manufacture, such as inspection reports and test data, calibration data, qualification reports of the personnel concerned, etc.

5.3. The notified body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system and must supply the manufacturer with an assessment report.

5.4. In addition, the notified body may pay unannounced visits to the manufacturer. At the time of such visits, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly. It must provide the manufacturer with an inspection report and, if a test has been carried out, with a test report.

6. Administrative provisions

6.1. The manufacturer must, for a period ending at least five years after the last product has been manufactured, keep at the disposal of the national authorities:

- the declaration of conformity,

- the documentation referred to in the fourth indent of Section 3.1,

- the changes referred to in Section 3.4,

- the documentation referred to in Section 4.2, and

- the decisions and reports from the notified body as referred to in Sections 3.3, 4.3, 4.4, 5.3 and 5.4.

6.2. The notified body must make available to the other notified bodies and the competent authority, on request, all relevant information concerning quality system approvals issued, refused or withdrawn.

6.3. In respect of devices subject to the procedure in Section 4, when neither the manufacturer nor his authorized representative is established in the Community, the obligation to keep available the technical documentation shall fall to the person responsible for placing the device on the Community market or the importer referred to in Annex I, Section 13.3 (a).

7. Application to devices in Classes IIa and IIb

In line with Article 11 (2) and (3), this Annex may apply to products in Classes IIa and IIb. Section 4, however, does not apply.

Annex B – Rules to classify medical devices

COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

ANNEX IX

CLASSIFICATION CRITERIA I. DEFINITIONS 1. Definitions for the classification rules

1.1. Duration

Transient

Normally intended for continuous use for less than 60 minutes.

Short term

Normally intended for continuous use for not more than 30 days.

Long term

Normally intended for continuous use for more than 30 days.

1.2. Invasive devices

Invasive device

A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.

Body orifice

Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma.

Surgically invasive device

An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.

For the purposes of this Directive devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, shall be treated as surgically invasive devices.

Implantable device

Any device which is intended:

- to be totally introduced into the human body or,

- to replace an epithelial surface or the surface of the eye,

by surgical intervention which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.

1.3. Reusable surgical instrument

Instrument intended for surgical use by cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or similar procedures, without connection to any active medical device and which can be reused after appropriate procedures have been carried out.

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.

1.5. Active therapeutical device

Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap.

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.

1.7. Central circulatory system

For the purposes of this Directive, 'central circulatory system' means the following vessels:

arteriae pulmonales, aorta ascendens, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachicephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior.

1.8. Central nervous system

For the purposes of this Directive, 'central nervous system' means brain, meninges and spinal cord.

II. IMPLEMENTING RULES 2. Implementing rules

2.1. Application of the classification rules shall be governed by the intended purpose of the devices.

2.2. If the device is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices. Accessories are classified in their own right separately from the device with which they are used.

2.3. Software, which drives a device or influences the use of a device, falls automatically in the same class.

2.4. If the device is not intended to be used solely or principally in a specific part of the body, it must be considered and classified on the basis of the most critical specified use.

2.5. If several rules apply to the same device, based on the performance specified for the device by the manufacturer, the strictest rules resulting in the higher classification shall apply.

III. CLASSIFICATION 1. Non-invasive devices

1.1. Rule 1

All non-invasive devices are in Class I, unless one of the rules set out hereinafter applies.

1.2. Rule 2

All non-invasive devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are in Class IIa:

- if they may be connected to an active medical device in Class IIa or a higher class,

- if they are intended for use for storing or channelling blood or other body liquids or for storing organs, parts of organs or body tissues,

in all other cases they are in Class I.

1.3. Rule 3

All non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body are in Class IIb, unless the treatment consists of filtration, centrifugation or exchanges of gas, heat, in which case they are in Class IIa.

1.4. Rule 4

All non-invasive devices which come into contact with injured skin:

- are in Class I if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates,

- are in Class IIb if they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent,

- are in Class IIa in all other cases, including devices principally intended to manage the micro-environment of a wound.

2. Invasive devices

2.1. Rule 5

All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device:

- are in Class I if they are intended for transient use,

- are in Class IIa if they are intended for short-term use, except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity, in which case they are in Class I,

- are in Class IIb if they are intended for long-term use, except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity and are not liable to be absorbed by the mucous membrane, in which case they are in Class IIa.

All invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to an active medical device in Class IIa or a higher class, are in Class IIa.

2.2. Rule 6

All surgically invasive devices intended for transient use are in Class IIa unless they are:

- intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III,

- reusable surgical instruments, in which case they are in Class I,

- intended to supply energy in the form of ionizing radiation in which case they are in Class IIb,

- intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class IIb,

- intended to administer medicines by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which they are in Class IIb.

2.3. Rule 7

All surgically invasive devices intended for short-term use are in Class IIa unless they are intended:

- either specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III,

- or specifically for use in direct contact with the central nervous system, in which case they are in Class III,

- or to supply energy in the form of ionizing radiation in which case they are in Class IIb,

- or to have a biological effect or to be wholly or mainly absorbed in which case they are in Class III,

- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class IIb.

2.4. Rule 8

All implantable devices and long-term surgically invasive devices are in Class IIb unless they are intended:

- to be placed in the teeth, in which case they are in Class IIa,

- to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class III,

- to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class III,

- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class III.

3. Additional rules applicable to active devices

3.1. Rule 9

All active therapeutic devices intended to administer or exchange energy are in Class IIa unless their characteristics are such that they may administer or exchange energy to or from the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are in Class IIb.

All active devices intended to control or monitor the performance of active therapeutic devices in Class IIb, or intended directly to influence the performance of such devices are in Class IIb.

3.2. Rule 10

Active devices intended for diagnosis are in Class IIa:

- if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum,

- if they are intended to image in vivo distribution of radiopharmaceuticals,

- 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.

Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.

Rule 11

All active devices intended to administer and/or remove medicines, body liquids or other substances to or from the body are in Class IIa, unless this is done in a manner:

- that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are in Class IIb.

3.3. Rule 12

All other active devices are in Class I.

4. Special Rules

4.1. Rule 13

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.

4.2. Rule 14

All devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in Class IIb, unless they are implantable or long term invasive devices, in which case they are in Class III.

4.3. Rule 15

All devices intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate, hydrating contact lenses are in Class IIb.

All devices intended specifically to be used for disinfecting medical devices are in Class IIa.

This rule does not apply to products that are intended to clean medical devices other than contact lenses by means of physical action.

4.4. Rule 16

Non-active devices specifically intended for recording of X-ray diagnostic images are in Class IIa.

4.5. Rule 17

All devices manufactured utilizing animal tissues or derivatives rendered non-viable are Class III except where such devices are intended to come into contact with intact skin only.

5. Rule 18

By derogation from other rules, blood bags are in Class IIb.

Annex C – Amendments to the Annex II and IX of 93/42/EEC Directive

DIRECTIVE 2007/47/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 September 2007amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market

2. Annex II shall be amended as follows:
(a) Section 2 shall be replaced by the following:
'2. The EC declaration of conformity is the procedure whereby the manufacturer who fulfils the obligations imposed by Section 1 ensures and declares that the products concerned meet the provisions of this Directive which apply to them.
The manufacturer must affix the CE marking in accordance with Article 17 and draw up a written declaration of conformity. This declaration must cover one or more medical devices manufactured, clearly identified by means of product name, product code or other unambiguous reference and must be kept by the manufacturer.';
(b) in Section 3.1, second paragraph, the introductory part of the seventh indent shall be replaced by the following:
'— an undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective action. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them:';
(c) Section 3.2 shall be amended as follows:
(i) the following paragraph shall be inserted after the first paragraph:
'It shall include in particular the corresponding documentation, data and records arising from the procedures referred to in point (c).';
(ii) in point (b), the following indent shall be added:
'— where the design, manufacture and/or final inspection and testing of the products, or elements thereof, is carried out by a third party, the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party;'
(iii) point (c) shall be replaced by the following:
'(c) the procedures for monitoring and verifying the design of the products, including the corresponding documentation, and in particular:
— a general description of the product, including any variants planned, and its intended use(s),
— the design specifications, including the standards which will be applied and the results of the risk analysis, and also a description of the solutions adopted to fulfil the essential requirements which apply to the products if the standards referred to in Article 5 are not applied in full,
— the techniques used to control and verify the design and the processes and systematic measures which will be used when the products are being designed,
— if the device is to be connected to other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when connected to any such device (s) having the characteristics specified by the manufacturer,
— a statement indicating whether or not the device incorporates, as an integral part, a substance or a human blood derivative referred to in section 7.4 of Annex I and the data on the tests conducted in this connection required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,
— a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Commission Directive 2003/32/EC (*),
— the solutions adopted as referred to in Annex I, Chapter I, Section 2,
— the pre-clinical evaluation,
— the clinical evaluation referred to in Annex X,

— the draft label and, where appropriate, instructions for use.
(*) Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin (OJ L 105, 26.4.2003, p. 18).'
(d) the second paragraph of Section 3.3 shall be replaced by the following:
'The assessment team must include at least one member with past experience of assessments of the technology concerned. The assessment procedure must include an assessment, on a representative basis, of the documentation of the design of the product(s) concerned, an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.';
(e) in Section 4.3, the second and third paragraphs shall be replaced by the following:
'In the case of devices referred to in Annex I, Section 7.4, second paragraph, the notified body shall, as regards the aspects referred to in that section, consult one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or the EMEA before taking a decision. The opinion of the competent national authority or the EMEA must be drawn up within 210 days after receipt of valid documentation. The scientific opinion of the competent national authority or the EMEA must be included in the documentation concerning the device. The notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the competent body concerned.
In the case of devices referred to in Annex I, Section 7.4, third paragraph, the scientific opinion of the EMEA must be included in the documentation concerning the device. The opinion of the EMEA must be drawn up within 210 days after receipt of valid documentation. The notified body will give due consideration to the opinion of the EMEA when making its decision. The notified body may not deliver the certificate if the EMEA's scientific opinion is unfavourable. It will convey its final decision to the EMEA.
In the case of devices manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC, the notified body must follow the procedures referred to in that Directive.';
(f) in Section 5.2, the second indent shall be replaced by the following:
'— the data stipulated in the part of the quality system relating to design, such as the results of analyses,
calculations, tests, the solutions adopted as referred to in Annex I, Chapter I, Section 2, pre-clinical and clinical evaluation, post-market clinical follow-up plan and the results of the post-market clinical followup, if applicable, etc.,';
(g) Section 6.1 shall be amended as follows:
(i) the introductory part shall be replaced by the following:
'The manufacturer or his authorised representative must, for a period ending at least five years, and in the case of implantable devices at least 15 years, after the last product has been manufactured, keep at the disposal of the national authorities:';
(ii) the following phrase shall be added to the second indent:
'and in particular the documentation, data and records referred to in the second paragraph of Section 3.2,';
(h) Section 6.3 shall be deleted;
(i) Section 7 shall be replaced by the following:
'7. Application to devices in Classes IIa and IIb.
7.1. In line with Article 11(2) and (3), this Annex may apply to products in Classes IIa and IIb. Section 4, however, does not apply.
7.2. For devices in Class IIa the notified body shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3.2(c) for at least one representative sample for each device subcategory for compliance with the provisions of this Directive.
7.3. For devices in Class IIb the notified body shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3.2(c) for at least one representative sample for each generic device group for compliance with the provisions of this Directive.
7.4. In choosing representative sample(s) the notified body shall take into account the novelty of the technology, similarities in design, technology, manufacturing and sterilisation methods, the intended use and the results of any previous relevant assessments (e.g. with regard to physical, chemical or biological properties) that have been carried out in accordance with this Directive. The notified body shall document and keep available to the competent authority its rationale for the sample(s) taken.

7.5. Further samples shall be assessed by the notified body as part of the surveillance assessment referred to in Section 5.';
(j) in Section 8, the words 'Article 4(3) of Directive 89/381/EEC' shall be replaced by the words 'Article 114(2) of Directive 2001/83/EC';

Annex IX shall be amended as follows:
(a) Chapter I shall be amended as follows:
(i) in Section 1.4, the following sentence shall be added:
'Stand alone software is considered to be an active medical device.';
(ii) Section 1.7 shall be replaced by the following:
'1.7. **Central circulatory system**
For the purposes of this Directive, "central circulatory system" means the following vessels: arteriae pulmonales, aorta ascendens, arcus aorta, aorta descendens to the bifurcatio aortae, arteriae
coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena
cava inferior.';

(b) in Chapter II, Section 2, the following section shall be added:
'2.6. In calculating the duration referred to in Section 1.1 of Chapter I, continuous use means "an uninterrupted
actual use of the device for the intended purpose". However where usage of a device is discontinued in
order for the device to be replaced immediately by the same or an identical device this shall be considered
an extension of the continuous use of the device.';
(c) Chapter III shall be amended as follows:
(i) the introductory phrase of the first paragraph of Section 2.1 shall be replaced by the following:
'All invasive devices with respect to body orifices, other than surgically invasive devices and which are not
intended for connection to an active medical device or which are intended for connection to an active
medical device in Class I:';
(ii) Section 2.2 shall be replaced by the following:
'2.2. **Rule 6**
All surgically invasive devices intended for transient use are in Class IIa unless they are:
— intended specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III,

— reusable surgical instruments, in which case they are in Class I,
— intended specifically for use in direct contact with the central nervous system, in which case they are in Class III,
— intended to supply energy in the form of ionising radiation in which case they are in Class IIb,
— intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class IIb,
— intended to administer medicines by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which case they are in Class IIb.';
(iii) in Section 2.3, the first indent shall be replaced by the following:
'— either specifically to control, diagnose, monitor or correct a defect of the heart or of the central
circulatory system through direct contact with these parts of the body, in which case they are in Class III,';
(iv) in Section 4.1, first paragraph, the reference '65/65/EEC' shall be replaced by the reference '2001/83/EC';
(v) in Section 4.1, the second paragraph shall be replaced by the following:
'All devices incorporating, as an integral part, a human blood derivative are in Class III.';
(vi) in Section 4.3, second paragraph, the following phrase shall be added:
'unless they are specifically to be used for disinfecting invasive devices in which case they are in Class IIb.';
(vii) in Section 4.4, the words 'Non-active devices' shall be replaced by the word 'Devices';