Secção Autónoma de
Ciências da Saúde

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Dispositivos médicos – Estágio Curricular no INFARMED, I.P.

Medical Devices – Curricular trainship at INFARMED, I.P.

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Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica da Dra. Maria Judite Neves, Diretora da Direção de Produtos de Saúde do INFARMED, IP., e do Professor Bruno Miguel Alves Fernandes do Gago, Professor auxiliar convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro

Dedico este trabalho aos meus pais por todos os anos em que lutaram por mim e pelos meus objetivos, e por toda a educação e espírito lutador que me deram.

Este trabalho é também dedicado à minha irmã por me fazer sempre acreditar em mim e nas minhas capacidades.

o júri

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palavras-chave

Dispositivos médicos, conformidade, segurança, desempenho, marcação CE, registos, distribuidores, fabricantes, mandatários.

resumo

Este relatório pretende relatar as actividades por mim desenvolvidas durante o meu estágio no INFARMED, I.P., mais concretamente na Direção de Produtos de Saúde.

Estando os dispositivos médicos dentro de um complexo sistema de regulamentação, este relatório começa por uma introdução aos assuntos regulamentares associados aos dispositivos médicos, e posteriormente a um relato das actividades desenvolvidas, principalmente ao nível da validação de registos de Distribuidores.

Tratando-se de produtos com finalidade médica e portanto usados no contexto da saúde, a sua segurança e o desempenho dos dispositivos são conceitos fundamentais aquando da avaliação destas tecnologias. O surgimento de novas tecnologias a um ritmo exponencial faz deste sector uma área em constante expansão e dinamismo. Assim sendo este é um sector com bastantes desafios para o próprio profissional, mas que também acompanha o bem-estar dos utilizadores durante toda a sua vida.

keywords

Medical device, conformity, CE mark, safety, performance, registries, distributor, manufacturer, authorised representative.

summary

The present report is intended to describe the activities done during my internship in INFARMED, I.P., more specific in the Health Products Directorate.

Since the medical devices are part of a complex regulatory system, this report starts by a brief introduction to medical devices' regulatory affairs, and then a description of the activities done, mainly in the validation of the Distributors' registries.

Being these products with a medical intended, and thus used in the health sector, the safety and performance of the products are the main concepts in the evaluation of these technologies. The accelerated time until the raise of new technologies makes this sector an area in constant expansion and dynamism.

Therefore this sector present many challenges for the professional, but at the same time goes along with the well-being of the users during all theirs life's.

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Abbreviations

AIMD	Active Impantable Medical Device
CA	Competent Authority
CDM	Code of the Medical Device – "Código do Dispositivo Médico"
CEIC	Ethic Comission on Clinical Investigation – "*Comissão de Ética para a Investigação Clínica"*
CNPD	National Commission on Data Protection – "*Comissão Nacional de Protecção de Dados*"
DPS	Health Products Directorate
EC	European Comission
EUDAMED	European Database on Medical Devices
FSCA	Field Safety Corrective Action
GMDN	Global Medical Device Nomenclature
INFARMED, I.P.	National Authority of Medicines and Health Products, I.P.
ISO	International Organization for Standardization
IVD	In Vitro Diagnostic Medical Device
MD	Medical Device
NB	Notified Body
NCAR	National Competent Authority Report
NPDM	Portuguese Nomenclature for Medical Devices – "Nomenclatura Portuguesa do Dispositivo Médico"
PMS	Post Market Surveillance
QMS	Quality Management System
SDIV	National Database for Distributors Registration of Medical Devices
SNS	National Health Service – "*Seviço Nacional de Saúde"*

1 Introduction

This report is intended to report the work done at INFARMED during my 9 months internship. However more than a work experience, this internship represents a unique opportunity to understand the medical device (MD) universe, from the side of the national authorities, which in medical device has a different role when compared to the drugs market. This training will complement the issues addressed during the university course, allowing me to obtain the final grade necessary for the conclusion of the master degree on Pharmaceutical Medicine.

During my course, the regulatory issues related to MD weren't one of the topics over explored, so my initial knowledge about it is a little limited. The main objective for this internship is to understand the complexity of place MD on the market, which are in compliance with the national and European rules. Since it is a huge goal, the better way to accomplish it is by settle more specific goals, like:

- Know the applicable European legislation to the MD sector, and the particularities of the national law;
- Understand the role of the national authorities on the MD market;
- Understand the meaning of market conformity and the CE mark;
- Identify the different steps for market conformity;
- Understand the MD's classification and how it affects the conformity evaluation.

Nevertheless there are as well other outcomes, more related to soft skills that can be only acquired with work experience, and are dependable of the type of work I'm going to do.

As so, my internship will consist mainly at the use of different functionalities of the database SDIV. This will include the validation and verification of the information available in the MD registries made by the distributors. Additionally it will comprise the verification of the documentations which demonstrate the conformity of the MD with the applicable legislation. These activities will be performed in order to accomplish the objectives stated above, and also to develop the necessary knowledge related to MD's regulatory affairs.

1.1 INFARMED, I.P.

INFARMED, I.P. – National Authority of Medicines and Health Products, I.P., is the Portuguese's national authority responsible for regulate and supervise medicinal products, medical device, cosmetic and products for body care, according to the applicable national and international laws. [4]

During 1993, the European Commission (EC) had elaborated a proposal to create a European Agency of Medicines. This proposal had foreseen an active role from the different national authorities and the experts of the European Community on medicine related issues. Consequently it was seen as necessary to have a national institute with the technical capabilities on the field, been at the same time strong and independent. In this way, by the application of the Decree-law nº 353/93, INFARMED, I.P. was created, with the necessary administrative and economic autonomy. [5]

Nowadays INFARMED, I.P structure can be decomposed on three, the management bodies, business functions and the supporting functions, each one contributing to the global mission of the institute. In total there are five management bodies, three units of supporting functions and seven units with business function (see Figure 1). [6]

1.1.1 Health Products Directorate

It was on the Health Products Directorate – *Direção de Produtos de Saúde* (DPS), business unit, that my internship had occurred. This Department is responsible for regulate, monitoring and by the surveillance of the conformity of the health products' market. Additionally it also plays a role in the establishment of the requirements for the clinical investigation with Health Products and evaluates the applications for clinical investigation. Another activity is related to the designation of new Notified Body (NB), and on monitoring the national ones, considering its role on market conformity. By doing this DPS is ensuring that the health products, which circulate on the national market, are in conformity with the requirements of the applicable legislation, and are safe for human use and in accordance to the performance stated by the manufacturer. [7, 8]

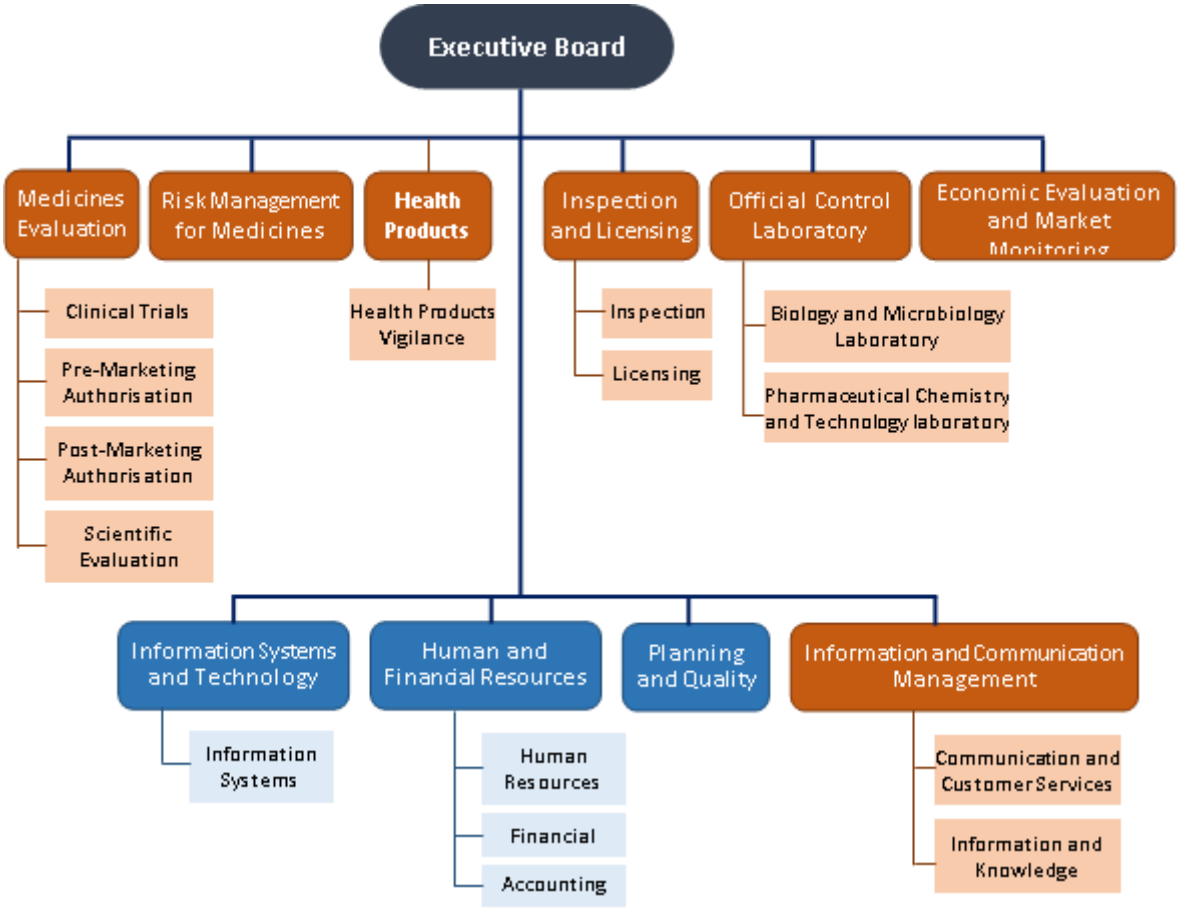

Figure 1 – INFARMED, I.P. organizational chart [(1)]; orange represent the business units, and white blue represent the support units

Although formally there is only one subunit at DPS, the reality is that DPS is subdivided in three functional areas. Being Health Products Vigilance Unit (UVPS) the official subunit of DPS, it is responsible for ensure the activities related to manufacturer's incidents reports, from the mechanism of collection of the information to the risk-benefit analysis and implementation of the safety measures related to the normal use of MD. It's also UVPS that coordinates the activities of the maintenance and disclosure of the national vigilance system on MD, and manage the information created by the European Union on the MD vigilance. The two unofficial subdivisions are for the issues related to the market surveillance, one for the MD and the other for cosmetics. [(9, 10)]

The DPS duties allow this unit to be an active participant in the public health protection.

1.1.2 Quality Management System of INFARMED, I.P. – ISO 9001

During my internship my colleagues clearly stated the importance of having an implemented Quality Management System (QMS). Their importance can be seen in an equal service for all the clients, but it also works as a safeguard for the institution. The QMS guarantee to the institution that it provides a quality service to clients, at the same time that it allows the identification of issues/problems, or potential improvements, and the consequent upgrade of the system. This is a reality in INFARMED, I.P. since they had implemented the ISO 9001. In my opinion the QMS just work as well as I had seen, due to the commitment of all the employees to make it work, as a plus they also transmit this feeling to the recently arrived workers.

1.1.2.1 Quality Manual

The quality manual of INFARMED, I.P. is available for all partner and clients at the institution website. Contrary to other companies, and as foreseen in the QMS, there are no controlled copies of the manual. It is available for all the collaborators in an informatics platform, as also all the procedures and other quality's documents. [(11)]

There we can have an overview of the QMS of INFARMED, I.P. regarding the application of ISO 9001, its documental structure and the informatics control of data. We are also introduced to the available processes which are covered by the QMS. [(11)]

1.1.2.2 Quality Policy

INFARMED, I.P.'s quality policy is based in four essentials supports that together allow the accomplishment of their mission. (see Figure 2). This supports include: [(12)]

- Guarantee the accomplishment of the applicable legal requirements:
    - An INFARMED, I.P. duty: regulate and supervise it, both for economic entities, products and health's professionals;
    - Qualified employees to play their roles according to the laws.
- Fulfil clients and partners expectations and needs:
    - Identification of clients and partners requirements;
    - Evaluate quality of services, including timings and avoiding conflict of interests.

- Workers' training/qualifications: higher importance taking in account the INFARMED, I.P.'s mission;
- Upgrade the process and efficacy of the QMS.

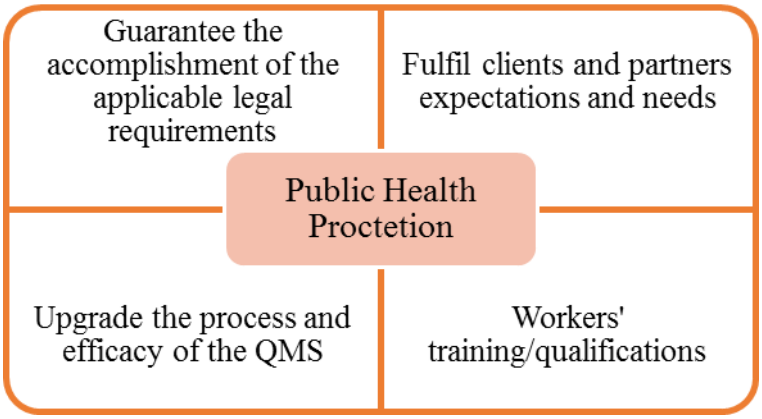

Figure 2 – Quality policy of INFARMED,I.P. [12]

1.2 State-of-the art

Although the concepts are similar, both here and in the United States of America, the process itself to been able to put on the market a MD is quite different. There is some arguing around whose system is the better one, however in my own opinion they are just different. One is not better than the other. This section will be dedicated to explain the European system, since it was the background for my internship.

1.2.1 European System

The European framework for MD evaluation is actually based in the so called "New Approach". This is based on the application of essential requirements, settled in the applicable legislation. The intended is to harmonise the requirements across Europe, allowing the free movement of goods. In order to achieve the harmonisation the following principles were established: [13]

- Legislative harmonisation applies to essential requirements (mainly performance and functional requirements) of products place on the EU market;
- The technical specification, which meets the essential requirements, should be laid down in harmonised standards;

- Compliance with the harmonised standards may represent the conformity with the essential requirements of the applicable legislation;
- Application of harmonised standards or others stills voluntary.

With the "New Approach" Member states should not limit the free movement of goods in their market of the products which was been correctly evaluated, which means it must be bearing a CE mark and be in conformity with the applicable legislation. This is valid for a huge variety of products such as elevators, mobile phones, medical devices, software, or even toys. [13]

The "New Approach" also relies on the principle of the responsibility and credibility of the participation of all the involved parties (manufacturers, NB, standardization bodies, Competent Authority (CA) and the users) in order to allow the system to properly work. Nevertheless the responsibility for the MD conformity belongs to its manufacturer. [14]

As my internship was related to MD only this kind of products will be address in this state-of-art, although the main principles are similar to other product types under the "New Approach", with the appropriate specifications for each product, such as the vigilance for MD.

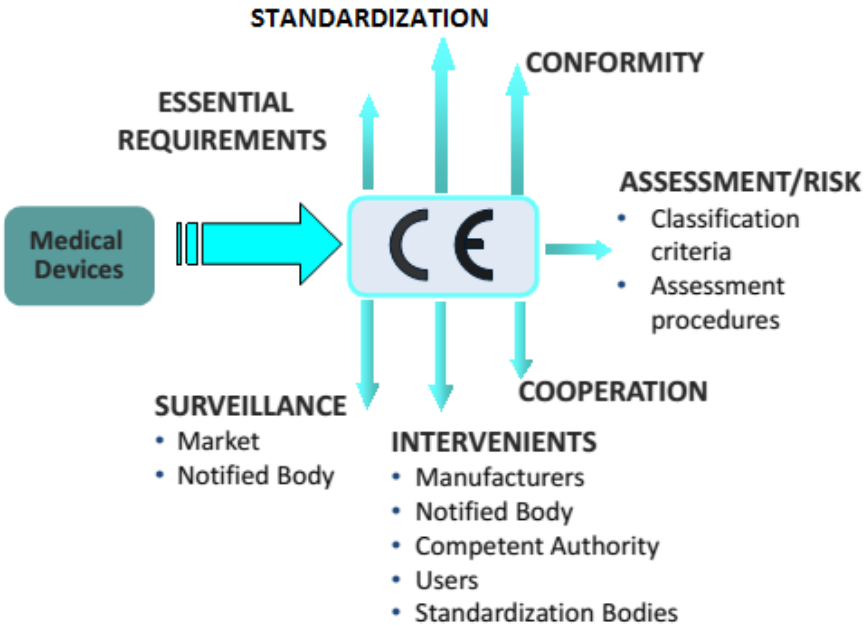

Figure 3 – Overview of the "New Approach" applied to Medical Devices; adapted from *Neves J* [14, 15]

According to the Council Directive 93/42/EEC, a MD is defined as: [2]

"*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 in its function by such means;"

In this definition a large number of products may be included, from a simple dressing to a complex pacemaker. The main criteria is that the product present, as foreseen by the manufacturer, a medical intended, not achieved by pharmacological, immunological or metabolic means. It is considered three main classes of MD, the Active Implantable Medical Devices (AIMD), the *In Vitro* Diagnostic Medical Devices (IVD) and the Medical Devices (class I to III). These different classifications reflect the different risk posed by the different devices, which allows to adequate the necessary legal requirements. [2, 3, 16-20]

Actually in the European framework there is a different Directive for each of the above indicated MD. The Directive 93/42/EEC, as its amended, is related to Medical Devices. For AIMD, the Directive 90/385/EEC settles the appropriate requirements for place into the market, and defines AIMD as "*any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure*". These directives were transposed to the Portuguese national's law at the Decree-law no 145/2009 (See Table 1). [2, 16, 18]

Regarding the IVD, and according to the Directive 98/79/EC, as transposed at national's law at Decree-law no189/2000 (See Table 1), IVDs are defined as: [19, 20]

"*any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:*

- *concerning a physiological or pathological state, or*
- *concerning a congenital abnormality, or*
- *to determine the safety and compatibility with potential recipients, or*
- *to monitor therapeutic measures."*

Table 1 – Listing of the main European Directives and the corresponding transposal for Portuguese's national law [21]

European Directive	National transposition
Directive 90/385/EEC – AIMD	Decree-law no 145/2009
Directive 93/42/EEC – MD	
Directive 2007/47/EC – Revision to AIMDD and MDD	
Directive 98/79/EC - IVD	Decree-law no 189/2000
Directive 2000/70/EC – MD with Human Blood Derivatives	Decree-law no 145/2009
Directive 2003/32/EC – MD with Animal Origin Derivatives	
Directive 2003/12/EC – reclassification of Breast Implants	Decree-law no 259/2003
Directive 2005/50/EC – reclassification of Implantable Prosthesis	Decree-law no 258/2007

Note: Regulations are not stated here since they are not transposed to national law.

Although different classification for MD may exist, the principles are the same. There is a manufacturer who wants to market a product. The manufacturer will be the one responsible for the MD compliance, and to prove its conformity with the applicable legislation. If needed the MD will be evaluated by a NB, or only by the manufacturer before affix the CE mark. Then the manufacturer should register its product in the appropriate CA.

Additionally the manufacturer needs to continuously verifying the MD's conformity regarding all the data collected on the use of the device. This was a brief overview of the life cycle (see Figure 4) of a MD, since it will be detailed in the following sections. [2, 16, 18-20, 22]

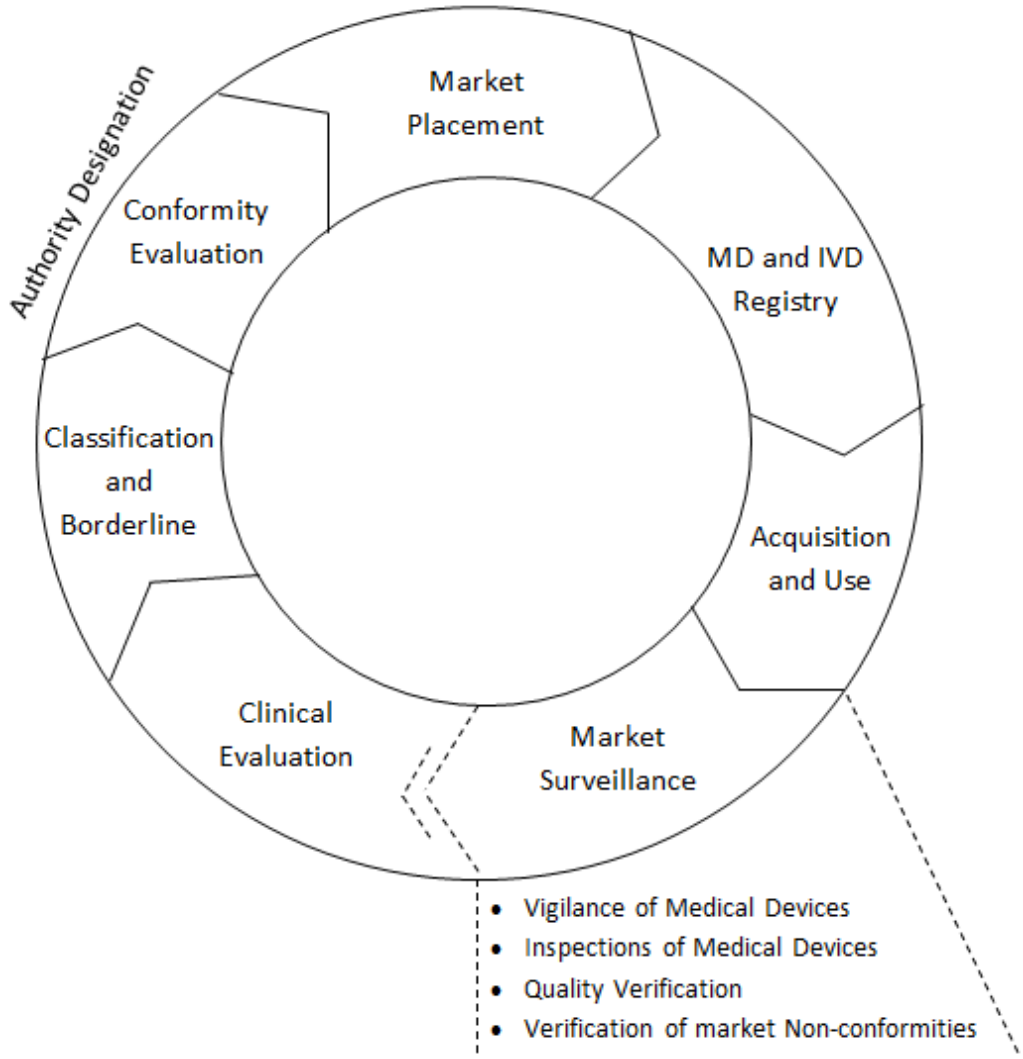

Figure 4 – Medical Device' life cycle, adapted [22]

From this overview we are able to state that the main responsibility will be attributed to the manufacturer. As so the manufacturer is the person or entity responsible for one or more of the following activities: design, manufacture, packaging and labelling. However if the manufacturer does not have a registered place of business in the Community, he shall designate an Authorised representative, who will assume some of the manufacturer's responsibilities, including being an interlocutor between the involved entities

(manufacturer and CAs). From now on when referring to manufacturer, I'm also referring to its Authorised Representative, if applicable.

1.2.1.1 Classification and Borderline

The first step to be able to market a device is to be sure about its true qualification. As so the manufacturer needs to evaluate if its product fulfil the MD's definition (stated above in section 1.2.1), or in other hand if its products is not a MD. When it's not clear if the product falls under the MD legislation, then the manufacturer may ask its national CA for advice. It is important that first the manufacturer consult the guidance on classification and qualification of MD available at the Commission's website. There the different stakeholder may consult numerous guidances on different subjects. These draft documents works as guidelines which can be used by stakeholders, however they are not legally binding. These documents are generally called MEDDEVs and offers guidance for the correct application of the rules and regulatory requirements applicable to the European System. The MEDDEV 2.4 present the applicable rules for MD classification as also give some examples of MD for each rule. [23]

Additionally there is available a Borderline Manual, which also resulted from the discussion of the Medical Devices Expert Group on Borderline. During the discussion on the Medical Devices Expert Group on Borderline and Classification are represent the CA, the Industry, the NBs, the Standardisation Bodies and COM services. [24] The manual on Borderline has already some entries of borderline issues (when it's not clear if the product fall under a MD legislation or not) which help to clarify and ensure the uniformity of the approaches in all the member states. There are essentially specific entries related to products from which had arisen doubt's regarding its qualification and classification. [25, 26]

When determining the qualification of the product, the manufacturer should look to the main purpose of the products and to the available scientific data. If the product has a medical purpose, it could be a MD or a medicinal product. Otherwise it will fall under other legislation, such related to biocides, software and cosmetics (see Figure 5 for frequent borderlines). The second part is to verify the main mode of action, also relying on scientific/clinical data. If is pharmacological, immunological or metabolic, then the product will be a medicinal product. If not the product is a MD. When doubt still exist

them by application of the article 2 of the Directive 2001/83/EC, it should be applied the Directive 2001/83/EC (legislation for medicinal products) to the product. [26-28]

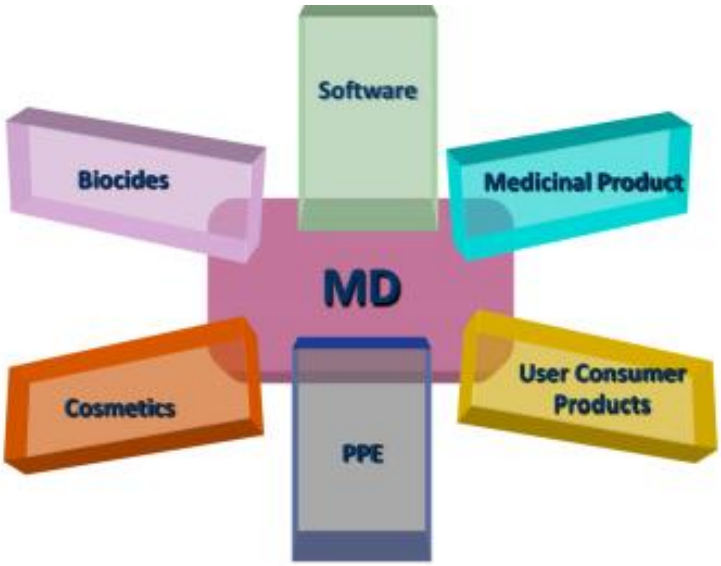

Figure 5 – Borderline with Medical Devices, common qualification [28]; PPE – Personal protection equipment

As far as the qualification is settled, the manufacturer may think about its classification. The MD legislation based its medical device classification according to the risk present by the device.

1.2.1.1.1 Medical Device

Relating to MD in general their classification is settled according to three major criteria: the intended use, the invasiveness and the duration of use. [2, 3, 18]

- Intended use: the one claimed by the manufacturer and stated at the technical documentation, including, but not limited to Instructions of Use, Labels and promotional materials;
- Invasiveness of the device;
    - Non-invasive devices;
    - Invasive devices:
        - Body orifice invasiveness – penetrates through natural openings of the body or a permanent artificial opening;

        - Surgically invasive – penetrates through the body surface in the context of a surgical operation:
            - Reusable surgical instruments – instruments for surgical use that can be reused;
            - Implantable devices – intended to be introduced in the body in a surgical context and to remain there after the procedure ends;

- Duration of the contact with the patients:
    - Transient use – for less than 60 minutes;
    - Short term use – use between 60 minutes and 30 days;
    - Long term use – use in more than 30 days.

These criteria allow the manufacturer to determine the device classification. As said before the classification of the MD represents its associated risk. So as higher the classification of the device, the higher will be the risk associated to the device. This will also represent different approaches of conformity evaluation for each MD class. These MD are classified in: [2, 3, 18]

- Class I – considered to have low risk, some initial issues should be considered in assess the associated risk, such as sterility and measuring function;
- Class II – medium risk associate:
    - IIa;
    - IIb;
- Class III – high risk medical device.

In order to attribute the correct classification the manufacturer must follow the rules present at the annex IX of Directive 93/42/CEE. Using the rule that most fits the medical device and its intended use. In those cases where more than one rule can be applied, the manufacturer should follow the one that attribute the higher class to the medical device. The mentioned rules can be divided in four sets of rules: (see Figure 6) [2, 3, 18]

- Non-invasive medical devices: from rule 1 to 4;
- Invasive medical devices: from rule 5 to 8;

- Active medical device: from rule 9 to 12;
- Special rules: from rule 13 to 18.

1.2.1.1.2 Active Implantable Medical Device

Devices classified as AIMD are implantable devices with a source of energy that convert the energy from the source into another type of energy. Taking in account the nature of the devices they are associated to a high risk, as so they are classified as itself, as AIMD, according to their own Directive (90/385/EEC). [16, 18] However the available draft regarding the new regulation for MD, others than IVD, foresees that AIMD will be classified as class III. [4]

1.2.1.1.3 In vitro Diagnostic Medical Device

In this case the risk is associated with the consequences of failure of the test (false positives and false negatives), and not with the direct risk for the user, as so their classification principles are different from the others medical devices. According to Directive 98/79/EC, IVD's are classified in: [17, 20]

- Self-testing IVD – devices to be used by lay persons;
- General IVD – intended to be used by trained professionals. The IVD's that are essential to medical performance and whose failure represent a serious risk for patients or public health are listed, and classified as:
    - List A; (see Annex A)
    - List B; (see Annex A)
    - Other – general IVD that do not fall under the list A or B.

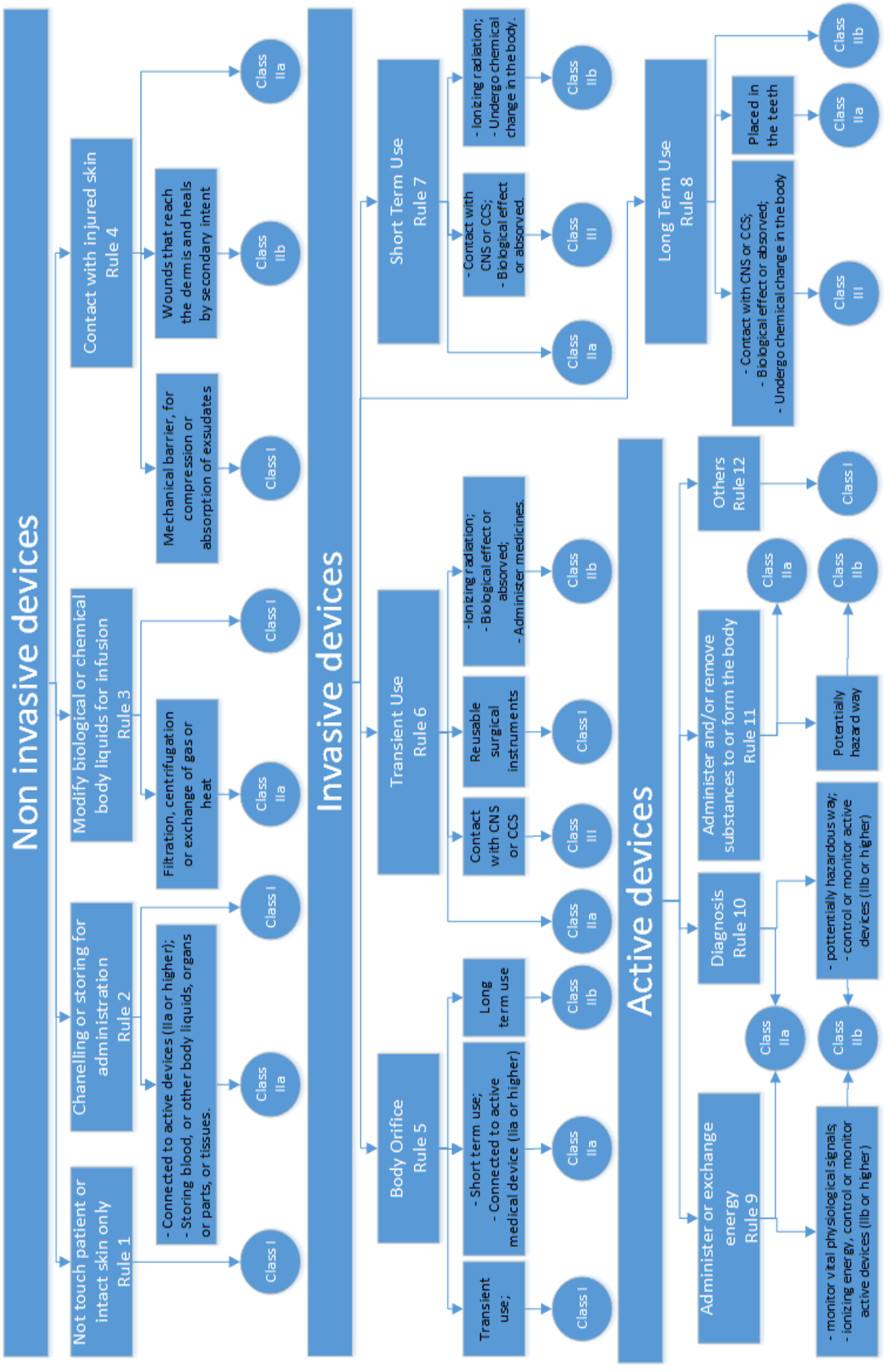

Figure 6 - Rules according to Directive 93/42/EEC [2, 3]

CNS – Central Nervous System; CCS – Central Circulatory System

1.2.1.2 Clinical Evaluation

One of the information that must be contained in the technical file is related with the clinical information regarding the MD, this information will and should support the safety and performance of the device. Although this information should be available before affix the CE mark, this is a continuous process during all the life cycle of a MD. This information may be collected by means of: [29, 30]

- Clinical investigation
- Literature search of a similar device, for which manufacturer had demonstrate the equivalence of the MD;
- Clinical experience: comprise the clinical use of the device and the post-market activities.

The comprehensive analysis of the available pre- and post-market clinical data is seen as the clinical evaluation, which may arise from the above mentioned sources. Figure 7 illustrate the necessary steps to perform a clinical evaluation. An additional step, which is not indicated in Figure 7, comprises the identification of the relevant essential requirement which need to be supported from clinical data. This identification helps in defining the clinical evaluation scope. [29]

The scope of the clinical evaluation may be defined only after identifying the essential requirements to be addressed on the clinical evaluation, and taking into account: [29]

- Any design features, from which may arise safety and performance concerns;
- The intended purpose and site of application;
- Any other specific claim made by the manufacturer;
- The presence or not in the market of a similar device;
- The types and sources of data that can be used.

Since the scope is defined then the manufacturer should identify the available clinical data, appraise it, and evaluate if he had collect the necessary information, or in the other hand if he needs to generate it. [29]

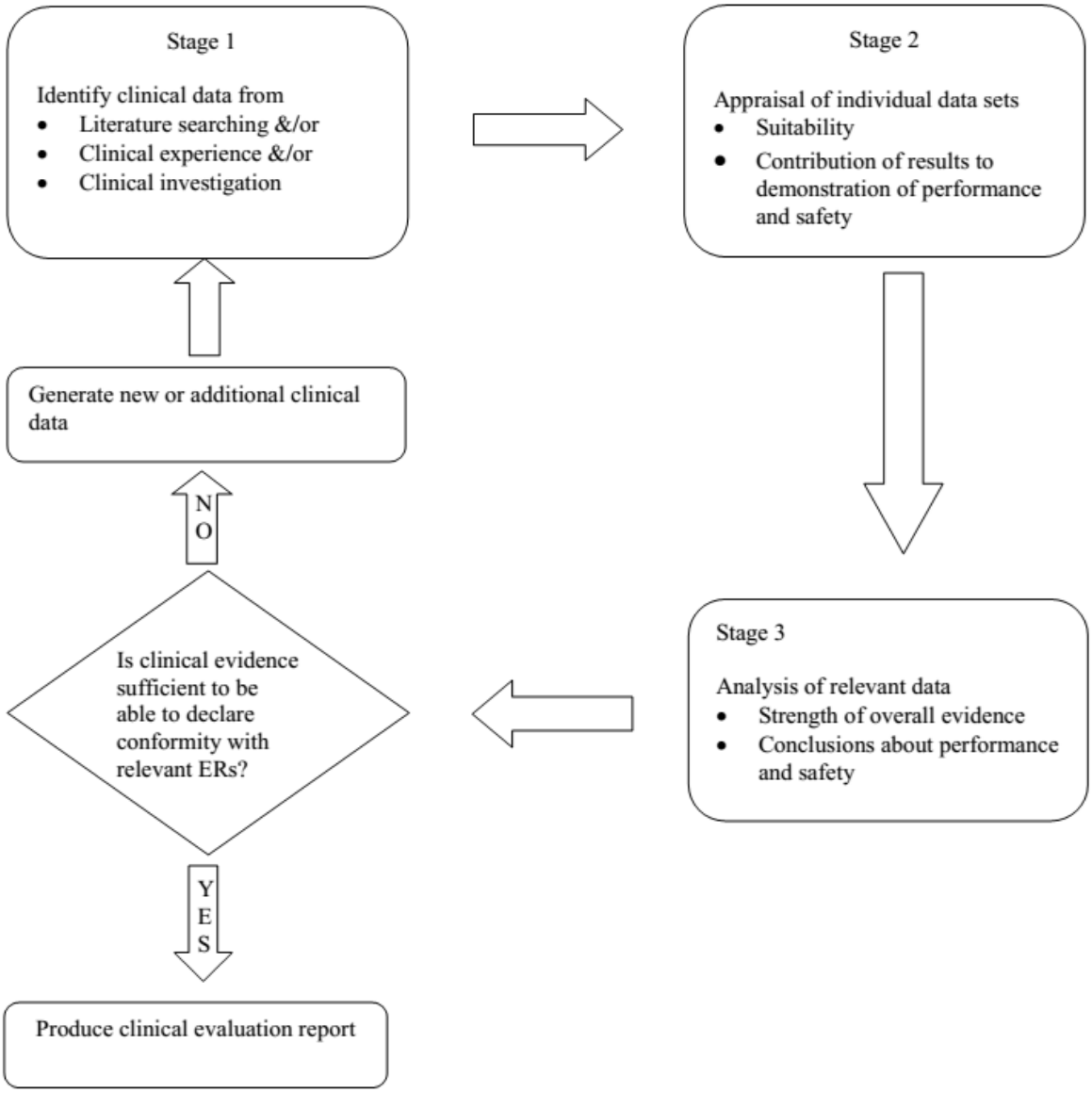

Figure 7 - Steps for a clinical evaluation [29]

When evaluating the collected information the manufacturers should have in account if the data they are using are from the same device or in other hand from similar devices. If it comes from similar devices, it's necessary to prove that the devices are equivalents (the comparative device should already be placed on the market). In order to prove equivalency the manufacturer should demonstrate the similarities between clinical, technical and biological characteristics of the devices (more information on Table 2). [2, 18, 31, 32]

Table 2 – MD's characteristic to take in account on equivalency [31, 32]

Clinical	Technical	Biological
- Intended use; - Severity and stage of disease; - Site of application; - Patient population; - Clinical performance.	- Specifications and physiochemical properties; - Critical performances requirements; - Principles of operations and use's conditions; - Related to the device design.	- Biocompatibility of the materials on same bodies' tissues/fluids.

If from the evaluation of the collected data, there still need more information to fulfil the essential requirements, then the manufacturer should generate clinical evidence. In order to generate it, manufacturer should promote clinical investigations (note that clinical evaluation is different from clinical investigation). [29]

To start any clinical investigation, according to ISO 14155 and the applicable directives, for AIMD, class III and implantable and long-term invasive devices, the ones that are classified as IIb and IIa, the manufacturers should notify within a maximum of 60 days the CA where the study will be conducted. This should be the full application for notification. However manufacturer should ensure that the process had already been approved by the local Ethic Committee, as well by the National Data Protection Authority (National Commission on Data Protection (CNPD) in Portugal). At the end the manufacturer should also send the report on clinical evaluation to the CA. [2, 16]

Since clinical evaluation should be conducted as well on post-market, some clinical investigations should as well be made. For those devices with a valid CE mark (except AIMD) that are under clinical investigation, it's not necessary to notify it, unless the device is not used for the same purpose as stated on the conformity process. [2, 16, 18]

Recently in Portugal a new law is applied to MD, the intended of law number 21/20014 is to uniform, as far as possible, the criteria for medicines, MD and cosmetics. This law had modified the way of notification of Clinical investigations in Portugal. Now the manufacturer must submit to INFARMED, I.P. and to the Ethic Comission on Clinical Investigation (CEIC) simultaneously, by way of an informatic platform (foresseen in the law, but not already working). CEIC will be the ethic committee responsible for the ethical evaluation, however he can delegate this activity to local ethic committees where the clinical investigation will be conducted. [33]

This new laws also modified the way INFARMED, I.P. should react in relation to a clinical investigation notification. Until the application of Law no 21/2014, the Manufacturer only need to notificate 60 days (calendar days) early related to the beginning of the study, and can start the clinical investigation even if INFARMED, I.P. doesn't pronounced itself. This law foresseens that INFARMED, I.P. must pronounce in 30 working days after the request notice for clinical investigation. However it also state that when any information request arise from INFARMED, I.P. the clock counting stops. [33]

1.2.1.3 Conformity Assessment

In order to place on the market any MD the manufacturer should assess the conformity of the device, for that he needs to elaborate and collect all the necessary information which will constitute the Technical file. There isn't a standard guidance for which documents or the precise information that must be present on the Technical file. However each of the Directives, applicable to MD, state what are the essential requirements that the manufacturer should fulfil. [2, 15, 16, 20]

Essential requirements are mandatory and seen as a necessary element for protecting the user's interests. They are divided in general requirements of safety and performance issues, and specific requirements, which may apply or not to the particular MD. It will be up to the manufacturer to decide and justify the non-application of any essential requirements. In order to help the manufacturer to accomplish the conformity with the essential requirements, there is a set of harmonised standards. These are only technical specifications that the manufacturer should decide to follow or not. [2, 15, 16, 20]

When technical documentation is elaborated and the conformity was evaluated, then manufacturer may affix CE mark. Depending on the MD class, the conformity assessment may require an external evaluation (MD of medium to high risk). In those cases the manufacturer should submit an application to a NB, who, if the product is in conformity, will issue an EC Certificate, which allows the manufacturer to affix the CE mark. [2, 16, 18-20]

According to the MD class there is a set of conformity assessment procedures for obtaining the CE mark, Table 3 and Table 4 reflects the corresponding procedure to the MD classification.

Table 3 – Procedures for Conformity assessment of MD and AIMD [2, 16]

Classes	Procedures for Conformity assessment	NB's evaluation
MD	**annex of Directive 93/42/EEC**	
I	VII	No
I sterile	VII+ (II (without point 4); IV; V; VI)	Yes
I measure function	VII + (II (without point 4); IV; V;VI)	Yes
IIa	II (without point 4); VII +(IV; V; VI)	Yes
IIb	II (without point 4); III + (IV; V; VI)	Yes
III	II; III + (IV; V)	Yes
AIMD	**annex of Directive 90/385/EEC**	
Active Implantable	II; III + (IV; V)	Yes

Table 4 – Procedures for Conformity assessment of IVD [20]

Classes	Procedures for Conformity assessment	NB's evaluation
IVD	**annex of Directive 98/79/EC**	
Others IVD	III	No
Self-testing IVD	III, point 6; IV; V + VII	Yes
List A	IV; V + VII	Yes
List B	IV; V + (VI;VII)	Yes

From the conformity assessment may result two kinds of documents which proves that the assessment was carried out and the product is in conformity, the EC Certificate and the Declaration of Conformity. Although the meaning it's similar, there is a main difference between the two document. The EC Certificate it's issued by the NB and is not applicable to all MD, and the Declaration of Conformity (See Annex B for minimum information), which is issued by the manufacturer and applicable to all the devices. [2, 16, 20]

Once the conformity assessment process is fully complete and the CE mark affixed, then the MD could be placed on the market. Additionally all the manufactures of class I device, should register theirs devices (class I) at the CA of the member state they are based in. For the remaining classes the manufacturer should have attention to the particularities of each country which may request, or not, the registration of the MD in the CA. Portugal requires

the registration of all MD from class IIa to III which are placed in the national market as a foreseen duty of the manufactures. Although Directives only mention as mandatory the registration of some MD classification (or some information regarding IVD) to the national CA were the manufacturer is established. [2, 16, 18-20]

In order to all the process stated before may occur, it is necessary that the NB, to whom the manufacturer submits the application, is legally designated by one national competent authority for designation. [14]

The CAs can have as well an indirect role on the conformity assessment since they may participate on the designation of the NB. Any candidate to be a NB should apply for designation to the designating authority of the Member State where he is established. Since the introducing of the Regulation no 920/2013 that the evaluation of the candidate must be done by the national designating authority and two representatives of two others designating authorities from others Member States. As said the CAs may participate on this process since they may act as well as designating authorities, for example in Portugal the designating authority is INFARMED, I.P.[34]

1.2.1.4 Market surveillance and vigilance

1.2.1.4.1 National Competent Authority

When talking about market surveillance of any medical device, the CA is responsible for monitoring the conformity of the products available in their market and of the manufacturer, and other players, located in their state. [18]

Regarding the market surveillance activities, according to the MD Directives, the member state is responsible for settle all the measures to ensure that the MD placed on the market are in accordance with the applicable legislation. In a general way this includes desk review, vigilance, inspection and laboratory control. [2, 35]

In Portugal these activities are carried by different units of INFARMED, I.P, desk review and vigilance are carried in DPS. However the remaining activities, inspection and laboratory control, are carried in other units. Due to different human qualification on the different units on INFARMED, I.P., laboratory control is done by the Control Laboratory unit, and the inspection are made by the resources of the Inspection and Licensing unit. By

one side laboratorial control its made to a product, and on the other side the inspecting acting is as well performed to the entities of the market and not only to the product. [35]

From the above stated activities for market surveillance, the only that will be focus here are desk review and vigilance. Those represents the activities carried out by DPS, the unit were the internship occurred. Despite that inspection and laboratory control may as well been carried in collaboration by the different units.

Desk review may comprise activities like: [35-37]

- Evaluation of registries/notifications made by manufacturers and distributors;
    - Issuing of Registry Declarations;
    - Declaration for exportation purposes;
    - Codification project;
    - Elaboration and publication of MD's list.
- Campaigns for specific groups of medical device;
- Documental review due to financial protocols with the Health Department;
- Technical opinions for importation issues.
- Cooperation with other national entities and European authorities.

Regarding the vigilance activities, Portugal created the national system of MD's vigilance in 2004, which is based on the Meddev regarding MD vigilance system and also on the pharmacovigilance system. The vigilance system is intended to: [38, 39]

- minimize the risks of MD use, by identify them on the real word;
- encourage the notification of any incident, by any player of the lifecycle;
- ensure the implementation of the corrective and preventive action taken by manufacturer;
- and reunite, analyse and share the information with other CA and the EC.

In the Vigilance system the CA should first of all encourage the notification of any incident by any individual involved in the life cycle of medical device. Because for the Vigilance system works efficiently it is necessary to report incidents, in order to have

feedback from the use of MD. This can be achieved by reinforce these issues to the health professional and users given them training or the necessary information. [40]

According to the Directive 93/42/EEC, all the national authorities should define and increment the routes in order to obtain the necessary information, and to disseminate it. Receiving the information is important, but transmitting it to the relevant stakeholder is also as important, and making that information reaches its destination can be harder than receiving it. [40]

When the CA receives notifications from the health professionals and/or users it should try to collect the maximum information possible and analyse it. When the notification fulfils the incident criteria (see Table 5) then the CA should inform the manufacturer about the incidents, without compromising the confidentiality of who notified. This is another way of ensuring that the events are being evaluated by the manufacturer. [40, 41]

Table 5 – Incident criteria to be met in order to notify the CA [39, 40]

Incident criteria for notification*
✓ **An event occurred;**
✓ **The incident may be related to the MD;**
✓ **The event led, or might have led to one of the following outcomes:** ▪ Death; or ▪ Serious deterioration in state of health: o Permanent incapacity or a threats to life; o Hospitalization, or increased time of hospitalisation, or medical or surgical intervention for prevent the damaged caused; o Foetal distress or death, congenital abnormally or malformation at birth; o Indirect harm, after an incorrect diagnose related to a MD.

***must full the 3 criteria**

In general the investigation of the incident is carried out by the manufacturer, but the CA monitors this evaluation and also verifies if it's needed to implement immediate corrective actions before the conclusion of the investigation. Besides to monitor, the CA can was well act on the action taken, by changing the direction of the investigation, verifying if the obtained results are enough or by recommend the alteration of safety information contained on the MD literature distributed to the public. Additionally, the CA can also perform their assessment of safety and performance of the medical devices, taking in account the tight

risk-benefit balance, for that they can rely on the reports of clinical investigations, and other information regarding the design and manufacture of the MD provided by the manufacturer.

When the incident investigation is finished and the manufacturer propose a Field Safety Corrective Action (FSCA), the CA also evaluates if the action taken is enough. Once the manufacturer communicates a FSCA, the CA where the manufacturer is placed should inform the Commission and the others member states through NCAR (National Competent Authority Report) on EUDAMED (European Database on Medical Devices). [17, 40, 41]

1.2.1.4.2 Manufacturer's Post market surveillance Plan and Vigilance duties

When marketing a device, the manufacturer should implement a market surveillance plan and a vigilance system, which is integrated at its QMS. These post-market activities are, in the majority of the cases, integrated on the quality system of the manufacturer. Both the quality management standards (ISO 9001 and ISO 13485) and the risk management standard (ISO 14971) require the manufacturer to conduct post-marketing activities. This can be divided in two kind of activities: [18, 42]

- Proactive: considered as the activities contemplated on the post market surveillance (PMS) plan;
- Reactive: the vigilance activities, which may or not including complaint handling.

Regarding the proactive activities, which mean doing something before it happens, it's not specifically indicated which one the manufacture must adopt. It is the manufacturer responsibility to ensure that he is collecting all the information regarding the use of the MD. This needs to cover the quality, safety and performance of the MD. As important as the collect the information, it is important to assure that all the involved parties are trained on how to collect and document the information. [42, 43]

Activities may include the analysis of market trends, literature review, client inquiries and post-market clinical follow-up. However they need to be planned, which needs to be translating on procedures, on how to do it. Some of these activities (according to the MD associated risk) should be planned before placing the MD on the market, since it would be this planning that will be evaluated by the NB. These include a pre-defined periodic revision, which should integrate the clinical evaluation and the risk management. [44, 45]

Like in other pharmaceutical sectors, the information gathered on the pre-market phase is only a little bit of we can know. And what happen when placing a MD on the market may differ from what were foreseen. Even if it didn't differ, there is the need of continuous evaluate the balance between risk and benefit. Check if new risks appear or even if the ones foreseen on the risk management analysis, made prior to marketing, needs to be adjusted to the reality. This is a continuous analysis of the system, which on a simple quality system can be called as continuous improvement, that it is no more than a tool as well to maintain the good functionality of the business. For this reason, the results from the PMS plan should interact with the risk management system of the manufacturer. [42, 44]

The PMS plan should be documented in the forms of procedures that will ensure the gathering of the information. This could be included on the quality system of the manufacturer or done and included as specific procedures for a MD. This difference and the need for specific procedures should be evaluated according to the MD associated risk. [44]

Contrary to the proactive activities that may result on the early detection of signals, which conduct to the reduction of the possible events, the reactive activities are taken only after the event occurred. This can be detected during the analysis of complaints, or as well during vigilance activities. [43, 45]

The vigilance activities occur when an event related to the MD had occurred. Which means the manufacturer will only act after something happens, that's why vigilance activities are reactive activities. As the responsible for the product, the manufacturer needs to notify the incidents to all the relevant CAs (where the device is placed) and the FSCAs to the National CA of the member state where they had occurred and where the manufacturer is located. [18, 40]

When a manufacturer knows that an adverse event has occurred with their devices, it should evaluate the nature of the event and verify if it needs to be notified to the CA (see Table 5). The manufacturer is the responsible to assess the need of a corrective action, and to implement it. As the responsible for the main investigation of the occurred event, the manufacturer should deliver an incident report to the CA that includes the investigation and the corrective actions to be implemented in order to minimize the risk of the MD. (See Table 6 for information about Portuguese timelines concerning notification) [18, 43, 46]

Table 6 - Timelines established on the Portuguese National Law for notification to Competent Authorities [18]

Type of notification	Timelines
Initial report	
Death or high risk for health	10 days
Other cases	30 days
Final report	After investigation conclusion
Death or high risk for health	10 days
Other cases	30 days
Safety corrective action	
Death or high risk for health	As soon as possible, even after the action was taken
Other cases	2 days before been applied

1.2.1.4.3 Notified Body

The main activity of the NB on the MD's lifecycle is on the pre-market phase. However even without a truly active role on the post-market, NB are the entities that ensure that the manufacturer foreseen all the activities needed for PMS and vigilance.

NB function as a support entity to ensure the quality of the vigilance and PMS procedures established by the manufacturer before market placement. In the post-market situation the NB should evaluate if the results from the PMS and vigilance activities have an impact on the EC certification, which means that if any result could change the result of the conformity evaluation. [40]

1.2.1.4.4 Distributor

Although in the actual European directive the distributor isn't mentioned anywhere, the Portuguese's law involved the distributor in the vigilance system as well on the market surveillance (some country may as well had apply their own national's laws). According to national law, distributor should notify all the information they have related to an occurred event on the Portuguese market. [14, 18, 19]

Regarding the market surveillance, they are supposed to participate directly and indirectly on the market surveillances activities. According to the national law they should ensure

that only the MD, which conforms to the applicable legislation, are made available in the market by them. Which means that the distributor should possess enough knowledge and information regarding the MD they are trying to sell, that allows them to verify its conformity. This could be done by verifying the correct affix of the CE mark on the product and the verification of the conformity documents (EC Declaration of Conformity, and EC Certificate, when applicable). [14, 18, 19]

The other role of the distributors is to notify to the CA all MD they are made available on the Portuguese market, as well with other information regarding those devices. This obligation of the distributors foreseen on the national law, allows the INFARMED, I.P. to know the Portuguese's market. This will constitute a source of information for the activities of desk review of the CA, but as well a possible database in cases related to vigilance. [14, 18, 19]

1.2.1.4.5 Health professional and Users

The health professional represents the main source of information regarding events. Been the ones who use the devices in the real world, and thus they are the ones who see things happening. According to the Portuguese national law, they are involved in the notification of the events to the CA, and if possible to the manufacturer and distributors. [17]

The role of the Health professional on the vigilance system is vital; however no legal requirement states that they must participate on the Vigilance system. Therefore, it is necessary to encourage them to actively notify the suspect events which they know about. [40]

2 On-Job Training

2.1 Market Surveillance

As stated before, in the MD context the activities of a CA is mainly in the post-market phase of the MD life-cycle, both in market surveillance and vigilance of MD. Although vigilance may be considered a part of the market surveillance and since my internship was not related with vigilance activities, these activities taken by INFARMED, I.P. will not be issued here.

Additionally to market surveillance or what can be considered as a complementary activity to market surveillance, INFARMED, I.P. also provide scientific and regulatory support, as far as its possible. During my internship I was asked to answer six information requests, one of which was not concluded until the end of the internship. These may come from different sources, from distributors, manufacturers, patients or other partners or economic agents. According to the source the type of information may also change, it can relate to the legal qualification of the products to simple doubts in one of the platform formats or legally binding. This had allow a different approach, than the usually related to the distributors' registries, as I consolidate my knowledge and go even deeper on the regulatory affairs in the MD world.

As for class III, IVD's and AIMD that already have a public list of the distributors' MD registered in the INFARMED, I.P.'s site [47], the goal is to achieve the same for class IIb MD. However, in order to make publically available a MD listing is necessary to validate all the information given on the registries made until the moment, and keep updating the listing monthly. When I arrive at DPS, this work had already started, but however it was paused due to the lack of human resources. I also contribute to this validation, which had shown me different devices although from the same class, but a wide variety of devices, from anticoagulant sprays to condoms.

Figure 8 represent my contribution to the class IIb's list. Although it stills a long way to the release of the list, it represented a huge opportunity to explore the huge variety of devices that exists on the Portuguese's market. Although I had the chance to evaluate a huge number of registries, the reality is that my work as dependent of the collaboration of the distributors. By this way 394 registries stayed under evaluation, even after the duration of

my internship, for these registries an information request was made, however it was not possible to answer to the doubts (qualification, classification …), which could had been due to lack of response of the distributors, insufficient response, and/or proceeding to a COEN.

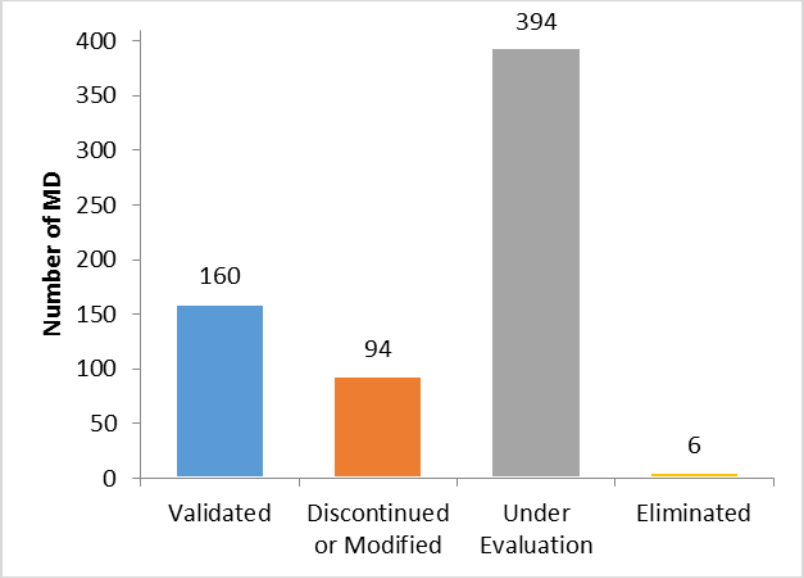

Figure 8 – Class IIb registries analysed during 2014 (January-July)

2.1.1 Codification project

My main task during the internship was to provide backup to this big project that is occurring. This project was officially created on 2012, due to economic restriction present on the memorandum of understanding between Portugal, the European Commission, the European Central Bank and the International Monetary Fund. The codification project started by INFARMED, I.P in order to provide an in deep knowledge of the available information on the national database, when at the same time provides to the health professional more information related to the health technologies. Secondary it is foreseen that this project may as well increase the efficiency and the ability to negotiate the acquisition of the health technology. Besides the above mentioned purposes, stated on the Order no 15371/2012, the codification project purpose is also to allow the different players to communicate on the same language, avoiding confusion and disseminating product traceability. [48, 49]

By the application of the Order no 15371/2012, services and entities belonging to the SNS can only acquire MD whose group was already been codified, which mean that it has a code attributed by INFARMED, I.P. . The codification process is made on phases, being the group (NPDM groups) order to be codified selected according the associated risk and the associated cost, both per unity and due to a broad utilization of that kind of device. [48, 50]

The NPDM group is a Portuguese's specific nomenclature for groups of MD, although it is based on other European nomenclature systems. These different groups allow to aggregate MD according to their intended use, the application site and their technological characteristics. [49]

In order to proceed with the codification of a new group of MD, a search is made on the available database (mainly on Distributor registries) for the detection of potential MD to be included on the new group. Internally the search's results are evaluated, and another team contact the owner of the registries to notify them about the new group. In that stage, I was able to evaluate the results for the Ostheosynthesis and tendo-ligament synthesis devices group and the ligaments prosthesis. However only the ostheosynthesis group was release for public until the end of my internship.

After this initial work of device selection, is necessary to validate the registry information. Since the code will only be given to the MD after the regulatory approval of the registry, and the validation by the codification team. Due to the obligation of obtain a code to the distributer, and in order to make it available for consultation by the SNS entities, the registries needed to be evaluated in a daily base. This regulatory evaluation is made similarly to the one made to obtain the Registry Declaration. From the data available on the registries, and the submitted documentation, it is possible to evaluate the product qualification and classification, as also check some of the requirements for placing MD into the market. Basically the codification process is based at the same principles of market surveillance, the registration of the information to prior validation.

As said above the registries were daily evaluated by the regulatory team, based on the already released groups, and secondly on the upcoming groups. Table 7 shows the groups of MD released until the end of the internship.

Table 7– Groups of MD with codification process completed (at the end of the internship) [50]

Groups	Available since	Groups	Available since
AIMD of cardiac function	07.02.2013	Implantable pumps	02.09.2013
Hip prosthesis	15.02.2013	Neurostimulators	08.10.2013
Knee prosthesis	15.02.2013	Hearing AIMD	08.10.2013
Intraocular lens	28.02.2013	AIMD - Other	08.10.2013
Heart Valves	31.03.2013	Peripheral vascular stent	20.10.2013
Coronary Stents	31.03.2013	Foot prosthesis	20.10.2013
Vascular endoprosthesis	30.04.2013	Ankle prosthesis	20.10.2013
Prosthesis for coronary and heart defects	30.04.2013	Hand prosthesis	20.10.2013
Cochlear implants	30.04.2013	Wrist prosthesis	20.10.2013
Shoulder implants	30.04.2013	Elbow prosthesis	20.10.2013
Breast implants	01.07.2013	Ear prosthesis	20.10.2013
Surgical meshes	01.07.2013	Spinal stabilization system and prosthesis	29.10.2013
Vascular Patches	01.07.2013	Urogenital prosthesis	02.12.2013
Cardiac and Vascular prosthesis - accessory	01.07.2013	Tissue extenders	02.12.2013
Surgical sutures	02.09.2013	Tissues Patches	02.12.2013
Vascular prosthesis	02.09.2013	Ostheosynthesis and tendo-ligament synthesis devices	03.02.2014

Adapted from the codification site [50]

At the beginning of the internship the above groups were split according to at seems to be a logical and functional combination of groups (see Table 8). Some of them were combined into major groups, given the similarities of the groups. As the groups were divided, then I start to evaluate the registries associated to the codification process.

Table 8 – Group distribution for regulatory review

My groups		My colleague groups	
Code	Group	Code	Group
P0901	Shoulder implants	J01	AIMD of cardiac function
P0902	Elbow prosthesis	J02	Neurostimulators
P0903	Wrist prosthesis	J03	Hearing AIMD
P0904	Hand prosthesis	J04	Implantable pumps
P0905	Ankle prosthesis	J99	AIMD - Other
P0906	Foot prosthesis	P0301	Intraocular lens
P0907	Spinal stabilization system and prosthesis	P06	Breast implants
P0909	Knee prosthesis	P07	Cardiac implants
P0912	Ostheosynthesis and tendo-ligament synthesis devices	P08	Urogenital prosthesis
		P9001	Tissue extenders
		P9002	Surgical meshes
		P9003	Vascular Patches
		P0201	Ear prosthesis
		C0104	Cardiovascular MD
		H01	Surgical sutures
		P0908	Hip prosthesis

First it is necessary to obtain the registries that are associated to each of the groups. In order to have access to those registries, the groups' code was searched in the backoffice (see Figure 9). The results were then displayed by references, however in the original database we aren't able to search for reference.

Associated to the reference is an ID number, this is the registry identification. Each ID may contain multiple references, if they represent the same MD. So what we will obtain is an extensive listing of references, where the interest is on the ID. Each ID is then searched at SDIV (see Figure 10 and Figure 11)

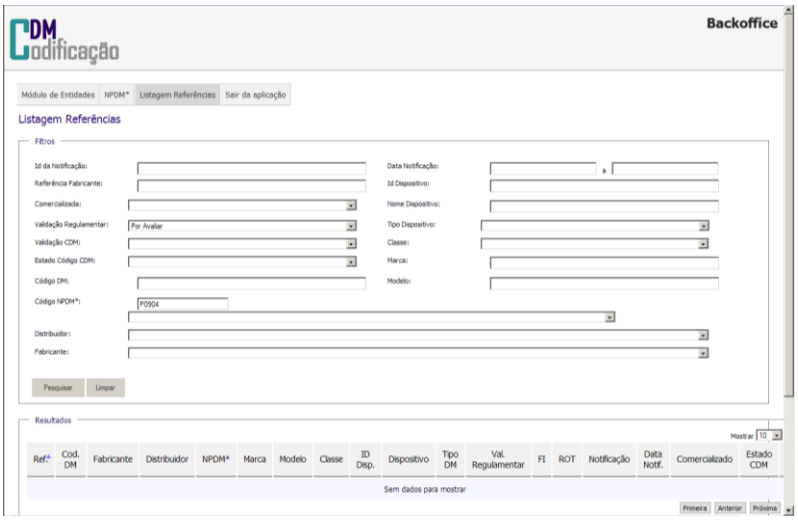

Figure 9 – Backoffice of Distributor's database for the codification process.

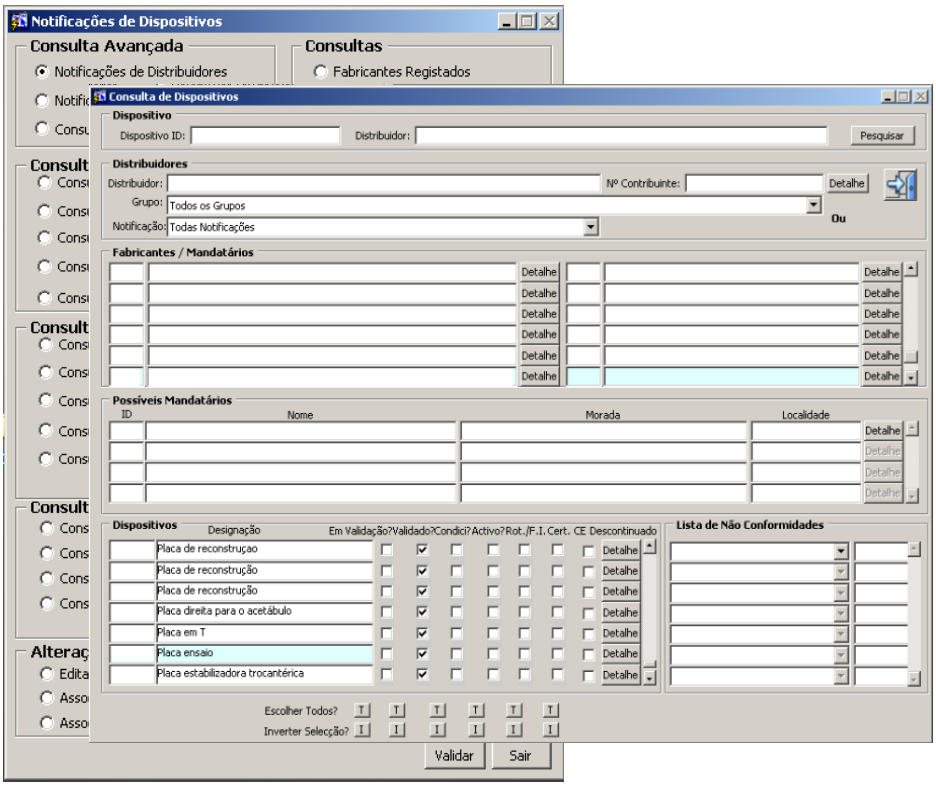

Figure 10 – SDIV layout

There, and in accordance to the Manual for On-line Registration [51], should be available the information regarding Designation, Classification, NB code, trademark and model, and GMDN code or Brief Description.

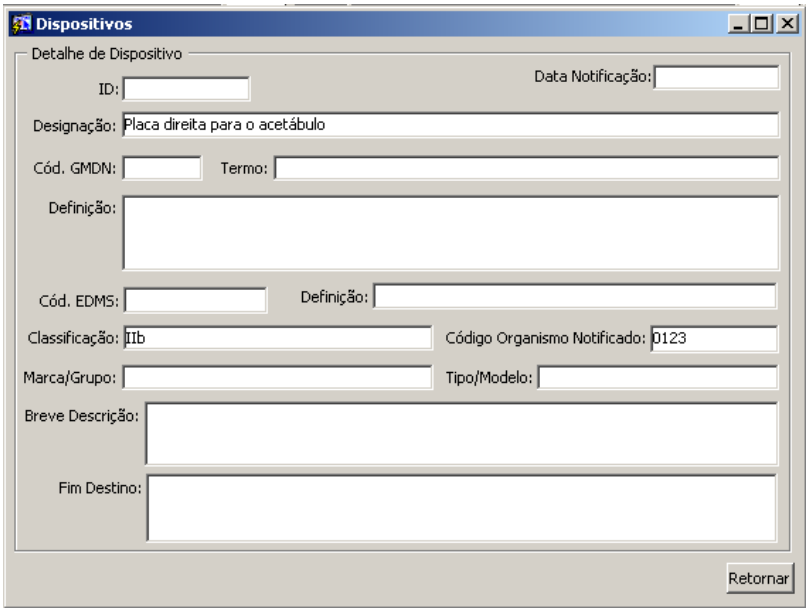

Figure 11 – Information obtained from SDIV, specific for each device

- Designation ("*Designação*") – correspond to the common name given to the MD;
- Classification ("*Classificação*") – defined by the MD's manufacturer, according to the applicable Directive;
- NB code ("*Código Organismo Notificado*") – NB responsible for the *conformity* assessment of the MD, if applicable;
- Trademark/Model ("*Marca/Modelo*") – commercial name/identification;
- GMDN code [52]– it's a Global Medical Device Nomenclature (GMDN), which aim to provide a single naming system (generic) for help in support patient safety (by providing harmonized terms);
- Brief Description ("*Breve Descrição*") – any MD feature which distinguishes it from the others.

After evaluate the above information, and to assess if everything is alright (for example intended use against classification, which also influence the presence or not of a NB code), then the codification team may also perform their corresponding validation. Codification team will be responsible for assess some of the information in the labels and Instructions for Use, such as reference and manufacturer. After the evaluation a unique code (CDM) for

the pair manufacturer/reference will be attributed, and so the MD and that specific reference may be acquired by the hospital or other SNS entity.

The following Figures and Tables show the number of analysed registries during the entire internship.

Table 9 – Registries analysed during 2013 (November-December)

Group	Validated[a]	Evaluated[b]	Information request	Concluded in 2014
P0901	3	0	0	0
P07	3	0	1	0
P0904	1	0	0	0
P0908	3	0	0	0
P0903	1	1	1	1
P0909	58	5	12	2
C0104	16	5	7	5
P0902	1	11	11	11
P0912	141	73	40	38
P0907	723	43	87	43

[a] registries validated (may include registries for which were necessary to require information);
[b] include eliminated or discontinued registries and registries which weren't validated (lack of response, errors in registries, …)

Table 10 - Registries reviewed during 2014 (January-July)

Groups	Validated[a]	Evaluated[b]	Information request	Under Evaluation
H01	3	0	0	0
J01	11	0	2	0
P0301	6	0	0	0
P07	3	0	0	0
P08	1	0	0	0
P0901	36	10	23	10
P0902	6	4	7	4
P0903	1	0	0	0
P0904	6	1	1	1
P0905	3	0	0	0
P0906	7	0	3	0
P0907	532	23	144	23
P0908	8	1	2	1
P0909	61	6	11	6
P0910	2	0	0	0
P0912	1218	64	146	59

[a] registries validated (may include registries for which were necessary to require information);
[b] include eliminated or discontinued registries and registries which weren't validated (lack of response, errors in registries, …)

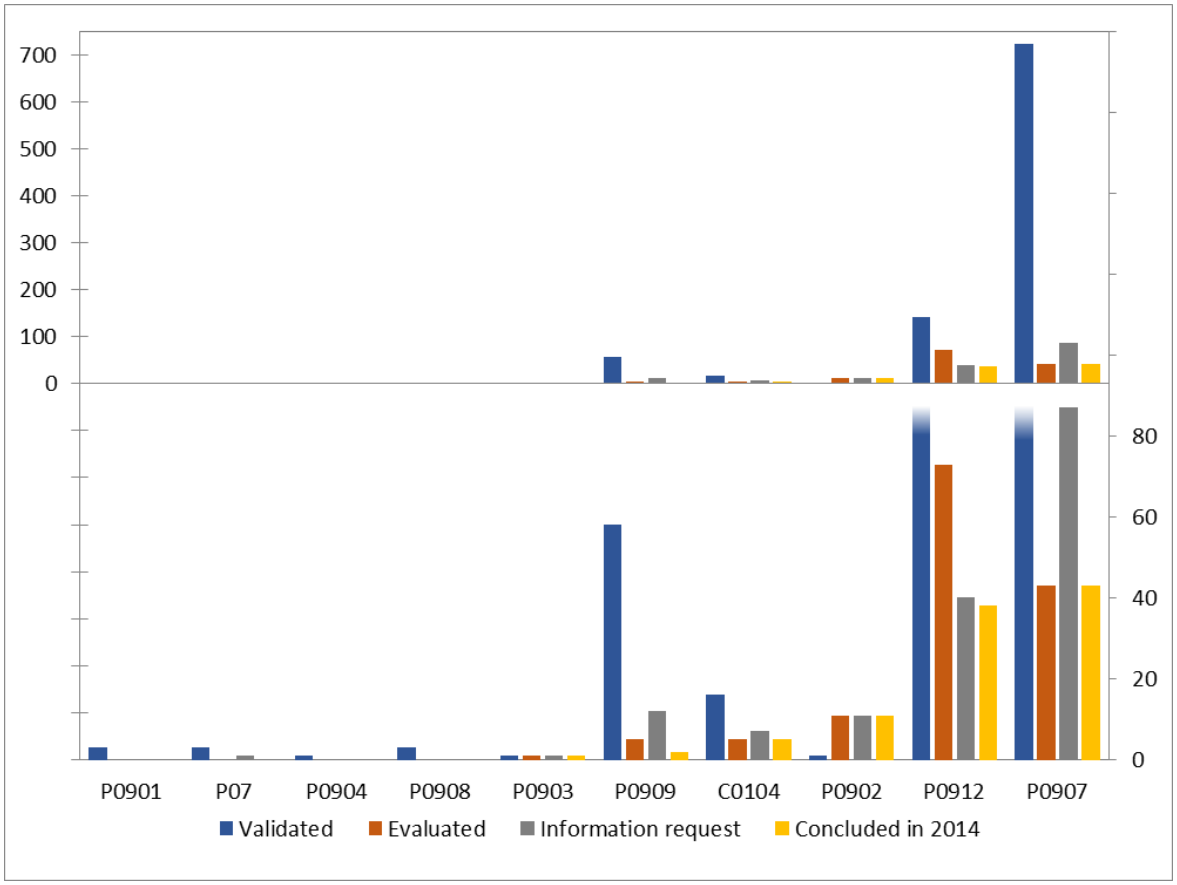

Figure 12 - Registries analysed during 2013 (see Table 9)

These numbers represent the analysed registries during the internship at INFARMED, I.P., however this does not represent the entire work made under the codification project. First they are only related to the groups I was responsible for, and even if on some groups there is a considerable amount of validated registries, the reality it there is lot of work behind these numbers.

From the first analyse of the registered information until the validation of the registry, there are exchange of information between the authority and the distributors, in the cases where there are any doubts of its conformity. This results on many registries staying on the classification of evaluated, which means the doubts where not solved but it's still working on solving them (under evaluation), or in the other hand the doubts were solved, so they were non-conforms (eliminated) or they aren't distributed anymore (discontinued).

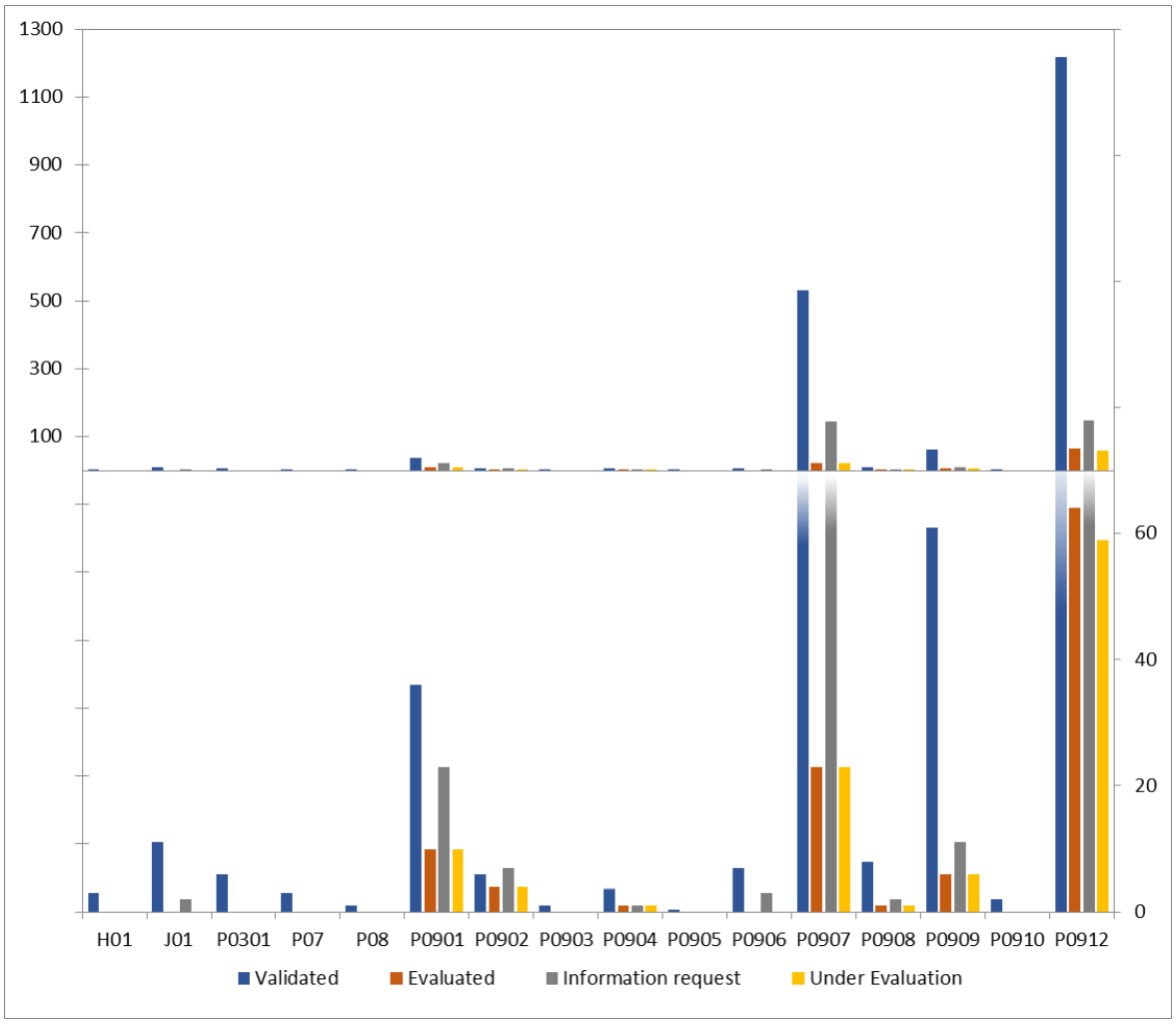

Figure 13 - Registries reviewed during 2014 (see Table 10)

The groups with the highest evaluated registries were without doubt the ones related to ostheosynthesis (P0912) and to spinal prosthesis (P0907) (see Figure 14). Both are mainly class IIb device, since they are implanted device intended to stay more than 30 days in the body, which require a mandatory NB assessment. However other class may apply, from a class I to III, depending if there is a reusable instrument (class I), or if any part is supposed to be absorbed by the human body (class III).

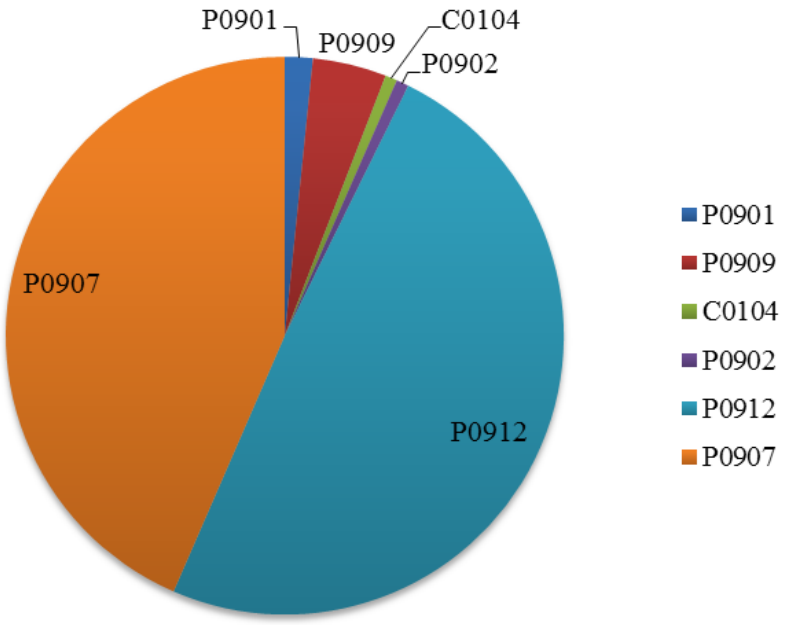

Figure 14 - Comparative representation of most evaluated groups (during all internship), see Table 8 for code group

Additionally to the validation and evaluation of registries made by distributors under the codification project, and due to the huge amount of registries there were the need for issuing Registry Declarations, as foreseen in the Order no 15371/2012 [48, 50]. These declarations are issued for a specific public tender, when the registries are already validated (regulatory validation), however it's not possible for the codification team codify the desired references in a timely way.

I had received a total of seven requests for Registry Declarations according to the Order no 15371/2012, however only two were issued. This huge difference happens due to the applicable rules, and also of the collaboration between the working teams. The first thing to do when we receive a request is to verify if the identified group of device are already under the codification project and if the group is released, if one of the principles fail, then the declaration will be not issued since it is not applicable. After this verification we check the status of the registry. Then the codification team is asked to codify the registries in a timely way. If the codification team can't codify the registries, then the declaration will be issued. In the other hand if the codification is possible then the codes will be made available for the distributor.

From the seven requests above mentioned three were related to MD which group wasn't been released until the date of internship's end, as so the Registry Declaration, according to Order no 15371/2012, does not apply.

As said this project had constitute the major part of my internship, it allowed me a full understand of the duties of the national distributors. As also providing a deep knowledge of how the platform works, regarding the notification process, and how the registries will be evaluated.

But even more important, was the understanding of the necessity of knowing the deep market that is the medical device, especially the ones operating on our national market. This knowledge and the tools that the national CA have in a distributor level, revealed a strong potential, and a useful tool for market surveillance. As well for the vigilance system, since it allow some traceability in the national cases but also the ones that came from the other European's CA.

First the obligation of the distributor to registry the device they sell, already provided some of the knowledge of which are the MDs operating in our national market, allowing a fast and efficient way for public health protection. And I'm not talking only about cases were the MD was found to be prejudicial, or the risk/benefit analysis turned negative. Since the validation of the registries is made, it's also possible the detection of nonconformity of products on the market, by safety issues, or even only by a wrong qualification.

Now with the codification project the registries are validated daily, which mean for the codified groups the registries are always up-to-date. The desk review is made daily allowing the CA to know the recent MD placed on our market. With the codification project the traceability of the MD goes even further, as it allows an easier way to know all the entities involved on the distribution of a certain MD. But since the SNS entities can only buy MD with a CDM code (when applicable), and are supposed to use this code as an internal reference, the application of the codification project will provide the traceability including on the hospital level. As said this is of great importance in cases were the Public Health, or even individual health may be compromised. Since it allows the traceability of the devices, from the health entity which used it, until the manufacturer and all the entities that are on between.

2.1.2 Registry Declaration

As foreseen in the Decree-Law no 145/2009, it's a distributor obligation to notify INFARMED, I.P. all MD that he made available in the market.[18] The way distributors have to prove they accomplish this obligation, it's by way of a Registry Declaration issued by INFARMED, I.P. (for those MD not belonging to class III, AIMD or IVD, and not yet under the codification project). Having this certificate means that their device, whose are mentioned in it, are registered and their information is valid. [46]

In order to obtain this certificate the distributor needs to request it to daps@infarmed.pt, and then it will be attributed to one of the DPS' collaborators. Due to an overwork season, it was asked to help the colleagues responsible for issuing the Registry Declarations. I end up issuing one Registry Declaration.

The issued certificate was related to 34 registries from one distributor. From that 30 registries were needed to be modified. In order to correct the registries it was needed to request information to the distributor, the first request were made in December of 2013, and the certificate were issued in February of 2014. Between the two dates, a lot of emails were exchanged and a lot of explanations were done, regarding both the registration system itself, but also the regulatory qualification and classification of the MD. This had represented my first Registry Declaration, which timelines were unusually, due the numerous stops on the clock for information requests.

The normal timelines for the issuing of the declaration is 10 working days. However the counting stops every time an information request is made in order to validate the registry or if the given information is not according to the applicable legislation. [46]

The Registry Declaration is the original way of validating the registries, as well of the SNS entities ensure that the MD are according to the law. It is supposed that this kind of declaration will ended, since the main purpose is to be able to attribute a CDM code to all MD.

2.2 Interaction between competent authorities

2.2.1 Inquiries and COEN's

Due to the free movement of goods on the European market, which MD benefits from, it's difficult to know exactly everything that is circulating on that market. Even a MD that is not usually encounter on a national level may enter the national market. In order to this free movement of goods may occur and at the same time protect the public health it's crucial that all the European's CA cooperate between them. The cooperation and the dialogue between the involved parties make possible the accurate exchange of information. Not only related to which kind of devices are on the market, but as well related to new information regarding the MD's risk.

There is two official ways of exchange information between authorities. And although I hadn't answer or elaborate any inquiry, I had the opportunity to look some, in a try to get more specific information, as also different perspectives, related to the product I was analysing at the moment. They are elaborated in cases where there are doubts on the legal qualification and/or on the risk classification of the device. The inquiries are spread between all the member states to obtain the desired information/opinion on a group of MD.

In the other hand COEN is a more specific way to exchange information between CAs. It's related to a MD or groups of devices for questions related to its conformity. I had filled out two COEN2 forms for which I did not receive the answer during my internship. One were related to claims made at the labelling and packaging of a MD which may induce in a pharmacological action, and thus the product will not been a MD. Since the manufacturer is located in another European country, INFARMED, I.P. couldn't act directly, so the solution was to communicate with the CA of that country. That situation clearly refers to the elaboration of a COEN since its specific for one product and directed to one CA for a specific issue of MD conformity.

The other COEN2 is related to shoulder resurfacing prosthesis that were classified by the manufacturer as a class IIb. However in our understanding they should belong to class III MD according to the Directive 2005/50/EC, which reclassify the shoulder joint replacements as a class III MD. After verify the documentation and the argument of the manufacturer for the attributed classification, we had decide to ask the opinion of the

national CA from which the manufacturer it's based. In this case it's not so clearly why a COEN was choose instead of an inquiry, since the inquiries are the ones used in classification issues. This is actually a controversial issue since the directive state that total joint replacement of the hip, knee and shoulder must be classified as class III. However it's still accepted some prosthesis as IIb, when manufacturer argues that they are not a total joint replacement only part of the joint, and their intended use it's only for parts of the joint. That was the main reason to use a COEN instead of an inquiry. Try to collect the opinion of the CA where the manufacturer were located, about that specific product, and not all the resurfacing prosthesis. However until the end of my internship, I didn't obtain an answer to the last COEN2 form that was sent. [53, 54]

Although the importance of the collaboration between entities represents a keypoint to the harmonisation of the market, I was unable to obtain an answer. This was one of the struggles pointed and also felted. Although the mechanisms for CA interaction exist the reality is that it takes times to obtain an answer. Additionally on the previous interactions some of the obtained answers were too evasive and not really justified. Although this represents useful tools, they aren't the more efficient ones. They limit the CA ability to respond or to obtain an answer in a reasonable time, which keeps some process to proceed further.

3 Discussion and Conclusion

During my internship a high positive interaction was present in a daily basis. I had the possibility of discuss any subject with working colleagues, this surprisingly increased the knowledge obtained in the internship, but also had allow a further understanding regarding the way of thinking in MD. Additionally the multidisciplinary team present at DPS is a plus on the MD field, since it conducts to a better discussion with different levels of knowledge and views allowing a more in deep understanding of the subject and the device. This way of working is very effective since it spread the knowledge, but also represents an extra motivation, since it allows a constant challenging of the collaborators.

Although this entire work environment that allows the easily exchange of information, the reality is that my internship was more focused on the validation of the distributor's registries. It was not possible to had work experience on the other MD's duties of DPS. I consider this as a weakness of the internship, since it didn't allow a more broad approach. Nevertheless the goals of the internship that were present at the beginning were fulfil. And even if they were not contemplating as practical issues, in the end I was still able to retain some of that information. This was provided both at the initial theorical training and as well on the thematic mornings where all the members of the team could exchange practical information, and even discuss it, with each other. These thematic mornings were done on a weekly basis, and were crucial to maintain all team members update, including on new regulatory feedback. As said I felt like been only focuses on the validation of the registries has a little limited to all we can learn related to MD, however these thematic mornings had exceed some of that limitation.

Nevertheless I recognize that on a country made mainly of distributors, the national database is of great value. It allows the knowledge of the market that can be very difficult to have, due to all the variety of the products. And this knowledge is of great importance for the protection of the public health. By knowing what is circulating on the market, INFARMED, I.P. can act much faster in cases of incidents reported outside the country or even on the ones reported here. It allows as well verifying if the product that are available to the public are in conformity, acting as a proactive measure to ensure the public health.

This was with the initial database, now with the codification project the traceability of the device and the market knowledge goes even further. First the devices belonging to a codified group are evaluated on a daily basis, which mean the conformity (desk review based on the literature provided) is checked daily. Additionally the traceability can go until the hospital level, meaning a better control in cases where it's needed. With the codification project the traceability allows an even faster action in situation where the public health is compromised, and can go as well to the level of the individual health, according to the quality of the hospital's registries.

In order to the codification project continues improving, it's very important the interaction between the two teams, codification and the regulatory team. More only than a merely interaction, it's important that the two teams are able to work together. Creating the same criteria to apply to all cases, even on the cases where a Registry Declaration is needed. During my internship the interaction between the teams were done by phone, and only for solving particular issues. For teamwork is important to increment positives interactions between the parties, ensuring that all the members are there for the same reason and that all understand the goal as only one, not like the individual perspectives of each one, even if on the practice they are doing different things. And although the two teams were working for the same final goal, there were different perspectives of what were important, and the desired outcomes, to the different team.

When I started the internship my knowledge related to MD was very limited, however as soon as I start to explore this new regulatory world, I kind of fall in love with it. I was presented with a huge variety of products and different application, which can vary between simple technologies to complex ones. Besides this huge variety, it had also allowed to understand how spread medical devices are in our daily life. MD represents a surprising amount of health solutions and we even don't totally understand the additional value of MD for public health. As said by MedTech "Medical Technologies is there throughout your life, from before you are born until the end of your life". And the reality is that even if you don't know we always use or will use a MD or even more than one. [55]

MDs are constantly evolving, changing, and challenge itself. It kind of comprises a cycle of continuous improvement, both due to technological advances and also deeper

knowledge related to Health Sciences. There are even more different types of technologies, things that in the past we didn't dream of or think they were actually a MD.

This constant evolution of the sector also brings some of the fragilities of the system to the surface. This happens mainly because what is laid down in the legislations is actually corresponding to the past knowledge and applied to a huge variety of products. Leading to a constant revision of the applied standards, which are better obtained with discussion between the different parties, the regulatory bodies and also by the manufacturers, who actually have the knowledge of the technology. However this discussion it's only possible to be done in relation to the products we already know, that are already in the market, even if before they weren't considered as MD. Additionally if we add the bureaucratic process to approve any kind of legislation to the MD market, what will happen is that what is been regulated is actually the knowledge associated to the products when the discussion started and not the ones corresponding to the newer technologies. This leads to legislations that only regulate the previous products/knowledge, the ones at the beginning of the discussion.

Although what mention above is a fragility, it also represent one big opportunity. This lack of ability to predict the products that will appear on the market, associated to the higher speed of new health technologies, only allows the discussion groups to harmonise what is already on the market. Creating a grey area where it is not possible to restrict new products to reach the market, if they fulfil the MD definition, even without having any guidance or legislation for that product. That is exactly why this market is always growing, even with all the legal requirements, there is always a space for new things, new improvements and new inventions.

In this field is extremely important, for the professional working in it, to always stay up-to-date, which is a little difficult with all the changes occurring at the technological level, but as well as in the regulatory. From new kinds of devices to new requirements, like the ones comprised on the proposal regulation that is coming, from the Unique Device Identification to the products accepted under the MD regulation that do not present a medical intended. However difficult turns on the curiosity and the challenging factor in the human being. And was exactly what the internship had done with me. It had introduced me to this regulatory framework, had made me stay focus and enthusiastic about medical devices' issues.

For all of this I can say that from my experience in the INFARMED, I.P., I brought a passion, a field in which I desire to work. As far as my knowledge allows me, MD field seems as a challenging world, which, if the professional know how to take profit from it, allows professional and personal growth.

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Annex A – IVD classification list (Annex II of Directive 98/79/EC)

(20)

ANNEX II

LIST OF DEVICES REFERRED TO IN ARTICLE 9(2) AND (3)

List A

— Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell,

— reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B

— Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd,

— reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies,

— reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis,

— reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria,

— reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia,

— reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B,

— reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA,

— reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21,

— the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

Annex B – Basic information for the Declaration of Conformity

(56)

ANNEX III

EU DECLARATION OF CONFORMITY

1. Name, registered trade name or registered trade mark of the manufacturer and, if applicable, his authorised representative, and the address of their registered place of business where they can be contacted and their location be established;

2. A statement that the declaration of conformity is issued under the sole responsibility of the manufacturer;

3. The UDI device identifier as referred to in item (i) of point (a) of Article 24(1) as soon as identification of the device that is covered by the declaration shall be based on a UDI system;

4. Product or trade name, product code, catalogue number or other unambiguous reference allowing identification and traceability of the device that is covered by the declaration (it may include a photograph, where appropriate). Except for the product or trade name, the information allowing identification and traceability may be provided by the device identifier referred to in point 3;

5. Risk class of the device in accordance with Annex VII;

6. A statement that the device that is covered by the present declaration is in conformity with this Regulation and, if applicable, with other relevant Union legislation that make provision for the issuing of a declaration of conformity;

7. References to the relevant harmonised standards or CTS used in relation to which conformity is declared;

8. Where applicable, name and identification number of the notified body, description of the conformity assessment procedure performed and identification of the certificate(s) issued;

9. Where applicable, additional information;

10. Place and date of issue, name and function of the person who signs as well as indication for and on behalf of whom he/she signs, signature.

Annex C – Minimum requirements for a EU certificate [56]

ANNEX XII

MINIMUM CONTENT OF CERTIFICATES ISSUED BY A NOTIFIED BODY

1. Name, address and identification number of the notified body;
2. name and address of the manufacturer and, if applicable, of the authorised representative;
3. unique number identifying the certificate;
4. date of issue;
5. date of expiry;
6. data needed for the identification of the device(s) or categories of devices covered by the certificate, including the intended purpose of the device(s) and the GMDN code(s) or internationally recognised nomenclature code(s);
7. if applicable, the manufacturing facilities covered by the certificate;
8. reference to this Regulation and the relevant Annex according to which the conformity assessment has been carried out;
9. examinations and tests performed, e.g. reference to relevant standards / test reports / audit report(s);
10. if applicable, reference to the relevant parts of the technical documentation or other certificates required for the placing on the market of the device(s) covered;
11. if applicable, information about the surveillance by the notified body;
12. conclusions of the notified body's assessment, examination or inspection;
13. conditions for or limitations to the validity of the certificate;
14. legally binding signature of the notified body according to the applicable national law.