UNIVERSITA' POLITECNICA DELLE MARCHE

ENGINEERING FACULTY

Master Degree in Biomedical Engineering

EUROPEAN CERTIFICATION PROCEDURES FOR MEDICAL DEVICES: TECHNICAL DOCUMENTATION FOR ANNEX XVI MEDICAL DEVICES IN RELATION TO THE NEW MEDICAL DEVICE REGULATION 2017/745

Advisor:

Prof. Laura Burattini

Candidate:

Federica Franconi

Co-Advisors:

Mauro Veroli

Andrea Santi

Academic Year: 2020/2021

Abstract

Regulation 2017/745 on medical devices (MD) upset the regulatory framework of the medical field. From 26 May 2021, when Medical Device Regulation (MDR) applied, manufacturers began the challenge to comply with the new requirements, despite having a certain period to adapt to them. MDR imposes obligations concerning the safety of MD, the risk classification procedure, the clinical evaluation, the traceability of MD, the post-market surveillance system, and many other requirements. The risk class of a MD defines the conformity assessment procedure for that device that may also involve a notified body. By the time the transitional period ends, manufacturers need to have passed the conformity assessment to place the CE marked devices on the market under Regulation 2017/745.

However, novelties have come also for manufacturers of devices without a medical purpose included in Annex XVI of MDR. These devices will have to comply with Regulation 2017/745 as soon as the regulation named Common Specifications (CS) will apply. Thus, the current work aimed to develop the technical documentation for aesthetic Annex XVI devices in view of the next certification procedure under MDR. Specifically, the documentation was produced for one laser for hair removal and two devices intended for lipolysis of the company Elits Group. The documents were developed following the Annex II of MDR, including risk management in line with ISO 14971:2019 and the clinical evaluation report.

From the results, it is possible to appreciate the main characteristics of the devices, such as the components, the principle of functioning, the technical characteristics, and several other features. They are active electrical devices driven by software and mains-operated. The laser emits light energy at 808 nm, regulated through the frequency, fluence, and pulse duration. Instead, the two devices for lipolysis act through several principles, including ultrasound, radiofrequency, mechanical pressure, light at low intensity, and electrical current. The applicators are made with materials biocompatible with human tissues according to ISO 10993-1:2018.

Regarding the risk analysis, many possible electrical, thermal, and mechanical hazards and those associated with errors of use and reduced functions were taken into account and qualitatively evaluated. When the risks were not acceptable, control measures were adopted to minimize them. These measures mainly regard the design and manufacture according to harmonized standards and the adoption of prescriptions contained in the instructions for use.
Instead, the clinical evaluation was carried out through data coming from equivalent MD from literature. The data collected provided sufficient evidence to prove that the devices under examination work efficiently and safely.

To conclude, manufacturers of Annex XVI devices are waiting for the official release of CS by the European Commission to begin the certification procedure under Regulation 2017/745. Thus, the documentation provided in this work for the aesthetic devices was an attempt to be prepared to comply with MDR in the near future.

INDEX

INTRODUCTION

The application of the New Medical Device Regulation (MDR) 2017/745 on 26 May 2021 introduced several changes compared to the previous Directive 93/42/EEC concerning medical devices (MD). The most relevant novelties brought by MDR refer to the new risk classification of MD, the Unique Device Identification (UDI) system, the registration of the economic operators to the European Database on medical devices (Eudamed), the inclusion of devices without a medical intent (devices of Annex XVI), and the need for companies to have a person in charge of regulatory affairs. Another thing to be highlighted is the establishment of Post-Market Surveillance (PMS) [1].
However, the most crucial topic remains device safety. Thus, manufacturers' production and post-production phases have to be conducted in line with the General Safety and Performance Requirements (GSPR).

For what concerns devices without a medical intent, these products have to be pursuant to Common Specifications (CS). However, at the moment, this regulation is only available as a draft since the European Commission has not released it yet [2]. But when CS will apply, MDR will also cover these devices and manufacturers will begin the conformity assessment procedure [1]. Actually, the main issue is for manufacturers of Annex XVI devices who are waiting for the CS official release.

This historical period represents a transition and manufacturers are allowed to place on the market MD compliant with the old Directive, having certificates expiring at last in 2024 [1].
Nevertheless, all manufacturers, including those of devices without a medical purpose, have started to adjust to MDR requirements. They have also begun to prepare the technical documentation related to the certification procedures under MDR to achieve the certificates and CE marking of conformity. For this reason, the current thesis aims to provide the technical documentation concerning Regulation 2017/745 [1] for aesthetic devices of Annex XVI, despite the CS have not been officially published.

CHAPTER 1
MEDICAL DEVICE REGULATION 2017/745

1.1 The application of Medical Device Regulation

Regulation 2017/745 of 5 April 2017 replaced Directive 93/42/EEC about medical devices (MDD) and Directive 90/385/EEC regulating active implantable medical devices (AIMDD) [1]. Originally, the Date Of Application (DOA) was set on 26 May 2020 (Fig. 1), delayed by one year due to Covid-19 [3].

The European Commission introduced important modifications in MDR as a consequence of MD industries and market growth in the past years. In addition, the Poly Implant Prothèse (PIP) scandal underlined the need to ensure patient safety [4]. PIP was a French company that manufactured and sold silicone breast implants. Unfortunately, lots of ruptures and complications happened due to non-compliant implants which were discovered in 2010. To overcome similar issues, the main scope of MDR became the high quality of MD and safety of patients and users [1].

The new Regulation applies to MD, implantable ones, accessories of MD, and devices with an aesthetic or any other non-medical purpose. A MD is defined as a tool, apparatus, implant, or software which can be used to diagnose, monitor, and treat diseases, injuries, or disabilities in a person. A MD may also replace or modify anatomical characteristics or physiological processes. An accessory of a MD can be used together with the MD itself to fulfil the intended purpose. Instead, an implantable device is totally introduced into the human body through surgical intervention and can be partially or totally absorbed by the human body [1].
MDR also applies to devices realized with derivatives of human tissues and cells and to products for the control and support of conception and those used for cleaning, disinfecting, and sterilizing other devices.

However, this regulation does not apply to the in vitro diagnostic MD, medicinal products, devices that administer a medicinal product, cosmetic products, food, human blood, blood products, plasma, and devices that incorporate the mentioned blood products. It neither apply to human nor animal tissues and cells. Finally, it does not apply to bacteria, fungi, and viruses [1].

Devices placed on the market under MDD/AIMDD before 26 May 2021, could still be there up to 26 May 2024. Instead, devices placed on the market after 26 May 2021 with an MDD/AIMDD certificate, could remain there until the expiry date of the certificate. The certificates released after 25 May 2017 expire at last the 27 May 2024 [1], [3], [5] (Fig. 1).

By the way, once devices comply with Regulation 2017/745, even if this happens before the end of the transitional period, they could be placed on the market with the new certificate of conformity [6].

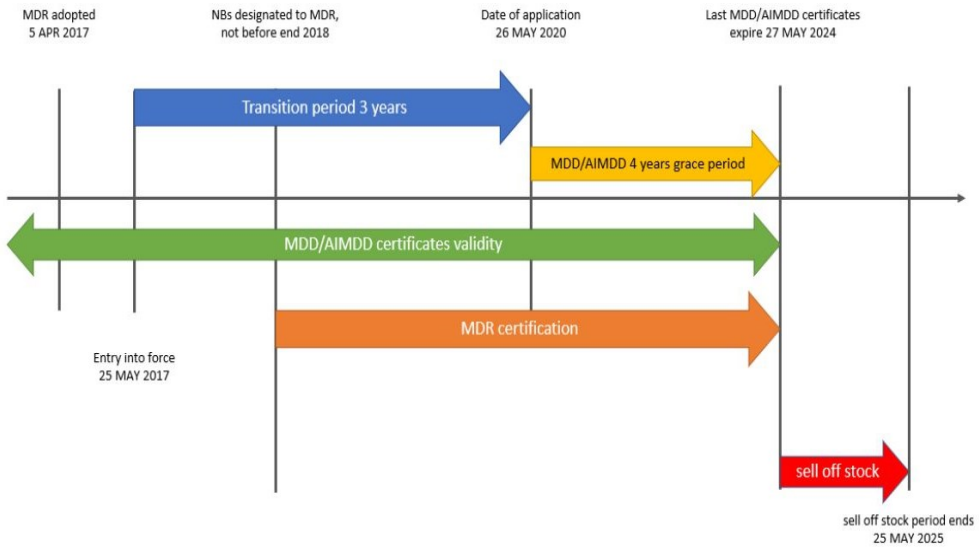


Figure 1. The figure shows the transition from MDD to MDR during the years. The date of application that is present in the figure is the old one (26 May 2020), then delayed by one year due to Covid-19 [5]. Actually, MDR applied on 26 May 2021.

1.2 Differences between MDR and MDD

After the DOA, differently from Directives, Regulation 2017/745 was accepted into all European Union (EU), without the need to be transposed into National Law. Thus, all Member States accepted the same laws, without different interpretations [7].

MDR is much more detailed compared to MDD; in fact, the first one consists of 123 articles and 17 annexes, instead, the second one contains 23 articles and 12 annexes. MDR has a wider scope because it includes implantable devices in the same legislation. Moreover, it addresses devices without a medical purpose, those for cleaning and disinfection, and diagnostic tools provided at a distance [6]. MDR also introduced a new risk classification for MD with a greater number of rules.

The most important issue of Regulation is still the quality and safety of devices that have to be maintained during their entire life cycle. For this reason, manufacturers are responsible for a PMS system in the post-production phase, proportional to the risk class of the device. Under Directives, requirements for manufacturers to report adverse events were stated in guidelines apart; instead, these statements have become part of the legal text in MDR [8]. Moreover, the need to perform a clinical evaluation is reinforced and manufacturers of devices belonging to class IIb and III shall consult expert panels for this scope.

Other changes introduced by MDR are the UDI system for the identification and traceability of devices and Eudamed. This last one incorporates several electronic systems, promotes cooperation between economic operators, notified bodies (NB), and competent authorities (CA), and provides a website accessible to everyone [1]. Another novelty is that organizations need to have a person responsible for regulatory compliance with knowledge in the medical field. This figure shall have the proper qualification or a degree in law, medicine, or engineering and also 4 years of experience in regulatory affairs or the Quality Management System (QMS) for MD [9]. More stringent rules apply to NB who need sufficient technical and

clinical knowledge to judge the clinical evaluations carried out by manufacturers. They also have the authorization to perform audits without prior notices [1].

Given the differences between MDR and MDD, the relevant parts of Regulation are explained in detail in the following sections.

1.3 Risk Classification Procedure

The risk classification procedure, which involves all the devices covered by MDR, follows the 22 classification rules of Annex VIII. Devices are divided into 4 classes: I, IIa, IIb, and III (from class I = less risky to class III = the riskiest). The classification depends on the intended purpose of the device and the risk related to the human body. The rules consider several aspects, including the type and duration of contact, invasiveness, possible energy emission (active device), and eventual local or systemic complications [10]. The duration of use is another criterium to be taken into account to identify the correct risk class of a device. This could be:

- transient: for continuous use of less than one hour;
- short term: for continuous use between one hour and one month;
- long term: for continuous use of more than one month [1].

All the rules are examined and, in case more than one apply, the device is classified in the higher risk class. The driving software is considered part of the device itself and it falls within the same class of the device. If a device is used together with another device, the classification is done separately for each one. Accessories of a MD are also classified separately from the MD under examination [10].

Classification rules

NON-INVASIVE DEVICES: Rules 1, 2, 3, 4 (Fig. 2)

Non-invasive devices in contact with intact skin belong to Class I.

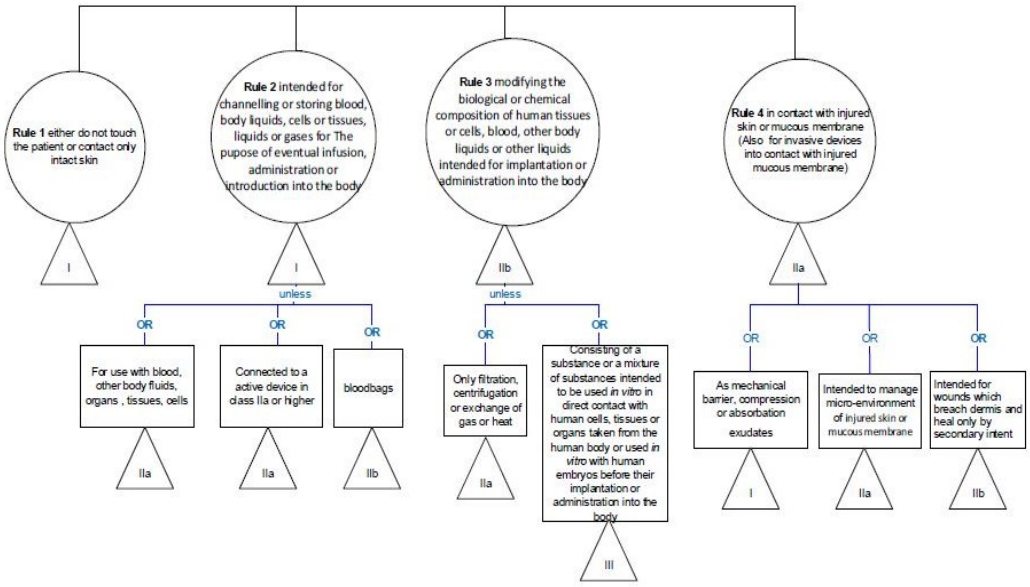


Figure 2. The figure shows the blocks containing the rules for non-invasive devices [10]. From the blocks, it is possible to see how non-invasive devices are divided into different classes.

Instead, higher risk classes are for devices containing body fluids, entering in contact with mucosal membrane or wounds, or modifying the chemical and biological composition of human cells and tissues [1].

INVASIVE DEVICES: Rules 5 (Fig. 3), 6 (Fig. 4), 7 (Fig. 5), 8 (Fig. 6)

The rules reported in Tab. 1 refer to invasive devices. Each rule addresses a different type of invasive device, but the distinct classification is determined by the device-specific scope [1].

Table 1. Rules for invasive devices [1].

Rule number	Target devices
Rule 5	Invasive devices in relation to body orifices, not used in surgery and not connected to active devices.
Rule 6	Surgically invasive devices intended for transient use.
Rule 7	Surgically invasive devices intended for short term use.
Rule 8	Implantable devices and surgically invasive devices intended for long term use.

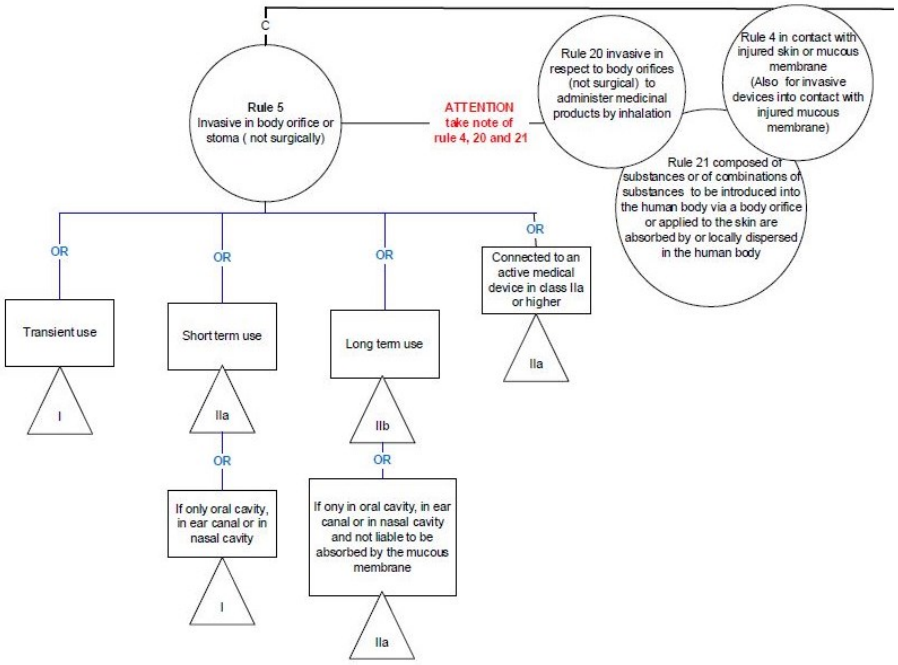


Figure 3. The figure shows the blocks containing rule 5 for invasive devices with respect to body orifices [10]. From the blocks, it is possible to see how these invasive devices are divided into different classes.

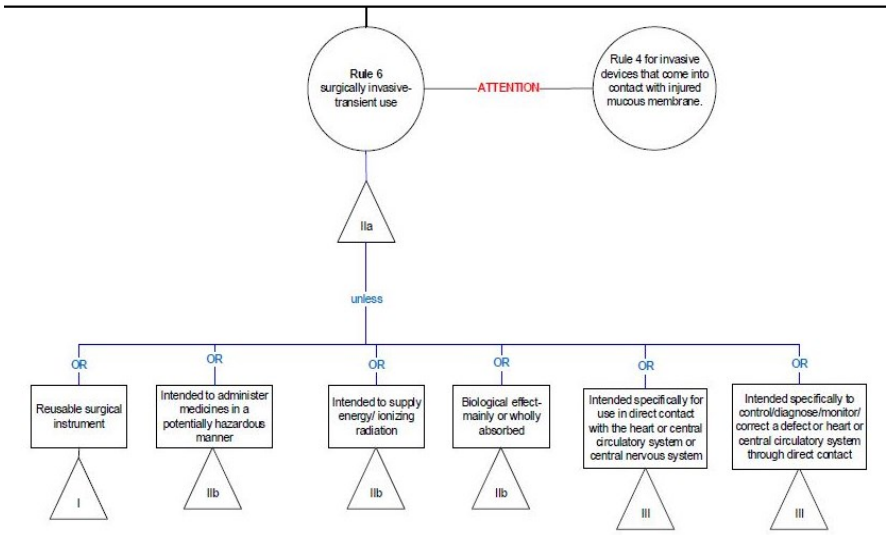


Figure 4. The figure shows the blocks containing rule 6 for surgically invasive devices for transient use [10]. From the blocks, it is possible to see how these invasive devices are divided into different classes.

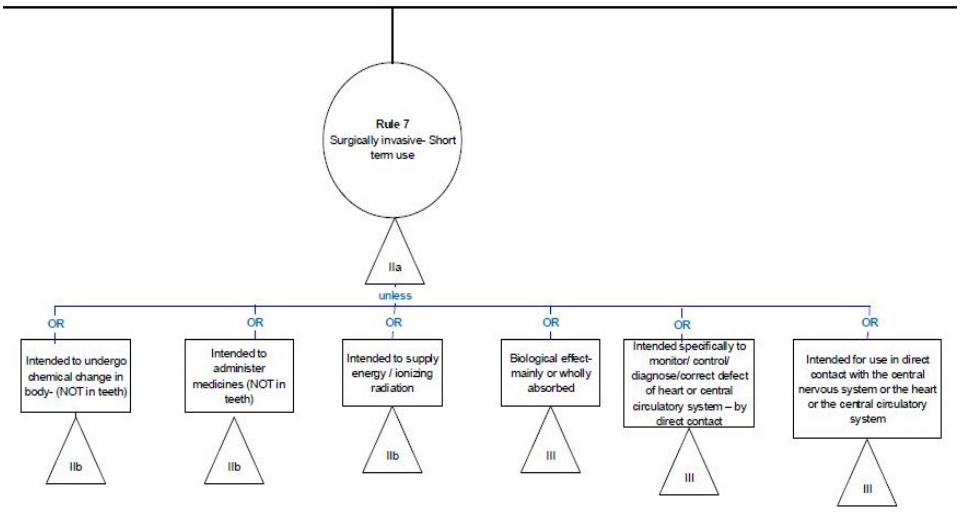


Figure 5. The figure shows the blocks containing rule 7 for surgically invasive devices for short term use [10]. From the blocks, it is possible to see how these invasive devices are divided into different classes.

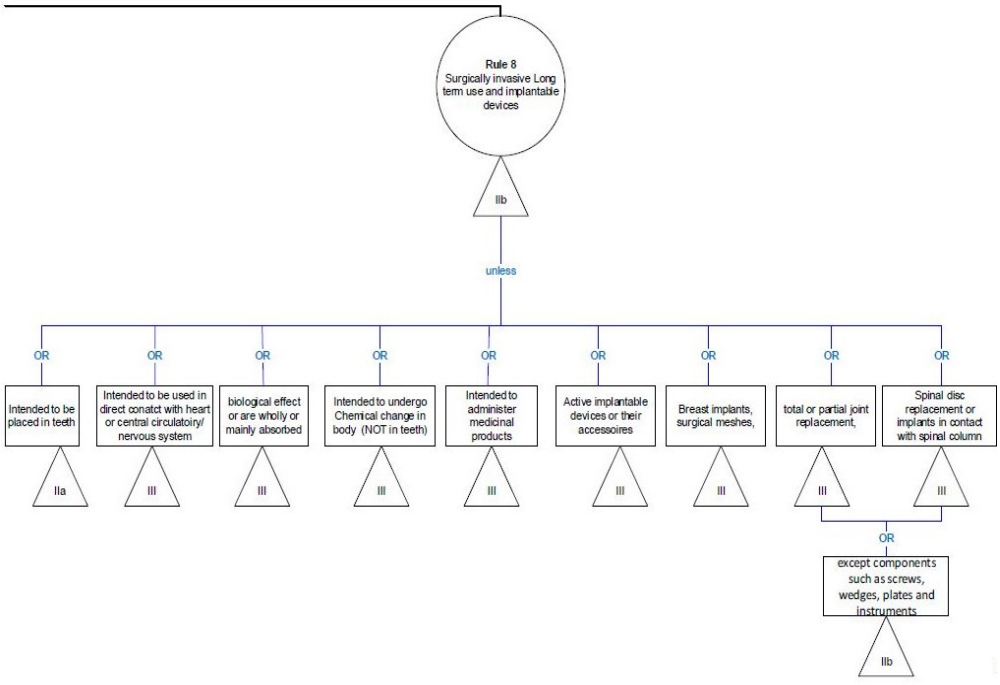


Figure 6. The figure shows the blocks containing rule 8 for surgically invasive devices for long term use and implantable devices [10]. From the blocks, it is possible to see how these invasive and implantable devices are divided into different classes.

ACTIVE DEVICES: Rules 9, 10 (Fig. 7), 11, 12, 13 (Fig. 8)

Active therapeutic devices which replace a function or a biological structure or treat a disease belong to class IIa. Active devices are also classified into class IIa when they make a diagnosis or administer medicinal products.
Instead, they belong to class IIb in case all the previous functions are performed in emergencies or in circumstances where the devices exchange energy in a hazardous way [1].

Also the software used to make diagnosis falls within class IIa or higher classes of risk, depending on the situation [1].

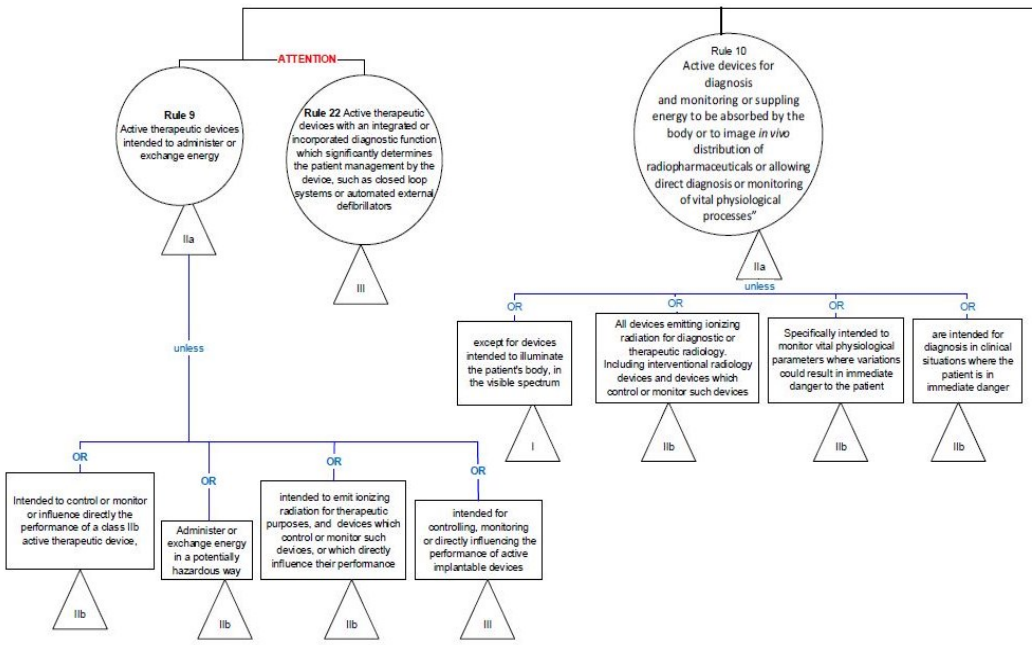


Figure 7. The figure shows the blocks containing rules 9 and 10 for active devices [10]. From the blocks, it is possible to see how these active devices are divided into different classes.

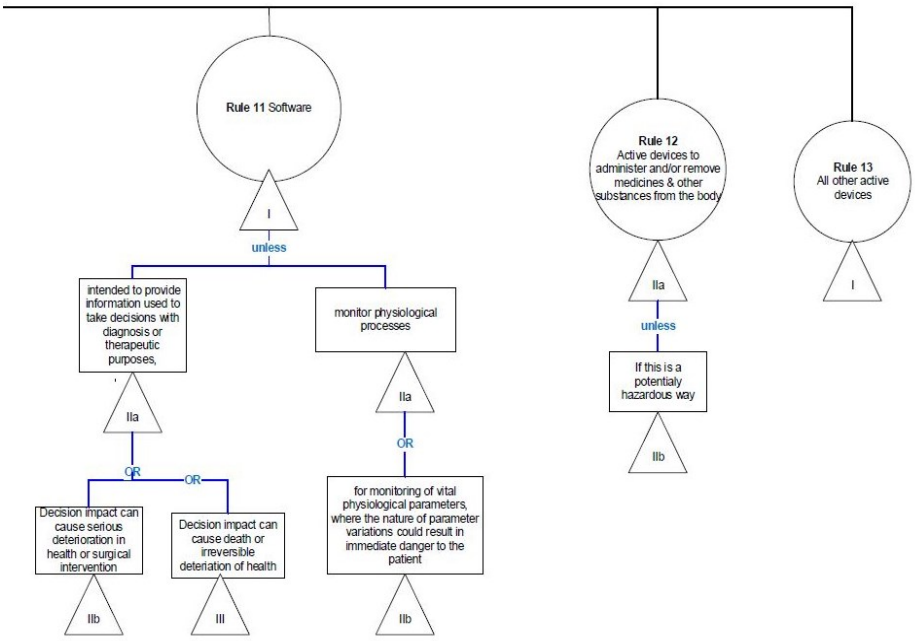


Figure 8. The figure shows the blocks containing rules 11, 12, and 13 for active devices [10]. From the blocks, it is possible to see how these active devices are divided into different classes.

SPECIAL RULES: Rules 14, 15, 16, 17, 18 (Fig. 9), 19, 20, 21, 22 (Fig. 10)

The special rules are reported in Tab. 2. Each one addresses a different type of device with particular characteristics.

Table 2. Special rules for medical devices [1].

Rule number	Target devices
Rule 14	Devices containing a substance that can be considered a medicinal product.
Rule 15	Devices for contraception.
Rule 16	Devices used for cleaning, disinfection, and sterilization of other devices.
Rule 17	Devices that record diagnostic images through X-rays.
Rule 18	Devices manufactured with cells or tissues of human and animal origin, non-viable or made non-viable.
Rule 19	Devices consisting of nanomaterials.
Rule 20	Invasive devices with respect to body orifices (not used for surgery) that administer medicinal products.
Rule 21	Devices made of substances that are introduced into the human body or applied on the skin and absorbed within the body.
Rule 22	Active therapeutic devices with a diagnostic function which is crucial for patient management.

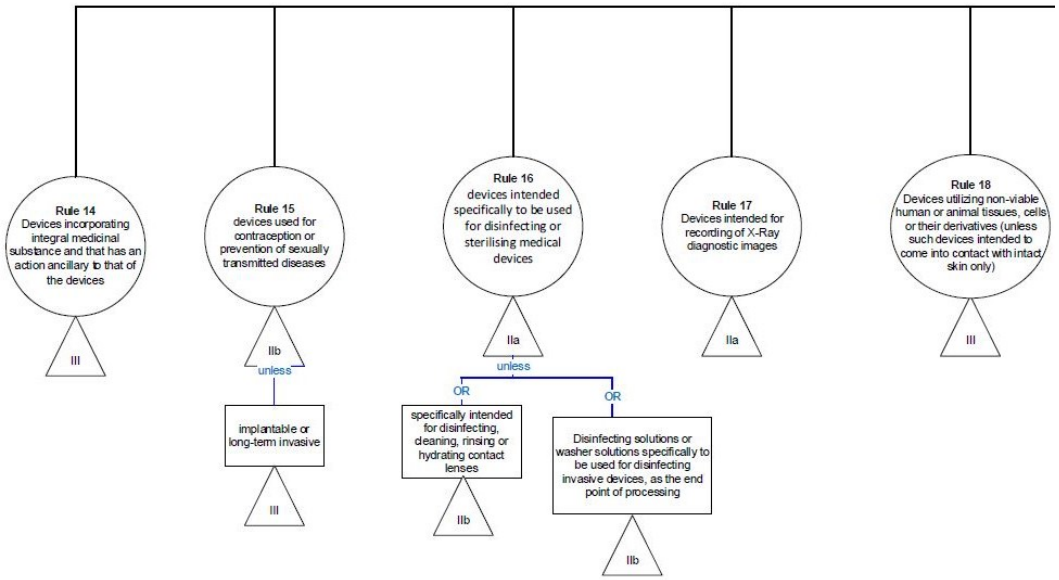


Figure 9. The figure shows the blocks containing special rules number 14, 15, 16, 17, and 18 [10]. From the blocks, it is possible to see how medical devices are divided into different classes.

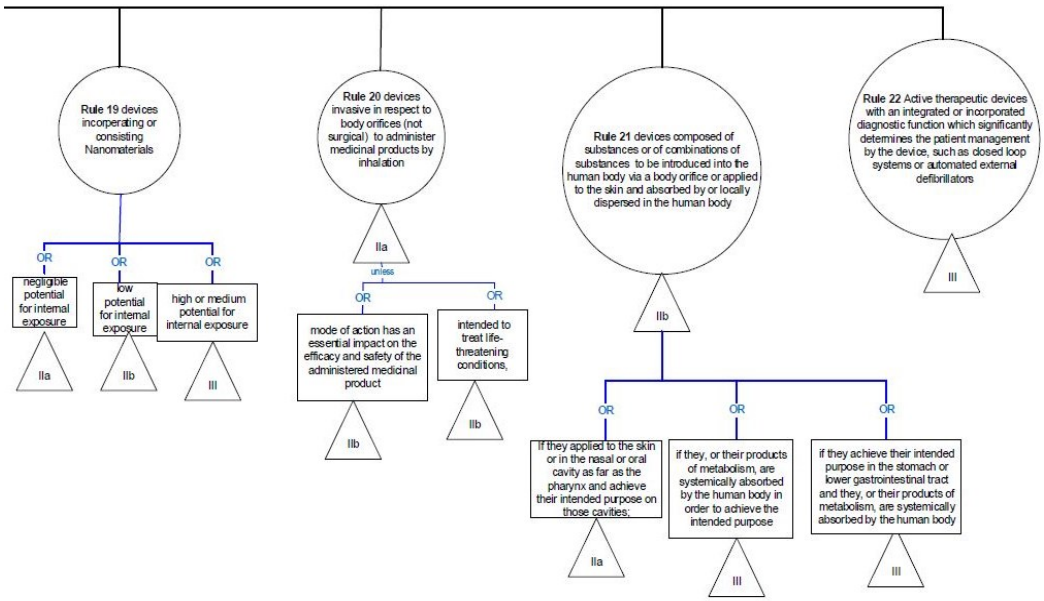


Figure 10. The figure shows the blocks containing special rules number 19, 20, 21, and 22 [10]. From the blocks, it is possible to see how medical devices are divided into different classes.

1.4 Identification and Traceability of Medical Devices

1.4.1 Unique Device Identification

A breakthrough brought by MDR is the Unique Device Identification (UDI) system, which allows the unique identification of devices placed on the market, except custom-made and investigational ones. The UDI is a code that consists of several numeric or alphanumeric characters and it is composed of two parts: the UDI-DI, identifying the device with its manufacturers and the UDI-PI related to the production unit (Fig. 11). It is affixed by manufacturers on the labels and packaging and represents an additional element with respect to the labels and CE marking [1]. The UDI, which is assigned by legal figures nominated by the Commission, is crucial for the device traceability and to avoid its falsification. Any time there is a relevant modification in the device, the UDI changes as well [1].

The UDIs are recorded by manufacturers inside the UDI database and anyone could have access to it [1]. The UDI-DI is the key element used to find one device inside the database. This last one is part of Eudamed together with other electronic systems. Even though a device is not placed on the market anymore, its UDI could still be found inside the database [1].

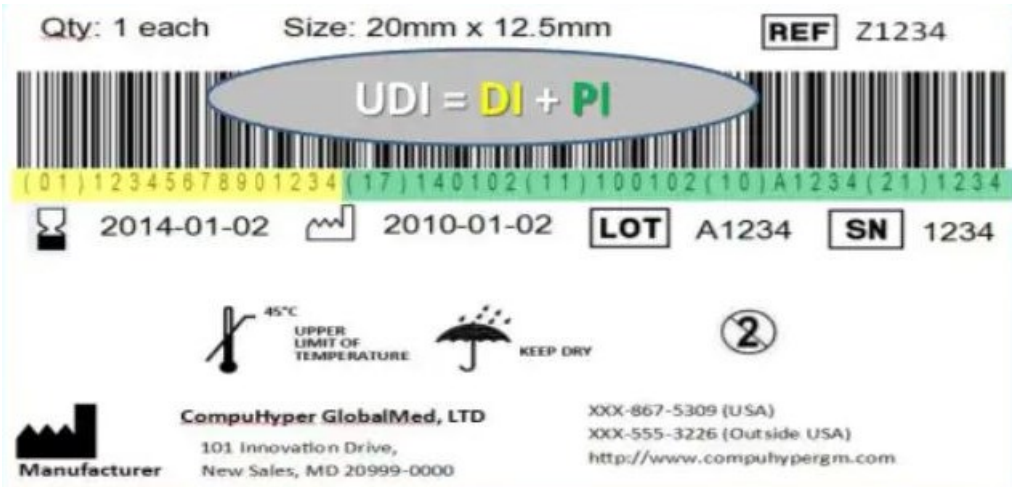


Figure 11. The figure shows an example of a UDI placed on the label of a device. It consists of a UDI-DI + UDI-PI.

1.4.2 European Database on Medical Devices

The European Database on Medical Devices, named Eudamed, has been set up to support the traceability of MD. The European Commission is working to turn over Eudamed fully operative in 2023. Eudamed acts as a registration and notification system, allowing multiple parts to cooperate. It incorporates several electronic systems, including the registration of economic operators (manufacturers, authorized representatives, and importers), the registration of MD with their UDIs, and the electronic system related to NB (Fig. 12) [1]. This last one shall contain information concerning the different conformity assessment procedures, information about NB themselves and certificates of conformity. Also, the electronic system of clinical investigation and PMS are part of Eudamed to let anyone know about incidents connected to MD use (Fig. 12) [11].

Eudamed consists of two parts: the restricted website accessed by the authors of MDR, who are responsible for any kind of data stored there and the public website accessible by any user to get information related to any MD in the EU market (Fig. 12) [11].

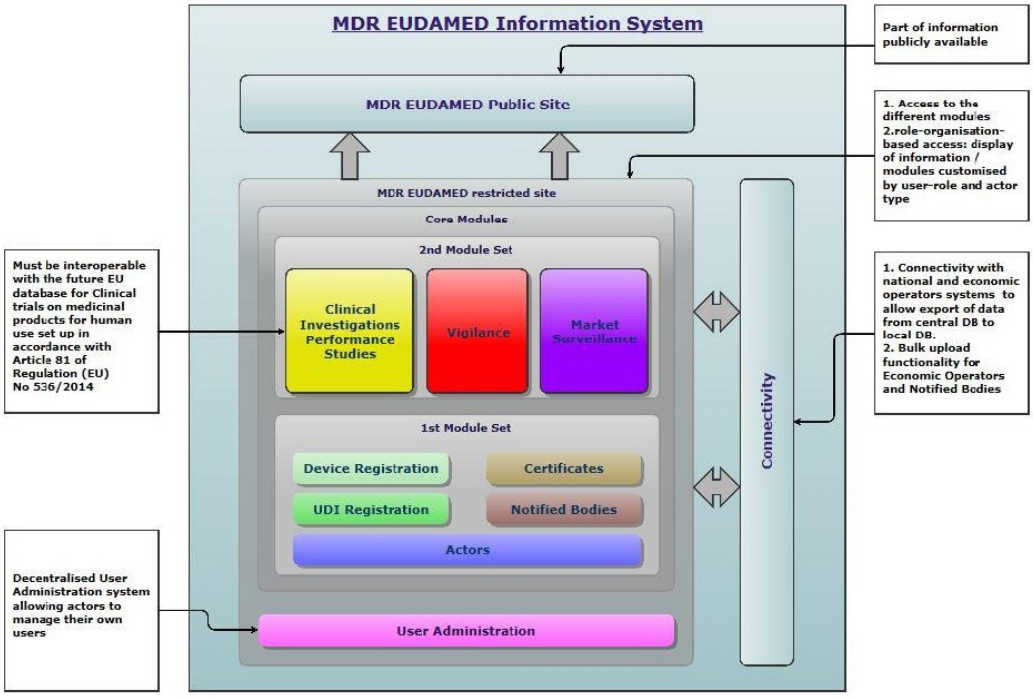


Figure 12. Eudamed database with its electronic systems and stakeholders [11].

By the time Eudamed will achieve its full functionality, the European Commission will have to handle and maintain it. In the meantime, all the actors are allowed to register voluntarily to Eudamed through the submission of the proper forms. People who make this registration are responsible for the data transmission and update [1].

1.5 General Safety and Performance Requirements

Both MD and those with a non-medical purpose achieve compliance with MDR when they are pursuant to the GSPR of Annex I. The majority of GSPR apply to all the devices whereas some dispositions are specific for certain categories of devices, such as active ones, implantable ones, devices with a diagnostic function, or sterile ones. The requirements stay how manufacturers have to carry out manufacturing and production of devices to guarantee the safety of patients and users during normal conditions of use. Moreover, they underline that devices have to fulfil their intended purpose safely without compromising the health status of the mentioned groups of people (clinical evaluation). These requirements are also in line with the harmonized standards and guidelines that manufacturers follow during the production phase [1].

To fulfil these requirements, several features of devices are analyzed and tested. Stringent rules apply to chemical, physical, and biological characteristics of the materials, which have to satisfy the compatibility with body tissues, body liquids, and cells. The biocompatibility aspect has to be in line with ISO 10993-1:2018 concerning biological evaluation [12]. Also, residues and contaminants released by the devices have to be taken into account. Moreover, manufacturers have to consider possible medicines and substances that could be introduced into the human body, as well as the presence of substances considered carcinogenic, mutagenic, or toxic to reproduction (CMR) and endocrine-disrupting (ED). Manufacturers shall also examine if the materials are of biological origin and the eventual presence of nanoparticles [1], [12].

Furthermore, all possible risks associated with the device need to be reduced (risk management) following harmonized standards, including the minimization of

electrical, mechanical, and thermal risks. Also unintended exposure of patients and users to radiations have to be minimized. In addition, the devices' interference with other equipment and the environment has to be avoided [1].

GSPR also contain prescriptions for labels and instructions for use (IFU). Labels have to be written in a human-readable way but they could also contain bar codes. They have to provide the essential information to identify the device and its manufacturers. Also, standard symbols to warn about possible hazards are shown on the labels. Indications have to be reported in case the device incorporates tissues or cells of human origin and their derivatives, blood, plasma, or medicinal products. For what concerns the IFU, they contain the same information present on the label, together with additional information for the users, such as indications about suitable environmental conditions to use, store, and transport the device. The IFU also provide contraindications and side-effects associated with device use. They also contain a description of the device with its functional elements and indications about the installation and replacement of some components. Moreover, the IFU provide indications about procedures to be performed before using the device, including its calibration, cleaning, and sterilization [1].

Considering the need to comply with GSPR, manufacturers have to include the demonstration of device conformity with these requirements in the technical documentation related to Annex II [1].

1.6 Clinical Evaluation and Clinical Investigation

Clinical evaluation and clinical investigation refer to two different processes, despite achieving the same scope.

- Clinical evaluation is the procedure of collecting and analyzing clinical data of the device under examination to ensure its safety and performance (Fig. 13). The amount of data needed depends on the intended purpose of the device and its risk class [13].

- ❖ Clinical investigation is a procedure performed for the same purpose of the clinical evaluation (to demonstrate the safety and performance of a device), but this involves one or a group of human subjects [7].

Clinical benefits (Fig. 13) and minimized side-effects have to be demonstrated through data coming from the clinical investigation of the device under study, clinical investigations or literature studies regarding an equivalent MD, and/or PMS [1]. The manufacturers decide the level of clinical evidence needed to demonstrate the clinical benefits, depending on the risk class and category of the device. For what concerns products with a non-medical purpose, clinical benefits are intended as device performance (Fig. 13).

The clinical evaluation may be performed for all the devices. It needs to be planned and well documented with documents regularly updated. The manufacturers have to provide a clinical evaluation report (CER) for each device, except for a custom-made one. An expert panel may be consulted to take decisions upon higher risk class devices [13]. Instead, clinical investigations are performed for implantable and class III devices, for which also a summary of safety and clinical performance has to be produced [1].

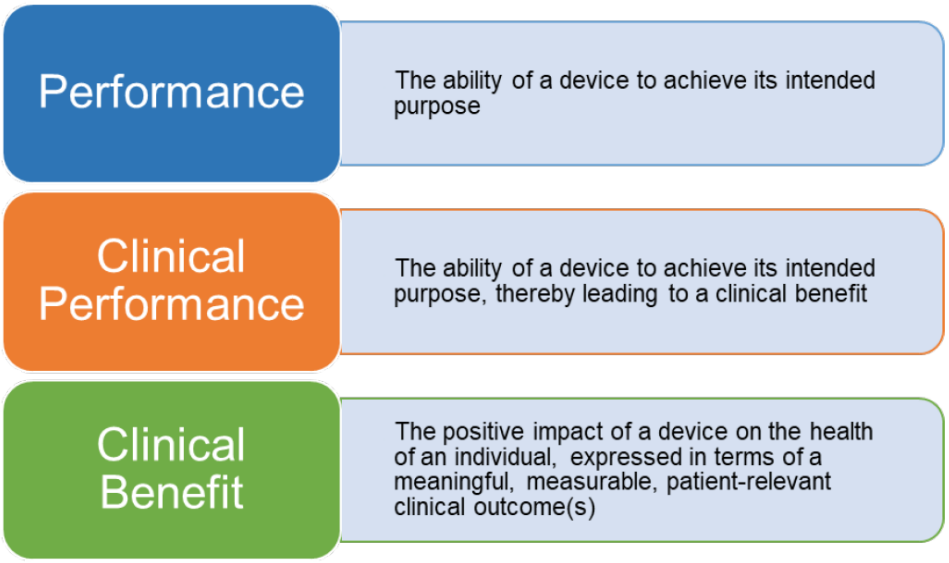


Figure 13. Definitions concerning concepts related to the clinical evaluation and investigation. Despite the names being similar, they are different procedures [7].

For all the other devices, any time a manufacturer is able to demonstrate that his device is equivalent to another already CE marked and compliant with MDR, he does not have to carry out the clinical investigation [1].

Even if a clinical evaluation has to satisfy a lot of stringent requirements, a clinical investigation is a more sensitive issue because it is subjected to a scientific and ethical review. The people who conduct the investigation have the proper technical and clinical knowledge. Regarding the subjects involved in the clinical investigation, they have to sign a written informed consent. Moreover, the clinical investigation requires a sponsor for its financing, who is also responsible for the regulatory pathway to be followed. The sponsor submits an application to the Member State where the investigation takes place and he reports any adverse event or device deficiency encountered during the examination. To facilitate the exchange of information, a dedicated electronic system was set up in Eudamed [1].

1.7 Post-market Surveillance and Vigilance Requirements

PMS indicates all the actions carried out by manufacturers to gather information from the use of devices already on the market and, in case of a defect or malfunction, they immediately implement corrective actions. This procedure is different from market surveillance which refers to the tasks performed by CA to check that the device maintains compliance with MDR requirements [9].

PMS is part of the QMS whose characteristics are determined by the risk class and type of device. PMS has to be set up and preserved for each device to ensure its quality, performance, and safety. It consists of proactive and reactive actions: on one hand, proactive activities are needed to foresee adverse events before they could happen and to implement preventive actions; on the other hand, reactive actions are applied as a consequence of any incident [9]. An incident refers to any deterioration or malfunction of the device parts and efficiency, whereas a serious incident leads to the worsening of a person health status and even to death [1].

Moreover, PMS is interconnected with other systems, like the vigilance one. This is part of Eudamed and allows exchanging information about serious incidents and corrective actions. PMS reports, concerning devices of class I, are data summaries coming from PMS, and they are available in the electronic vigilance system. Instead, the Periodic Safety Update Reports (PSURs) is compiled for higher risk class devices [1].

The information collected through PMS comes from several sources, such as serious incidents and complaints from patients, users, and economic operators. This information is used for different purposes:

- to correct device design and manufacturing;
- to modify IFU and labels;
- to update the CER;
- to conduct the risk analysis;
- to implement corrective actions;
- to monitor incidents [9].

1.8 Devices of Annex XVI

The European Commission will shortly release CS for devices without an intended medical purpose. By the time CS will apply, also devices with an aesthetic or any other non-medical purpose will be covered by MDR [2]. This is a great novelty for these devices because they have always been subjected to less stringent rules compared to MD. For instance, in Italy, aesthetic devices followed predispositions from the ministerial decree number 206 of October 2015, according to which aesthetic electromechanical devices could not exceed certain limited ranges of values [14].

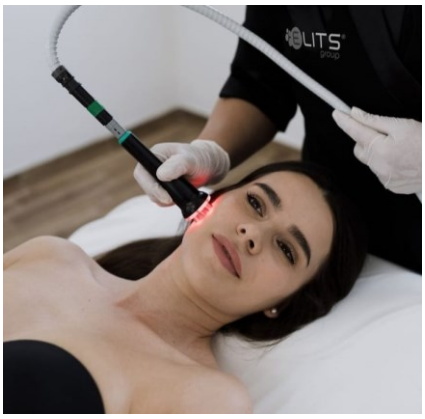
Devices without a medical purpose are listed in Annex XVI of MDR and they are:

- contact lenses;
- products introduced into the human body to fix body parts (tattoos and piercings are excluded);

- substances or items for facial, dermal, and mucous membrane filling;
- equipment emitting electromagnetic radiation for different kinds of skin treatments (Fig. 14), such as hair removal and skin rejuvenation (sunbeds are excluded);
- equipment for lipolysis or lipoplasty (Fig. 15);
- equipment for brain stimulation in which electrical and electromagnetic currents penetrate the cranium (invasive devices are excluded) [1].

At the moment, a draft of CS is available to be consulted and it consists of a general part + one general annex about risk management + 6 annexes describing the technical characteristics for each group of devices [2].

a



b

Figure 14. Equipment emitting visible light for different kinds of skin treatment. 14a. A laser for hair removal. 14b. Red light-emitting equipment can be used in case of acne problems.

Figure 15. The figure shows the applied parts intended for adipose tissue removal.

CS might be published in the Official Journal of the EU in the first half of 2022. This regulation will apply six months after they enter into force the twentieth day after the official publication [2]. However, manufacturers of Annex XVI devices are preparing for the novelties. In fact, these devices will be subjected to the same requirements and legal dispositions concerning the certification procedures as all the MD. Thus, manufacturers have to:

- set up and control a QMS;
- comply with GSPR;
- prepare the technical documentation according to Annex II and III;
- classify their devices according to the New Risk Classification;
- meet the UDI and Eudamed requirements;
- conduct the clinical evaluation or the clinical investigation to support device safety and efficiency;
- perform and document risk management according to the general requirements of Annex I;
- be in charge of the PMS system [1].

In case a NB will be involved in the conformity assessment or the device will be subjected to a clinical investigation, manufacturers shall have more time to comply with the new requirements. However, in the first case, by 3 months after CS application, a written agreement has to be signed by both manufacturers and the NB; in the other case, by 6 months after CS application, the sponsor has to apply for the clinical investigation [2].

The task force that is developing CS is also discussing the classification of active devices with a non-medical purpose because some classification rules are still ambiguous for Annex XVI devices. Definitely, the key issue will be the official publication of CS, which might present some differences compared to the draft version. Certainly, the introduction of CS will bring a lot of changes for the manufacturers of Annex XVI devices.

CHAPTER 2
SOCIAL ENVIRONMENT AROUND MDR

2.1 Economic Operators

2.1.1 Manufacturers

Manufacturers inside the EU

Manufacturers are the first responsible for MD safety. They have to care about the design and production of their device before placing it on the market, but they have to check its quality also in the post-production phase through the PMS system. Starting from the production phase, the manufacture has to be done in line with GSPR. For this purpose, manufacturers need to prove that their device is compliant with harmonized standards and they carry out a clinical evaluation to confirm its safety and performance. In addition, they generate the technical documentation for each device and update it through data collected from the post-production phase. Before they place a device on the market, after its conformity assessment, they need to prepare the EU declaration of conformity and put the CE marking of conformity on the device. They also set up and preserve a QMS which is interconnected with risk management and they establish a system to monitor incidents and apply corrective actions. Regarding this issue, any subject who experiences an injury or health's deterioration shall ask for compensation; thus, manufacturers need to have the proper financing suitable for the risk class of their device [1].

Other obligations imposed by MDR to manufacturers are related to the UDI system, the registration to Eudamed, and the support provided by a person in charge of regulatory affairs [1].

Manufacturers outside the EU

If manufacturers are outside the EU, they appoint an authorized representative to commercialise a device in the EU. This figure is legally liable for an eventual unconformity of the device placed in the market of a Member State. The tasks of the authorized representative are decided with the manufacturers and documented

in the mandate. The duties concern checking the technical documentation, the certificates of conformity, the EU declaration of conformity, and the registration to Eudamed. Moreover, he cooperates with CA to ensure device safety.
Manufacturers can change the authorized representative. In this case, the terms of the cessation of the outgoing representative's mandate are agreed upon with the manufacturers [1].

2.1.2 Importers and Distributors

Importers are the figures who place a device coming from a third country on the EU market.
Distributors are the figures distributing a product from manufacturers inside the EU on the EU market.

Importers and distributors perform similar tasks. They are responsible for checking that the device is in line with the dispositions concerning the EU conformity assessment procedures, including the EU declaration of conformity, the CE marking, the UDI, and the registration of the device. Moreover, they verify that the information associated with the devices, such as the trade name, the labels, and the IFU, respect the requirements of MDR. They report incidents to the manufacturers and the authorized representative and work with them to adopt solutions to minimize any device risk.
In addition, importers, not distributors, have to register to Eudamed together with manufacturers and authorized representatives [1].

Sometimes obligations for the manufacturers apply to importers and distributors. This happens when importers or distributors:

- place a product on the market with their name;
- change the intended purpose of a device already on the market;
- modify some characteristics of the device so that its compliance has to be proved again [1].

2.2 Medical Device Coordination Group

The Medical Device Coordination Group (MDCG) consists of people designated by the Member States. The members of MDCG cover their role for three years, then the designation has to be renewed. Each Member State can appoint one member and an alternate with the proper knowledge in the MD field and the same two figures for the in vitro diagnostic MD. The tasks of the MDCG include:

- the assessment of the NB who did application;
- the development of standards or CS related to MD;
- possible modifications to the general requirements;
- collaboration with the CA in important decisions, such as classification, clinical investigation, vigilance, and PMS;
- advisory activity about Regulation 2017/745 [1].

Upon Commission or Member States' request, the members of the MDCG meet to discuss. Also, other experts can take part in these meetings. Decisions are taken with consensus or the majority decides [1].

2.3 Notified Bodies

A NB is a figure designated by a Member State for a particular conformity assessment activity and category of device. For each figure, the Member State has to designate an authority responsible for the NB [1].

The NB applies to the authorities responsible for them, specifying the activities they would like to perform and the devices they would like to work with. This application is checked by those authorities together with the joint assessment team, appointed by the Commission and the MDCG and composed of experts for this assessment. The NB will have time to apply corrective actions in case of non-conformities. Once the application's compliance is confirmed, an electronic notification regarding the NB's designation is sent by the Member State. Each NB receives also an identification number. The designation becomes valid the day after

the notification when the NB shall begin to perform their conformity assessment activity. After the designation, the NB have to continue to fulfil obligations of MDR and, once a year, the authorities have to re-assess the compliance with Regulation. Moreover, the authorities could check the appropriateness of the conformity assessment activity performed by the NB [1].

It is requested that NB are not involved in designing, manufacturing, or other activities linked to the device production. They need to have the proper competent personnel to perform the multiple functions of the conformity assessment procedures, such as audits, product testing, clinical evaluation, technical documentation review, and issues regarding biocompatibility and sterilization. The NB need also to have the proper financing to carry out the conformity assessment activities. [1].

It is interesting to stress that before 2012, under Directive 93/42/ECC, there were more than 90 NB designated for the EU conformity assessment procedures. At the moment, only 27 NB in the EU have the designation under Regulation 2017/745 (Tab. 3) [15].
Out of the 27 already designated, there are still around 50 NB who have applied for the designation.

Table 3. List of designated notified bodies under Regulation 2017/745 [15].

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 0546	CERTIQUALITY S.r.l.	Italy
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 2460	DNV Product Assurance AS	Norway
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 0537	Eurofins Expert Services Oy	Finland
NB 0477	Eurofins Product Testing Italy S.r.l.	Italy
NB 0459	GMED SAS	France
NB 0051	IMQ Istututo Italiano del Marchio di Qualità S.P.A.	Italy
NB 0373	Istituto Superiore di Sanità	Italy
NB 0426	ITALCERT SRL	Italy
NB 2862	Intertek Medical Notified Body AB	Sweden
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 1912	Kiwa Dare B.V.	Netherlands

NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 1639	SGS Belgium NV	Belgium
NB 0598 (ex-0403)	SGS FIMKO OY	Finland
NB 1936	TUV Rheinland Italia SRL	Italy
NB 0044	TÜV NORD CERT GmbH	Germany
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany
NB 2696	UDEM Adriatic d.o.o.	Croatia

NB= notified body.

2.4 Expert Panels

Given all the requirements and tests to be performed to pass conformity, manufacturers and NB may need advice about product testing, clinical evaluation, or any other issue related to MD. Thus, the Commission can nominate members to form expert panels to provide advice for specific groups of devices. These members have the needed know-how to provide the support needed. The Commission shall also designate expert laboratories to carry out tests regarding physicochemical characterization, biocompatibility, or other tests [1].

Both expert panels and laboratories may contribute:

- to support clinical evaluation and conformity assessment activities;
- to identify emerging problems related to MD;
- to develop guidelines about critical procedures [1].

Considering the issues related to MDR, such as clinical evaluation, biocompatibility, and special categories of MD, the Commission is in favour of this type of consultancy [1].

CHAPTER 3
EUROPEAN CERTIFICATION PROCEDURES

3.1 From Device Manufacturing to CE Marking

The following scheme (Fig. 16) shows the pathway from device manufacturing to its placing on the market.

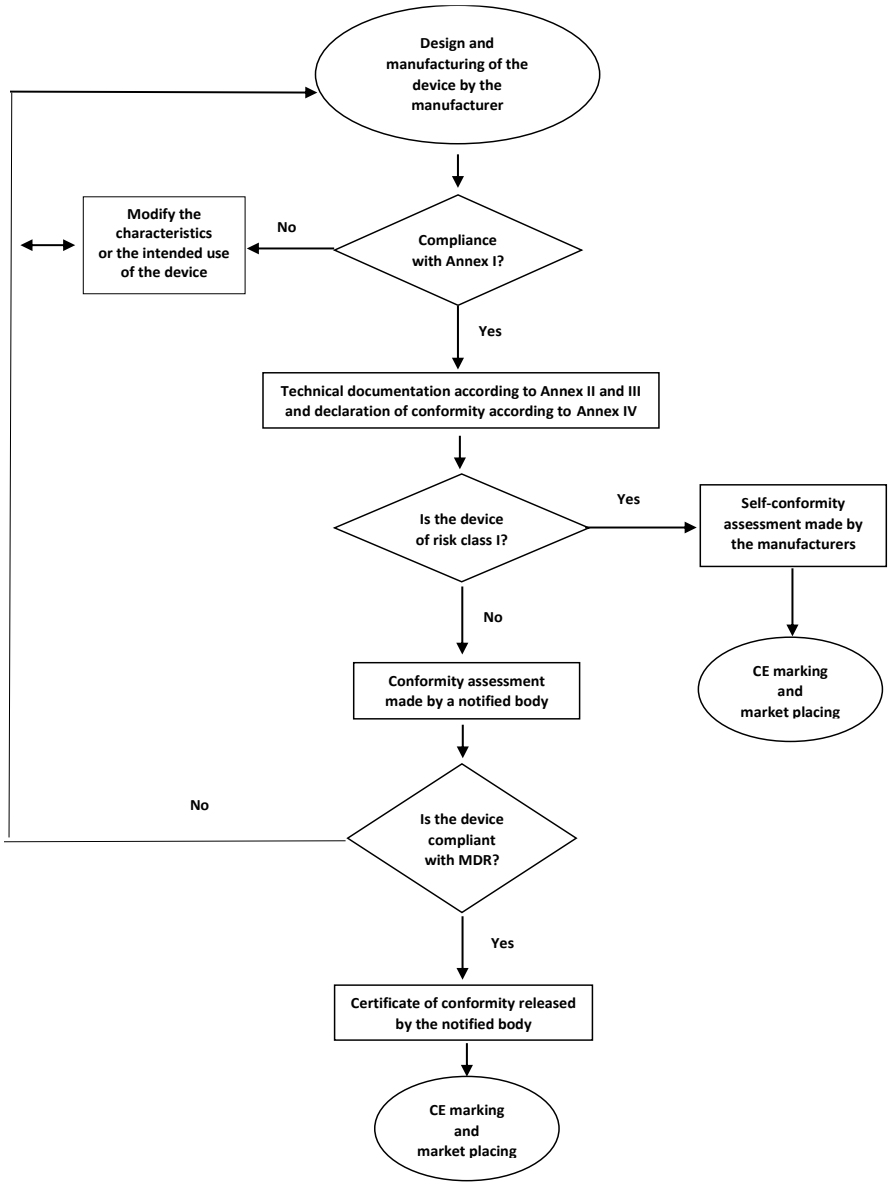


Figure 16. The scheme shows the European Certification procedure from the design and manufacturing of the device to its placing on the Market, passing through the conformity assessment.

As the scheme shows (Fig. 16), the pathway to get to the EU market starts from the production phase. After the design and manufacturing of the device following GSPR, manufacturers carry out tests, based on harmonized standards, to prove the device safety. The number and type of tests depend on the risk class of the device and its intended use. The higher the risk class of the device, the more complicated tests have to be performed. Among them, there are those regarding electrical safety and biocompatibility of materials in contact with human tissues. The manufacturers have also to carry out a clinical evaluation or a clinical investigation to demonstrate that the device's clinical benefits overcome possible harmful situations and side effects [13]. To comply with GSPR, manufacturers also implement risk management to analyze all possible hazards and adopt control measures to make risks acceptable.

Once the compliance with GSPR has been proved, manufacturers prepare the technical documentation for each device according to Annex II and III and the EU declaration of conformity. If the device belongs to risk class I, they simply make a self-conformity assessment, declaring that their device is in line with MDR requirements, put the CE marking on the device, and place it on the market. Instead, if the device falls within class IIa, IIb, or III, the conformity assessment involves a NB and takes a longer time. In this case, the procedure is based on the evaluation of the QMS and technical documentation. If the NB declares the non-conformity of the device, manufacturers have to make corrections or modify the intended use. Once the conformity assessment is passed, the NB releases the certificate of conformity and the manufacturers, after affixing the CE marking, can place the device on the market [1].

Despite not being reported, after the last block in Fig. 16, there is the PMS system that guarantees device safety after the commercialization. Any time a serious incident verifies, manufacturers apply corrective actions. In the worst case, the withdrawal of the device with non-conformities is possible, until it complies again with Regulation 2017/745 [9].

3.2 EU Declaration of Conformity

The EU declaration of conformity, written and signed by the manufacturer, is a document that attests to compliance of the device under examination with Regulation 2017/745. Also, compliance with any other Union legislation and CS is declared if the device is in line with those requirements [1].
The declaration of conformity is written in the official language of the Member State where the device is made available. The document contains the name, the trade name, and the single registration number (SNR) of the manufacturer and information regarding the device, including its name, UDI-DI, and risk class. Sometimes, additional information for the unambiguous identification of the product is reported, such as a photograph or a product code. Furthermore, when a NB is in charge of the certification procedure, the EU declaration of conformity reports the NB's name and a description of the conformity assessment procedure [1].

3.3 Conformity Assessment Procedures

To place a device on the market, manufacturers have to conduct a conformity assessment procedure according to Annex IX, X, XI [1]. Depending on the risk class and features of the device, there are different pathways to be followed.

Class I devices

Manufacturers of class I devices, except for custom-made and investigational ones, after having prepared the technical documentation, follow a self-conformity assessment. They evaluate the device compliance on their own and, if the device fulfils the requirements of Regulation 2017/745, they submit the EU declaration of conformity [1]. If devices of class I are sterile, have a measuring function, or are reusable surgical instruments, manufacturers have also to undergo the QMS evaluation [1].

Class IIa, IIb, and III devices

Manufacturers of devices belonging to classes IIa, IIb, and III are subjected to a conformity assessment procedure that involves a NB and is based on the assessment of the QMS and technical documentation [1].

The documentation to be submitted for the evaluation of QMS includes the documents related to PMS, the clinical evaluation plan, the organization of the company, the procedures related to the design, manufacturing, testing, and validation of the device. The QMS assessment could be performed within an audit and, if conformity is respected, an EU QMS certificate is released. To verify that manufacturers continue to maintain a QMS in line with the one certified, the NB performs an audit at least every 12 months. Moreover, once every 5 years, the NB could carry out an audit without any announcement [1].

The NB also examines the technical documentation related to Annex II and III and may ask the manufacturers to perform additional tests to prove conformity with GSPR. Moreover, they analyze the clinical evaluation performed by manufacturers and for this purpose, they could involve an expert panel. In the end, they provide a final report about the documentation assessment and, if conformity is satisfied, an EU technical documentation certificate is released [1].

Additional procedures

Special dispositions are needed when devices under examination are:

- class III implantable devices,
- class IIb active devices administering a medicinal product,
- devices incorporating a medicinal substance,
- devices consisting of animal or human origin, or their derivatives [1].

Custom-made devices

For custom-made devices, manufacturers have to follow the conformity procedure set out in Annex XIII [1].

Investigational devices

The requirements to be observed are those for devices under clinical investigation [1].

3.4 CE Marking of Conformity

The CE marking of conformity is the unique symbol indicating compliance with Regulation 2017/745 [16] and it is affixed on devices before placing them on the market. The manufacturer and the authorized representative are the only two figures who can affix this symbol [16]. The CE marking is put visibly on the device. Only when it is not possible to affix the symbol on the device, due to its shape or intended purpose, it can be placed on the packaging. The CE marking may appear also in the IFU. In case a NB performed the conformity assessment, his identification number appears near the symbol [1]. The letters "CE" have the appearance shown in Fig. 17 and, even when dimensions change, the proportions have to be respected [1].

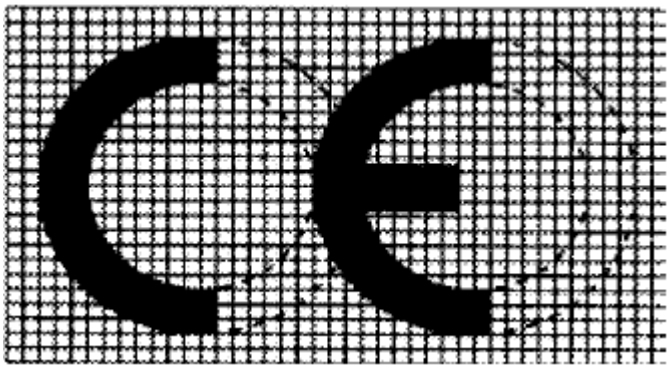


Figure 17. The CE marking is affixed on devices compliant with the requirements of Regulation 2017/745 [1].

CHAPTER 4
MATERIALS AND METHODS

4.1 Experimental Study

In the current work, the technical documentation needed by manufacturers to pass the conformity assessment was produced for aesthetic Annex XVI devices of MDR. The procedure followed for these devices, which is explained in the following sections, is the same as for MD. Specifically, the experimental study applied to aesthetic devices designed, manufactured, and produced by the company Elits Group. They are:

- one laser for hair removal named Epil808 2.0 (Fig. 18) [17];
- two devices for lipolysis, eCosmo (Fig. 19a) and Slim pAct (Fig. 19b), grouped under the name family eCosmo [17].

Figure 18. Epil808 2.0: a laser for hair removal [17].

a **b**

Figure 19. Devices for lipolysis: the family eCosmo [17]. 19a shows the device eCosmo, instead 19b shows the device Slim pAct.

4.1.1 Laser for Hair Removal

The first device examined is Epil808 2.0 (Fig. 18), a laser for hair removal. It emits visible light for the purpose of aesthetic epilation [2].

4.1.2 Devices for Lipolysis

The other two devices examined are the ones of the family eCosmo. This family consists of eCosmo (Fig. 19a) and Slim pAct (Fig. 19b). Both of them are intended to destroy localised adipose tissue through lipolysis [2]. The difference between the two devices is the distinct technologies used for their intended purpose.

4.2 Technical Documentation according to MDR

4.2.1 Documentation according to Annex II

In this work, two different technical documents were generated: one for the laser and one for the family of lipolysis devices.

The technical documentation was produced according to Annex II of MDR, whose requests include:

- information to identify the device;

- the device description;
- the intended users and patients;
- the risk class of the device;
- the description of the materials with particular attention to those in contact with the human body;
- the technical characteristics of the device;
- the labels;
- the IFU;
- information about design and manufacturing;
- the results of validation tests, such as biocompatibility, physicochemical and biological characterization, electrical safety, electromagnetic compatibility, and software validation [1].

Risk management and the CER are also part of the technical documentation [1].

4.2.2 Risk Management File

Risk management was developed according to ISO 14971:2019 concerning the application of risk management to MD [18]. This legislation applies also to devices without a medical purpose [2] and it was followed to prepare the risk management documents for Epil808 2.0 and family eCosmo.

The following scheme (Fig. 20) shows the relevant steps of risk management, which is an iterative process, set up in the production phase of a device and maintained during its entire life cycle [18].
All the foreseeable hazards and hazardous situations related to the use, transport, and storage of the device, in normal conditions and for a single fault condition, were identified and evaluated [18]. The single fault condition refers to a device defect or malfunction, but also to the case in which prescriptions from the IFU are not followed. For the risk evaluation, two indexes were considered: the severity and the probability of harm occurrence for the subjects and/or the environment [18]. One score from 0 to 6 was assigned to each index, depending on the degree of harm severity and its probability of occurrence.

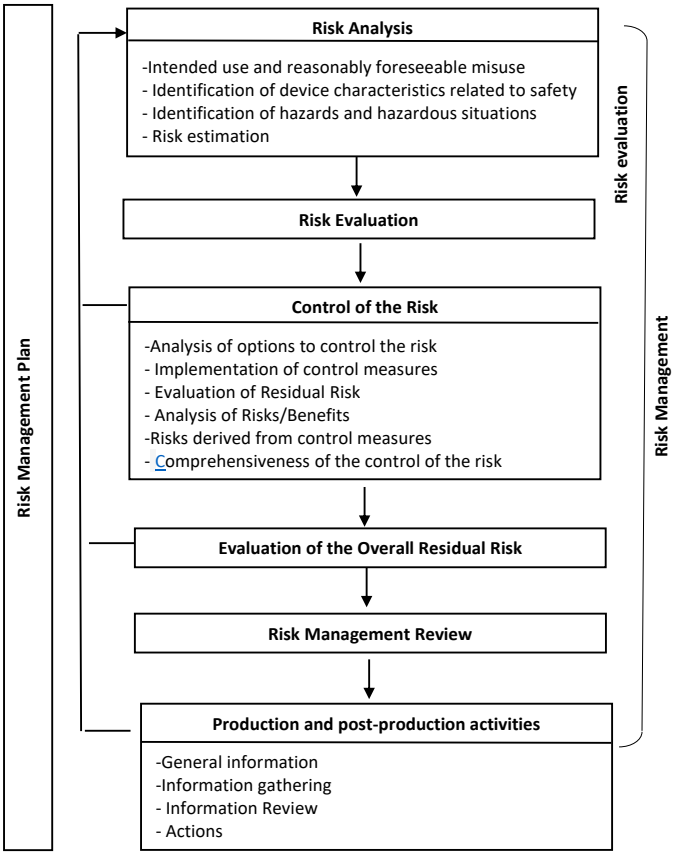


Figure 20. Schematic representation of Risk Management with the main steps: the risk analysis, the risk evaluation, the risk control, and the risk management review [18].

IG = Index of Gravity (Severity)

0 = Not applicable (NA) (no harm)

1 = Negligible (scare)

2 = Minor (discomfort)

3 = Marginal (lesion with no medical intervention)

4 = Severe (lesion with medical intervention)

5 = Critical (permanent lesion)

6 = Catastrophic (patient and/or user's death)

IP = Index of Probability

0 = NA (No harm at all)

1 = **Improbable**: P = 1/1.000.000 (almost impossible event)

2 = **Remote**: P = 1/100.000 (extremely low probability)

3 = **Rare**: P = 1/10.000 (low probability)

4 = **Occasional**: P = 1/1.000 (medium/high probability)

5 = **Probable**: P = 1/100 (high probability)

6 = **Frequent**: P = 1/10 (extremely high probability)

The risk estimation was done by combining the two indexes. Thus, each risk was associated with one cell of Tab. 4. The risk could result:

- **Acceptable (Acc.)**: the risk is acceptable because IG and IP are low;
- **As Far As Possible (Afap)**: the risk could be further reduced by adopting control measures;
- **Not Acceptable (Not acc.)**: the risk cannot be accepted and the manufacturer has to implement control measures to reach the acceptable area of the risk [18].

Any time the risk did not result acceptable, control measures were adopted. To reduce the risk, manufacturers could act to minimize one of the two indexes or both. Control measures did not have to introduce new hazards. They include:

Table 4. Risk estimation.

Levels of probability	**AREA OF THE RISK**					
Frequent 6						
Probable 5						
Occasional 4						
Rare 3						
Remote 2						
Improbable 1						
Levels of gravity	1 Negligible	2 Minor	3 Marginal	4 Severe	5 Critical	6 Catastrophic

Green cell= acceptable risk; yellow cell= as far as possible risk; red cell= not acceptable risk.

- safe design and manufacturing;
- protective measures in the device or in the manufacturing processes;
- information for safety and training for users [2], [18].

After control measures were implemented, the residual risks were evaluated. In case one residual risk was not acceptable, an analysis of the risks/benefits was conducted. The benefits had to overcome the risks.
Lastly, the overall residual risk was evaluated. This one had to result acceptable to pass the risk analysis, otherwise, manufacturers had to make corrections or change the intended use of the device [18].

4.2.3 Clinical Evaluation Report

The clinical evaluation was carried out to demonstrate the performance and safety of the devices under study. The CER was developed following the requirements of Annex XIV [1] and the guidelines on MD clinical evaluation under Directives [13]. For the current CER, data came from equivalent MD of literature studies. The stages for the clinical data gathering are explained below (Fig. 21). The search of papers went on until sufficient clinical evidence was achieved to declare conformity with the relevant GSPR.

STAGE 1

Clinical data were collected from scientific literature databases, mainly from PUBMED and ReserchGate.

STAGE 2

The papers were analyzed to find the following features:

1. clinical, technical, and biological characteristics to demonstrate the equivalence of the MD from literature with the device under evaluation [19];
2. appropriate device application;
3. appropriate patient group;
4. acceptable report/data.

All these elements were fundamental to choosing the literature study. If one of these features was not satisfied, the paper was discarded.

STAGE 3

Data from the studies were analyzed and evaluated in terms of:

1. appropriate outcomes concerning the intended use of the device;
2. enough follow-up to assess treatment effects and/or complications;
3. statistical significance of outcomes;
4. clinical significance of outcomes.

- To demonstrate the performance and safety of the laser technology, the following studies were chosen from literature: A.1 (***) = [20]; A.2 (***) = [21].

  (*** the study addresses performance and safety)

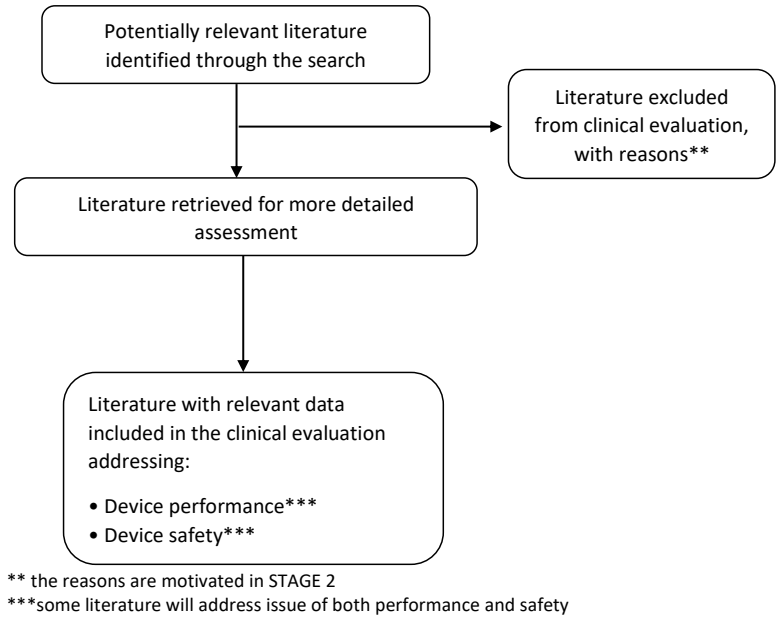


Figure 21. Search strategy to gather sufficient clinical data to demonstrate the safety and performance of the devices under evaluation.

- ❖ To demonstrate the performance and safety of the technologies of the two lipolysis devices, the following studies were chosen from literature:
  Capacitive radiofrequency (RFc) (***)=[22]; resistive radiofrequency (RFr) (***)=[23]; electroporation (EP) (***)=[24]; electrostimulation (EST) (***)=[25]; low-level laser therapy (LLLT) (***)=[26]; photobiostimulation (PS): PS.1 (***)=[27] and PS.2 (***)=[28]; ultrasound (US) (***)=[29]; cavitation (CV) (***)=[30]; pressotherapy (PT) (***)=[31].
  (*** the study addresses performance and safety)

For each study, scores were assigned in this way:

- A score from 0 to 2 to "**Suitability Criteria**" (referring to STAGE 2) ->
  0: not compliant;
  1: there is little difference;
  2: compliant.

- A score of 0 or 1 to "**Data Contribution Criteria**" (referring to STAGE 3) ->
  0: not compliant;
  1: compliant.

The maximum total score achievable was 13. A total **positive score** was >50% (>6.5), indicating enough clinical evidence to prove conformity with GSPR.

CHAPTER 5
RESULTS

The technical documentation is reported for the laser and the lipolysis devices, including the risk management file and the CER.

5.1 Technical Documentation

5.1.1 Technical Documentation for the Laser

General device description

Epil808 2.0 is an electrical active device for hair removal. It has a handpiece containing a laser diode which emits light energy at 808 nm. The device is driven by software and the user regulates the parameters to perform the epilation through a user-friendly touch-screen.

Intended purpose

The device is intended for the aesthetic purpose of hair removal.

Intended users

The device is used by qualified personnel of the aesthetic environment.

Subjects under treatments

The device is intended to be used on a healthy adult population greater than 16 years old. It cannot be used on:

- peacemaker wearers and people with implanted electrical devices,
- carriers of an internal defibrillator,
- individuals with acute inflammation,
- individuals with severe arterial hypertension,
- individuals with neurological disorders,
- individuals with cardiac problems,
- individuals with renal failure,

- individuals with alterations of liver functions,
- subjects with infected or traumatized skin,
- individuals with epilepsy,
- individuals with glycemic problems,
- diabetic subjects,
- individuals with allergic disorders,
- individuals with immune deficiency syndromes,
- pregnant women.

Precautions for use and warnings

- The equipment cannot be used in orifices, on genitalia, and close to eyes.
- The equipment cannot be used in the vicinity of the eyeball, the brain region, and the heart.

Contraindications

- Folliculitis can appear after laser treatment.
- Rare cases of side-effects are erythema, edema, and hyperpigmentation.

Principle of operation

The device has a handpiece with a diode emitting monochromatic, coherent, and unidirectional light energy (wavelength of 808 nm). During the treatment, the applicator enters in contact with intact skin. The user varies parameters, such as frequency, pulse duration, and fluence to provide effective treatment on subjects with different phenotypes and different hair thicknesses and colours.

The methodology is based on the thermic selective destruction (selective photothermolysis) of a specific target: the germinative cells of hair follicles. Specifically, light is absorbed by the melanin, the main chromophore of hair follicles, not by the surrounding tissues [21].

Risk class of the device

Class **IIb** according to Rule 9 of Annex VIII [1].

The laser is an active device that provides energy in a **hazardous way**. In fact, it releases high-intensity light energy, which could burn the epidermal tissue if the

intensity is not controlled and provoke sight damage, in case the beam is erroneously directed towards the eyes.

Accessories

- double ignition key,
- goggles for the patient (completely darkening),
- goggles for the operator,
- funnel for water loading,
- power cable,
- pedal,
- test interlock connector,
- test pedal connector,
- handpiece port.

Connection with other devices

The device is not used in combination with other electrical devices.

Configurations/variants of the device

There is no other device configuration or variant with respect to the one adopted in the normal use.

Functional elements

The key functional elements of the device are reported in the scheme below (Fig. 22).

The device consists of 3 blocks: the display unit, the hydraulic case, and the base with wheels. There is an additional fundamental element shown in Fig. 23, the handpiece, through which the treatment is provided.

- The device is mains-operated with a tension of 230 Vac, then converted into 9 Vdc and 24 Vdc to supply all the other components.
- The display unit is the electronic unit of control, containing the driver for the diode laser and the Central Processing Unit (CPU).

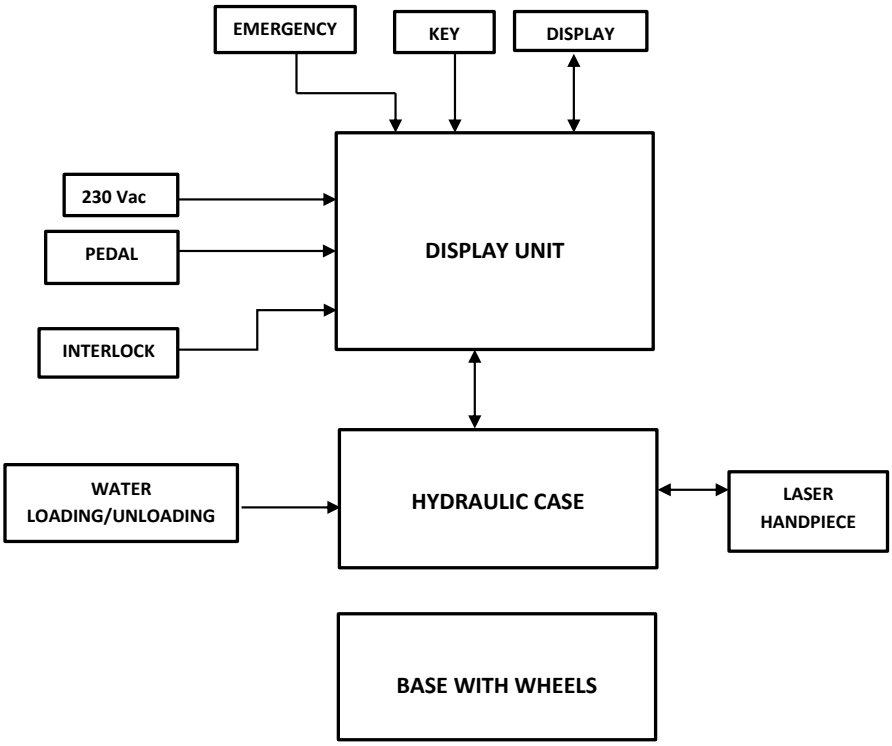


Figure 22. Block scheme showing the key functional elements of the laser.

Figure 23. Picture of the laser showing the 3 independent blocks assembled together, including the display and the handpiece [17].

- The hydraulic case contains the cooling circuit which is connected to the water loading/unloading system.
- The pedal has a double consent function for the emission of light energy. For the treatment, after pressing “START” on the touch-screen, both the pedal and the button on the handpiece have to be pressed.
- The interlock connector is connected to safety equipment, such as the switch, to let the laser deliver the treatment only in safe conditions.
- The display (8”) has a resolution of 800x600 pixels and allows the regulation of parameters through a touch function.
- The software allows to set up and regulate parameters, including the choice of phototype, hair colour, hair thickness, fluence, working frequency, and pulse duration. The user interacts with the device through a user-friendly touch-screen (Fig. 24).

Materials of the functional elements

- The device contains electrical and electronic components.
- The case is made of galvanized sheet and aluminium with the outer layer in polyvinylchloride (PVC).

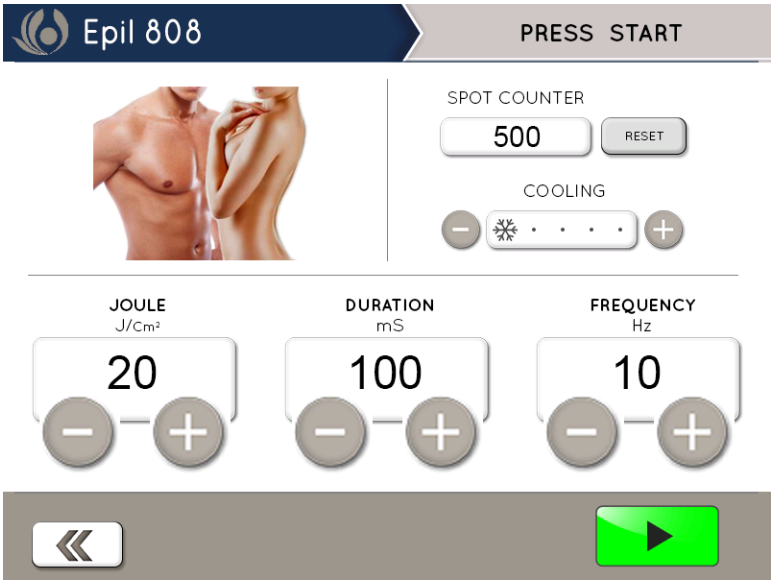


Figure 24. The graphic interface where the parameters for the laser treatment are set up.

- The part of the handpiece handled by the user is made of acrylonitrile butadiene styrene (ABS) whereas the applied parts which enter in contact with the patient skin is made of anodized aluminium and inorganic glass.

The materials of the applicator are analyzed in detail in the "Biocompatibility" section.

Technical characteristics

The technical characteristics of the laser technology are reported in Tab. 5.

Other characteristics of the device

- The device is **non-invasive**.
- It is an **active** device.
- It does **not incorporate** any medicinal substance, tissue or blood product.
- It is **not sterile**.
- It does **not emit** ionizing radiation.
- It is **reusable**.
- It is **not implantable**.
- It is **transportable**.
- It is for **transient use.**

Table 5. Technical characteristics of the laser technology.

Power source	100÷240 V, 50÷60 Hz
Maximum absorbed power	1200 VA
Electrical safety class	I BF
Class of the laser	IV
Wavelength	808 nm
Maximum fluence	40 J/cm^2
Pulse duration	10 ÷ 200 ms
Repetition rate	1 ÷ 10 Hz
Spot dimension	12 x 16 mm
Nominal Ocular Hazard Distance (NOHD)	90 cm
Laser cooling	Through water with forced air cooled
Skin cooling	Peltier cells
Duration of the handpiece	5.000.000 spots
Display	8" colour touch-screen

Product testing and validation

This section shall include the documentation about the tests performed by manufacturers to ensure electrical safety, electromagnetic compatibility, software validation, the usability of the device, and in general conformity with GSPR.

Biocompatibility

The biocompatibility of the materials of the applied parts in direct contact with the subjects are analyzed according to the standard ISO 10993-1:2018. The tests to be performed depend on the type and duration of contact (Tab. 6) [12].

Table 6. Endpoints to be addressed in a biological risk assessment [12].

Device category	Surface device
Type of contact	With intact skin
Duration of contact	Limited (≤ 24 h).
Tests required for the biological evaluation	• Cytotoxicity • Sensitization • Irritation or intracutaneous reactivity

Materials in direct contact with the subject under treatment

Anodized aluminium: for the handpiece tip (Fig. 25).

Chemical composition: aluminium + anodizing treatment.

Physical properties:

- corrosion resistance,
- surface hardness,
- resistance to wear,
- ductility and malleability,
- insulator.

Manufacturing process: the aluminium is subjected to anodization (anodic oxidation) which enhances physical properties, especially corrosion resistance. After treatment, a finishing procedure removes any residue from the manufacturing process. Die-casting is carried out to get the finishing product.

Use in the medical field: this material is mainly used in alloy with other metals. An example is the titanium alloy (Ti6Al4V, Ti7Al8Nb) for orthopaedic surgery and the alloy Fe-20Cr-5Al for knee and hip prosthesis.

Figure 25. The applicator contains the laser diode emitting visible light at 808 nm [17]. The pink tip is made of anodized aluminium and contains an inorganic glass crystal in the middle. The white part in the user's hands is made of ABS.

Moreover, the aluminium is used to produce walking sticks, where the metal is in contact with the patient skin for a limited period.

Considerations: the anodized aluminium can be used in contact with intact skin for a limited period. The anodizing treatment enhances corrosion resistance and consequently biocompatibility.

Inorganic glass: through which light is emitted (Fig. 25).

Chemical composition: a mixture of silicates melted and then cooled at solid-state without crystallization.

Physical properties:

- chemical stability,
- transparency,
- hardness,
- ductility, malleability, and plasticity,
- tension resistance [32].

Manufacturing process: milling to get the finishing product, without any residue.

Use in the medical field: this material has been used for many years to realize applicators of intense pulsed light devices with the same modality of use (same type and duration of contact).

Considerations: episodes of irritation and sensitization are excluded as well as toxicological effects [32]. The inorganic glass is considered biocompatible for its intended use.

Materials in contact with the user's hands

ABS: for the part handled by the user (Fig. 25).

Chemical composition: thermoplastic amorphous polymer$(C_8H_8 \cdot C_4H_6 \cdot C_3H_3N)_n$).

Physical properties:

- dimensional stability,
- stiffness,
- chemical resistance,
- impact resistance,
- insulator [33].

Manufacturing process: subjected to injection moulding. The process does not release any residue.

Use in the medical field: used to produce breathing equipment (inhalers), infusion systems, insulin pen, and outer casings of MD.

Conclusions for the biological evaluation

Given the type and duration of contact of these materials, which are the same (same physical and chemical characteristics and same manufacturing processes) as the ones of MD already CE marked, they are considered **biocompatible for the intended purpose**.

Tests needed for the biological evaluation: **NO TESTS**. No test concerning cytotoxicity, sensitization, irritation, or intracutaneous reactivity [12].

Information for specific cases

Additional information for specific cases: not applicable.

- The device does **not incorporate** any medicinal product.
- The device is **not manufactured** with tissue or cells of human or animal origin.

- The device does **not incorporate** substances introduced into the human body and absorbed.
- The device does **not incorporate** CMR or ED substances.
- The device is **not** placed on the market in a **sterile** or microbiological condition.
- The device has **not** a **measuring** function.

5.1.2 Technical Documentation for the Lipolysis Devices

General device description

eCosmo and **Slim pAct** are electrical active devices used in the aesthetic environment.

- **eCosmo** has the following technologies:
    - Radiofrequency (RF) resistive and capacitive,
    - Ultrasound (US),
    - Low-frequency ultrasound =cavitation (CV),
    - Electroporation (EP),
    - Photobiostimulation (PS).
- **Slim pAct** has the following technologies:
    - Resistive RF,
    - Electrotherapy or electrostimulation (EST) with Kotz (KZ) waves,
    - Pressotherapy (PT),
    - Low-level laser therapy (LLLT).

Intended purpose

Radiofrequency

To face cellulite and skin laxity.

Electroporation

For the inoculation of active principles in cutaneous and/or subcutaneous layers.
It is used in the case of orange peel, cellulite, and to promote muscle toning, sebum regulation, and anti-aging.

Electrotherapy

- To reduce hypotrophy from non-use (in case of normally innervated muscles).

- To maintain the muscular tropism (in case of partially innervated and/or denervated muscles).

Ultrasound

A frequency of 1 MHz is used to improve endothelium vasodilation.

Cavitation

A frequency of 38 kHz is used to reduce excessive localized fat.

Pressotherapy

To promote venous return, lymphatic drainage, and to restore the physiological movement of fluids.

Low-level laser therapy

To reduce excessive localized fat.

Photobiostimulation

- The red and blue light are used to face acne problems.
- The yellow light is used in case of photoaging.

Intended users

The devices are used by qualified personnel of the aesthetic environment.

Subjects under treatments

The devices are intended to be used on healthy adult populations greater than 16 years old. Subjects **not** suitable for the treatments are:

- pacemaker and other electronic devices bearers,
- pregnant women,
- bearers of prostheses and metallic osteosynthesis,
- subjects with abrasions, wounds, and skin diseases localized,
- subjects suffering from epilepsy,
- multiple-sclerosis subjects,
- subjects with Parkinson's disease,
- subjects with thrombophlebitis,
- subjects with compromised liver function or kidney failure,

- subjects with heart disease,
- subjects with vein thrombosis and varicose veins,
- subjects with tattoos or scars in the treatment areas,
- subjects with inflammatory processes,
- subjects with autoimmune disease,
- subjects with thyroid disease,
- subjects with diabetes,
- subjects with pulmonary edema or embolism.

Contraindications

RF

- Redness, erythema, and/or edema can occur after the treatment.

EP and EST

- Redness, erythema, and/or edema can occur after the treatment.
- Applying electrodes over the carotid sinuses has to be avoided not to stimulate the vagal reflex.

US

- Redness, erythema, and/or edema can occur after the treatment.
- The hum experienced during the treatment can last up to few days after the treatment.

PT

- Possible capillaries rupture.
- Excessive pressure facilitates the occurrence of side effects.

LLLT and PS

The following side-effects may occur:

- acne,
- dryness/itching,
- facial rashes,
- redness of scar tissue.

Principles of operation

Radiofrequency

Electrical energy is transformed into heat when penetrating the human tissues. The heat generated depends on the tissue impedance (Joule effect). This destroys the hydrogen bonds in the triple helix collagen structure (partial protein denaturation). In this way, the technology promotes the decomposition of damaged collagen by the collagenase enzyme and the generation of new collagen. Moreover, the high body temperature enhances blood circulation and membrane permeability. This phenomenon promotes the elimination of toxins and water trapped in fat cells [34].

Electroporation

It inoculates active principles in cutaneous and/or subcutaneous layers through electrical pulses, which open aqueous channels in the cellular membranes and temporarily enhance membrane permeability.

Electrotherapy

It exploits Kotz waves (2.5 kHz) to excite muscle contraction to face a state of muscular hypotonia.

Ultrasound

Acoustic pressure waves at 1 MHz provoke a hyperthermic effect due to the energy absorbed by human tissues. The major effect is vasodilation which enhances blood circulation and mobility of liquids. As a consequence, the intake of oxygen and nutritive substances and the acceleration of waste removal are promoted [29].

Cavitation

Acoustic pressure waves at 38 kHz induce the cavitation effect which reduces localized fat through fat cell destruction [30]. This is due to the formation of micro-bubbles employing compression and decompression of interstitial fluids and, when these bubbles implode, they destroy fat cells.

Pressotherapy

Pressure is generated by a pneumatic pump that inflates pads contained in the leggins and armbands (applied parts). The bags are sequentially inflated from the periphery towards the base of the limbs to promote venous return and to restore the physiological movement of fluids [31].

Low-level laser therapy

It is a non-thermal technique based on the emission of monochromatic light. LLLT induces the temporary formation of micro-pores in the cell membranes of adipocytes, allowing leakage of intracellular lipids. The released fat enters the bloodstream via the lymphatic system and it is treated as the fat entering the systemic circulation after meal consumption.

Photobiostimulation

Biochemical reactions in the organic molecules or chromophores within the tissues are stimulated by the emission of coherent or not coherent visible or near-infrared light. This is absorbed by cytochromes within the mitochondrial membrane. This phenomenon is associated with the regulation of the mitochondrial cytochrome electron transport pathway, leading to increased production of ATP, which is used in many cellular processes [28]. In this specific case:

- yellow light enhances collagen synthesis [28];
- blue light stimulates photomodulation in porphyrins to improve acne;
- red light stimulates the release of cytokines which have anti-inflammatory benefits [27].

Risk class of devices

Class IIa according to rule 9 of Annex VIII [1].

The two devices provide energy in several forms: US, RF, electrical, light energy at low intensity, and mechanical (pressure). These kinds of energy are **not** administered in a **hazardous way**.

Accessories

- **eCosmo** has the following additional accessories:
  - power supply cable,
  - remote control door,
  - control foot pedal,
  - 8-pole handpiece for resistive RF and PS (455 kHz) (Fig. 26a),
  - 4-pole handpiece for resistive RF and PS (455 kHz) (Fig. 26b),
  - 2-pole handpiece for resistive RF and PS (455 kHz) (Fig. 26c),

- US handpiece (1 MHz) (Fig. 27a),
- CV handpiece (40 kHz) (Fig. 27b).

❖ **Slim pAct** has the following additional accessories:

- power supply cable,
- kit 8 leggings' sectors,
- pouch,
- plates for resistive RF + LLLT + Kotz,
- remote control holder,
- wired remote control.

a **b** **c**

Figure 26. 26a. 8-pole handpiece (455 kHz). 26b 4-pole handpiece (455 kHz). 26c. 2-pole handpiece (455 kHz) [17].

a **b**

Figure 27. 27a. Ultrasound handpiece (1 MHz). 27b. Cavitation handpiece (40 kHz) [17].

Connection with other devices

The devices are not used in combination with other electrical devices.

Variants of the devices

The family eCosmo provides two variants: eCosmo and Slim pAct with different technologies already mentioned.

Configurations of the devices

Combining some or all the technologies in different ways, it is possible to achieve 46 different configurations for eCosmo and 16 different configurations for Slim pAct.

Functional elements

The key functional elements of eCosmo are reported in Fig. 28, whereas the ones of Slim pAct are shown in Fig. 29.

- The devices are mains-operated with a tension of 230 Vac.
- The display unit is the electronic unit of control, containing the drivers for the different technologies and the CPU to control the functions.
- The pedal has a double consent function to provide the treatments. For the emission, both “START” on the touch-screen and the pedal have to be pressed.
- The handpieces are used to provide the treatments.
- The plate specific for capacitive RF (RFC) is used together with the proper handpiece for this technology (Fig. 28).
- The plates for resistive RF, Kotz Waves and LLLT (RR-KZ-LP) are the means through which these technologies are emitted (Fig. 29).
- The wired remote control allows the patient to stop the treatment whenever needed.
- The leggings’ sectors have one part for the legs and the other for the abdomen. They consist of 8 sections which are inflated by compressed air.

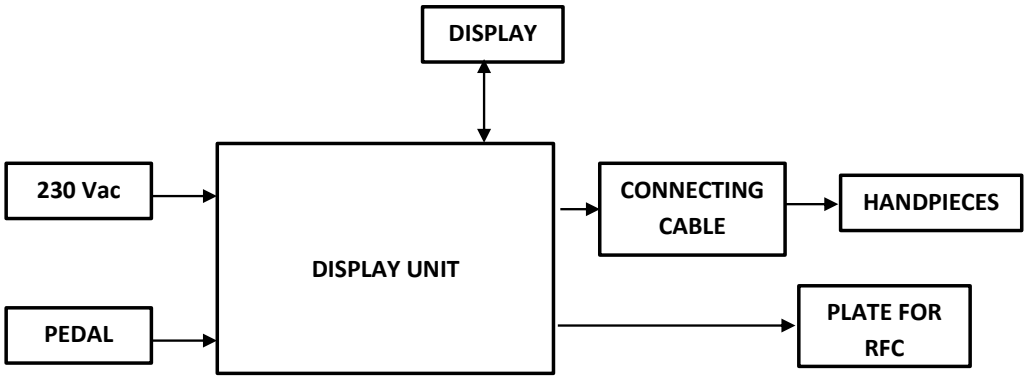


Figure 28. Block scheme showing the key functional elements of eCosmo.

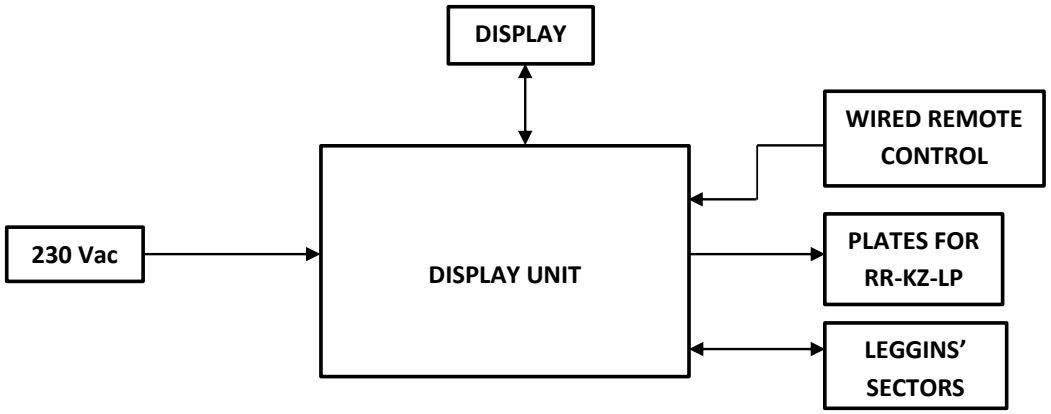


Figure 29. Block scheme showing the key functional elements of Slim pAct.

- The software allows to set up and regulate parameters, including the choice of time, power, and intensity of energy. The user interacts with the device through a user-friendly touch-screen (Fig. 30).

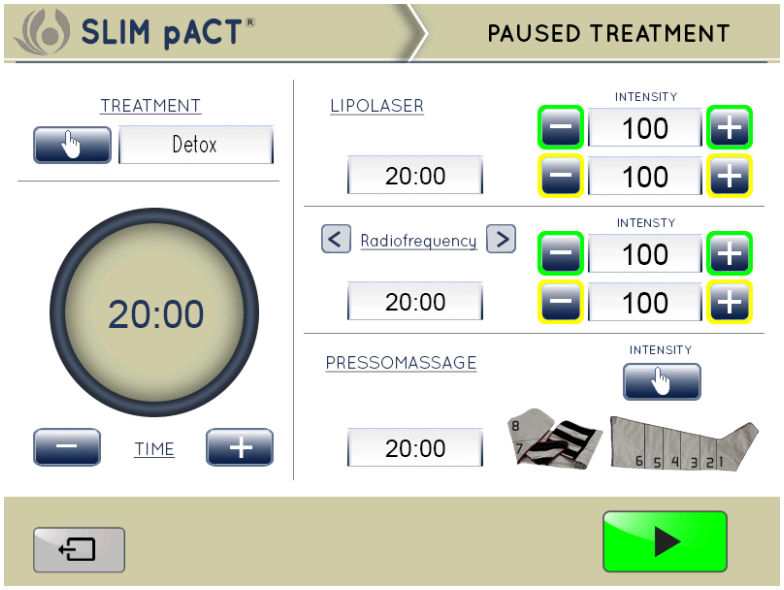


Figure 30. The graphic interface to set up the parameters for the treatments provided by the technologies of Slim pAct.

Materials of the functional elements

- The device contains electrical and electronic components.
- The case is made of galvanized sheet and aluminium with the outer layer in PVC.
- Polyoxymethylene is used for the applied parts in the user's hand;
- For the applicators in contact with the subjects under treatment, different materials are used, depending on the distinct technologies:
    - ❖ Stainless steel for:
        - RF resistive,
        - EST,
        - US,
        - PS,
        - plates for RF and EST.
    - ❖ Polymer Rilsan for RF capacitive.
    - ❖ PVC sheet for the outer film over the applied parts of LLLT.
    - ❖ Synthetic fabric for the internal lining of PT.

Technical characteristics

The technical characteristics of eCosmo are reported in Tab. 7.

The technical characteristics of Slim pAct are reported in Tab. 8.

Table 7. Technical characteristics of eCosmo.

GENERAL CHARACTERISTICS	
Power source	230 V, 50÷60 Hz
Maximum absorbed power	250 VA
Electrical safety class	I BF
MONOPOLAR CAPACITIVE RADIOFREQUENCY	
Operating frequency	455 kHz ± 10%
Maximum output power	60 Watt
RESISTIVE RADIOFREQUENCY	
8-poles handpiece frequency	455 kHz ± 10%
Maximum output power	90 Watt
4-poles handpiece frequency	455 kHz ± 10%
Maximum output power	45 Watt
2-poles handpiece frequency	455 kHz ± 10%
Maximum output power	45 Watt
ELECTROPORATION	
Wave frequency	Modulated from 1.600 Hz to 2.100 Hz
Maximum output voltage	120 Vac p-p
Maximum output current	3 mA
ULTRASOUND	
Ultrasound Frequency	1 MHz ± 10% via software modulation (max 3 W/cm^2)
Cavitation Frequency	40 kHz ± 10% via software modulation (max 3 W/cm^2)
PHOTOBIOSTIMULATION	
Red light	Wavelength: 635 nm – max radiance 2.5 mW/cm^2
Yellow light	Wavelength: 590 nm - max radiance 1.0 mW/cm^2
Blue light	Wavelength: 456 nm – max radiance 4.5 mW/cm^2

Table 8. Technical characteristics of Slim pAct.

GENERAL CHARACTERISTICS	
Power source	230 V, 50÷60 Hz
Maximum absorbed power	300 VA
Electrical safety class	I BF
BIPOLAR RESISTIVE RADIOFREQUENCY	
Operating frequency	455 kHz ± 10%
Maximum output power	90 Watt
ELECTROSTIMULATION (KOTZ)	
Carrier frequency	2.5 kHz
Carrier modulation frequency	75 Hz
Maximum output current	5 mA
LOW-LEVEL LASER THERAPY	
Wavelength	635 ÷ 760 nm
Maximum radiance per single LED	60 mW/m^2
Number of LEDs per applicators	10 LEDs
PRESSOTHERAPY	
Maximum pressure	120 mmHg per areas
Levels of pressure to be regulated	10 levels

Other characteristics of the devices

The devices are **non-invasive**.

They are **active** devices.

They **do not incorporate** any medicinal substance, tissue, or blood product.

They are **not sterile**.

They do **not** emit ionizing radiation.

They are **reusable**.

They are **not implantable**.

They are **transportable**.

Product testing and validation

This section shall include the documentation about the tests performed by manufacturers to ensure electrical safety, electromagnetic compatibility, software validation, the usability of the device, and in general conformity with GSPR.

Biocompatibility

The biocompatibility of the materials of the applied parts in direct contact with the subjects are analyzed according to the standard ISO 10993-1:2018. The tests to be performed depend on the type and duration of contact (Tab. 9) [12].

Table 9. Endpoints to be addressed in a biological risk assessment [12].

Device category	Surface devices
Type of contact	With intact skin
Duration of contact	Limited (≤ 24 h).
Tests required for the biological evaluation	• Cytotoxicity • Sensitization • Irritation or intracutaneous reactivity

Materials in direct contact with the subject under treatment

Stainless steel: for resistive RF, US, EP, PS applicators.

Chemical composition: the elements constituting this alloy are: chrome (Cr), carbon (C), silicon (Si), manganese (Mn), phosphorus (P), sulfur (S), nickel (Ni), nitrogen (N).

Physical properties:

- corrosion resistance,

- chemical stability,
- weldability without pre-heating,
- workability,
- low conductivity coefficient.

Manufacturing process: subjected to turning to get the finishing product. The process does not leave residues.

Use in the medical field: this material has been used for years in orthopaedic implants and stomatology, despite a low quantity of Ni is required to avoid episodes of sensitization. It is also used to realize scalpels, syringes, and medical scissors.

Polymer Rilsan: for the outer shell of capacitive RF.

Chemical composition: polyamide resin of vegetable origin.

Physical properties:

- mechanical and impact resistance,
- tensile and stretching resistance,
- low friction coefficient,
- wear resistance,
- good resistance to solvents [35].

Manufacturing processes: subjected to injection mould for plastic materials. The process does not leave residues on the finishing material.

Use in the medical field: the use of resin in the medical sector is established. Moreover, this material is used to make undergarments that enter in contact safely with intact skin.

PVC: film for LLLT.

Chemical composition: thermoplastic amorphous polymer made of carbon, hydrogen, and chlorine $(CH_2CHCl)_n$.

Physical properties:

- stiffness,
- corrosion resistance,
- resistance to chemical agents,
- impact resistance,
- chemical stability,

- easily deformable [36].

Manufacturing process: subjected to extrusion. The process does not leave residues.

Use in the medical field: PVC use is established, also in the "compound" form, which means that it is admixed with other substances to improve chemical and physical properties. It is used to realize catheters and accessories intended for dialysis, infusion, and transfusion. Since it is also used to produce disposable gloves, it can be considered biocompatible for the intended purpose, given the same duration and type of contact.

Synthetic fabric: film for LLLT.

Chemical composition: PVC at 73.5% + cotton at 26.5% .

Physical properties:

- wear resistance,
- resistant to moulds,
- resistance to corrosive chemical substances,
- low electrical conductivity,
- lightness,
- easily deformable [37].

Use in the medical field: PVC use was already discussed. For what concerns cotton, it is one of the most wearable materials in contact with skin, thus it can be considered biocompatible for the intended purpose.

Considerations: this material passes the test about cutaneous irritation [37].

Materials in contact with the user's hands

Polyoxymethylene: for the parts handled by the user.

Chemical composition: technopolymer made of chains repeating one methylene group + one atom of oxygen.

Physical properties:

- high mechanical resistance,
- stiffness,
- hardness,
- chemical resistance to solvents,

- optimal workability,
- dimensional stability,
- electrical insulator.

Manufacturing process: subjected to extrusion. No residue is left.

Use in the medical field: used in operations regarding articular reconstructions, traumatology, and interventions on the spinal column. It is also used when replacing knee, hip, and shoulder prostheses. No relevant episodes of cytotoxicity and sensitization have been experienced for invasive applications. Thus, it could be used safely for non-invasive applications.

Conclusions for the biological evaluation

Given the type and duration of contact of these materials which are the same (same physical and chemical characteristics and same manufacturing processes) as the ones used in the medical field for many years, they are considered **biocompatible for the intended purpose**.

Tests needed for the biological evaluation: **NO TESTS**. No test concerning cytotoxicity, sensitization, irritation, or intracutaneous reactivity [12].

Information for specific cases

Additional information for specific cases: not applicable

- The devices **do not incorporate** any medicinal product.
- The devices **are not manufactured** with tissue or cells of human or animal origin.
- The devices **do not incorporate** substances introduced into the human body and absorbed.
- The devices **do not incorporate** CMR or ED substances.
- The devices are **not** placed on the market in a **sterile** or microbiological condition.
- The devices do **not** have a **measuring** function.

5.2 Risk Management

In the following Tab. 10 and Tab. 11, all the possible **Hazards** (**H**) related to the device use, transport, and storage are reported.
In the column **IPN** (Index of Probability in Normal Conditions) and **IPF** (Index of Probability in a single Fault Condition) there are the indexes related to the probability of occurrence of the harm, respectively in normal conditions and the case of one single fault condition. The values for the indexes IG and IP follow the ones in section 4.2.2.
The evaluation of the Risk is reported in the column **IR** (Index of Risk evaluation), whereas the evaluation of the Residual Risk (RR) after implementing control measures is provided in the column **IRR** (Index of Residual Risk evaluation). The risk could be: **acc.** = acceptable; **afap** = as far as possible; **not acc.** = not acceptable.
The solutions adopted to reduce the level of risk are reported in the column **control measures**.

5.2.1 Risk Management File for the Laser

The application of the risk analysis for Epil808 2.0 is reported in Tab. 10.

Table 10. Hazards connected to the laser.

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
1	Mains voltage	6	4	4	The device is mains-operated with a power supply compliant with the standard CEI EN 60601-1 [38]	1	1	2
		IR: **not acc.**				**IRR: acc.**		
2	Leakage current - earth leakage current - patient leakage current	6	4	4	Design and manufacturing according to the standard CEI EN 60601-1 [38]	1	1	2
		IR: not acc.				**IRR: acc.**		
3	Electric fields	4	1	2	Design and manufacturing according to the standard CEI EN 60601-1 [38]	1	1	2
		IR: afap				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
4	Magnetic fields	4	1	2	Design and manufacturing according to the standard CEI EN 60601-1-2 [39]	2	1	2
		IR: afap				**IRR: acc.**		
5	Electric discharge	4	3	4	Design and manufacturing according to the standard CEI EN 60601-1-2 [39] and prescriptions about the proper environmental conditions for use	2	1	2
		IR: afap				**IRR: acc.**		
6	Ionizing radiation	N.A.	N.A.	N.A.	The device does not emit ionizing radiation	N.A.	N.A.	N.A.
		IR: **N.A.**				**IRR: N.A.**		
7	Not ionizing radiation	5	1	2	Design and manufacturing according to the standard CEI EN 60601-1-2 [39] and CEI EN 60601-2-22 [40]	2	1	2
		IR: afap				**IRR: acc.**		
8	High temperature	5	3	5	Design and manufacturing according to the standard CEI EN 60601-1 [38] and prescriptions about temperature of use and storage	2	1	2
		IR: **not acc.**				**IRR: acc.**		
9	Low temperature	2	1	3	Prescriptions about temperature of use and storage	1	1	2
		IR: acc.				**IRR: acc.**		
10	Cinetic energy -Falling objects -Mobile parts	2	1	3	Prescriptions about correct installation and use by qualified personnel	1	1	1
		IR: **acc.**				**IRR: acc.**		
11	Cinetic energy -Fluid injection at high pressure -Vibrating parts	N.A.	N.A.	N.A.	The device does not inject any fluid and it does not consist of vibrating parts	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
12	Gravitational force	2	1	2	Prescriptions about correct installation	2	1	1
		IR: **acc.**				**IRR: acc.**		
13	-Flexion -compression -tension -torsion	N.A.	N.A.	N.A.	The device is not subjected to these kinds of forces	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
14	-Infrasound energy -Ultrasound energy	N.A.	N.A.	N.A.	The device does not emit acoustic energy	N.A.	N.A.	N.A.
		IR: **N.A.**				**IRR: N.A.**		
15	-Bacteria -Fungi -Viruses -Toxins	4	1	4	Prescriptions about cleaning	3	1	2
		IR: **afap**				**IRR: acc.**		
16	Allergens	4	2	2	Prescriptions about cleaning and integrity of applied parts. Anallergic materials in contact with the skin	2	1	2
		IR: **afap**				**IRR: acc.**		
17	Irritanting substances	3	1	3	Prescriptions about correct cleaning and removal of cleaning residues	1	1	2
		IR: afap				**IRR: acc.**		
18	Carcinogens, mutagens, toxic substances	N.A.	N.A.	N.A.	The device does not cointain carcinogens and mutagens	N.A.	N.A.	N.A.
		IR: **N.A.**				**IRR: N.A.**		
19	Exposure of respiratory tracts to: acids, alkalines, oxidants	4	1	2	Prescriptions about correct cleaning and maintenance	1	1	2
		IR: afap				**IRR: acc.**		
20	Inflammable, explosive substances, fumes, vapoures	N.A.	N.A.	N.A.	The device does not enter in contact with inflammable and explosive substances and it does not emit fumes and vapoures	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
21	Particles (micro and nano)	N.A.	N.A.	N.A.	The device does not cointain these particles	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
22	Solvents	3	1	3	Prescriptions about cleaning of applied parts (not of all the device)	1	1	2
		IR: afap				**IRR: acc.**		
23	Cleaning and disinfecting agents	3	3	3	Prescriptions about cleaning	1	1	2
		IR: afap				**IRR: acc.**		
24	Not correct functions (alarms)	4	2	5	Redundant safety control on the hardware (HW) system	1	1	2
		IR: **not acc.**				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
25	Lost or reduced functions	2	1	5	Alarms, error messages, or warnings about the need of technical support	1	1	2
		IR: afap				**IRR: acc.**		
26	Errors of attention	4	3	3	Prescriptions about use by qualified personnel	2	1	2
		IR: **afap**				**IRR: acc.**		
27	Errors related to experience, violation of procedures	4	3	3	Prescription about use by qualified personnel	1	1	1
		IR: afap				**IRR: acc.**		
28	Incomplete IFU	4	2	3	Usability test	1	1	2
		IR: **afap**				**IRR: acc.**		
29	Inadequate description of performance characteristics	4	1	3	Description of the technology used	1	1	2
		IR: afap				**IRR: acc.**		
30	Inadequate description of the intended use	4	1	3	Indications about the intended use	2	1	2
		IR: afap				**IRR: acc.**		
31	Inadequate provision of limitations	4	1	3	Indications about contraindications and side-effects	2	1	2
		IR: afap				**IRR: acc.**		
32	Inadequate description of accessories to be used with the device	5	1	3	Usability test	1	1	2
		IR: **afap**				**IRR: acc.**		
33	Inadequate description of preliminary controls before use	5	1	4	Usability test	1	1	2
		IR: not acc.				**IRR: acc.**		
34	Complicated IFU	2	4	4	Usability test	1	1	2
		IR: afap				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
35	Side effects	4	1	4	Warnings about contraindications and side effects	2	1	2
		IR: **afap**				**IRR: acc.**		

H= hazard; IG= index of gravity; IPN= index of probability in normal conditions; IPF= index of probability in a single fault condition; IR= index of risk evaluation; IRR= index of residual risk evaluation; acc.= acceptable; afap= as far as possible, not acc= not acceptable; N.A.= not applicable.

5.2.2 Risk Management File for the Lipolysis Devices

The application of the risk analysis for the family eCosmo is reported in Tab. 11.

Table 11. Hazards connected to the lipolysis devices.

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
1	Mains voltage	6	4	4	The device is mains-operated with a power supply compliant with the standard CEI EN 60601-1 [38]	1	1	2
		IR: **not acc.**				**IRR: acc.**		
2	Leakage current - earth leakage current - patient leakage current	6	4	4	Design and manufacturing according to the standard CEI EN 60601-1 [38]	1	1	2
		IR: not acc.				**IRR: acc.**		
3	Electric fields	4	1	2	Design and manufacturing according to the standard CEI EN 60601-1-2 [39]	1	1	2
		IR: afap				**IRR: acc.**		
4	Magnetic fields	4	1	2	Design and manufacturing according to the standard CEI EN 60601-1-2 [39]	2	1	2
		IR: afap				**IRR: acc.**		
5	Electric discharge	4	1	3	Design and manufacturing according to the standard CEI EN 60601-1-2 [39] and prescriptions about the proper environment for use	2	1	2
		IR: afap				**IRR: acc.**		
6	Ionizing radiation	N.A.	N.A.	N.A.	The device does not emit ionizing radiation	N.A.	N.A.	N.A.
		IR: **N.A.**				**IRR: N.A.**		
7	Not ionizing radiation	4	1	2	Design and manufacturing according to the standard CEI EN 60601-1-2 [39]	2	1	2
		IR: afap				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
8	High temperature	4	1	3	Design and manufacturing according to the standard CEI EN 60601-1 [38], prescriptions about temperature of use and storage	2	1	2
		IR: **afap**				**IRR: acc.**		
9	Low temperature	2	1	3	Prescriptions about temperature of use and storage	1	1	1
		IR: acc.				**IRR: acc.**		
10	Cinetic energy -Falling objects -Mobile parts	2	1	1	Prescriptions about correct installation and use by qualified personnel	1	1	1
		IR: **acc.**				**IRR: acc.**		
11	Cinetic energy -Fluid injection at high pressure -Vibrating parts	N.A.	N.A.	N.A.	The device does not inject any fluid and it does not consist of vibrating parts	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
12	Gravitational force	2	1	1	Prescriptions about correct installation	1	1	1
		IR: **acc.**				**IRR: acc.**		
13	-Flexion -compression -tension -torsion	N.A.	N.A.	N.A.	The device is not subjected to these kinds of forces	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
14	-Ultrasound energy	4	1	3	Only for eCosmo: design and manufacturing according to the srandard CEI EN 60601-2-5 [41]	1	1	2
		IR: **afap**				**IRR: acc.**		
15	-Bacteria -Fungi -Viruses -Toxins	4	1	3	Prescriptions about cleaning	1	1	1
		IR: **afap**				**IRR: acc.**		
16	Allergens	4	2	2	Prescriptions about cleaning and integrity of applied parts. Anallergic materials in contact with the skin	2	1	2
		IR: **afap**				**IRR: acc.**		
17	Irritanting substances	3	1	3	Prescriptions about correct cleaning and removal of cleaning residues	2	1	2
		IR: afap				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
18	Carcinogens, mutagens, toxic substances	N.A.	N.A.	N.A.	The device does not cointain carcinogens and mutagens	N.A.	N.A.	N.A.
		IR: **N.A.**				**IRR: N.A.**		
19	Exposure of respiratory tracts to: acids, alkalines, oxidants	4	1	2	Prescription about correct cleaning and maintenance	1	1	2
		IR: afap				**IRR: acc.**		
20	Inflammable, explosive substances, fumes, vapoures	N.A.	N.A.	N.A.	The device does not enter in contact with inflammable and explosive substances and it does not emit fumes and vapoures	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
21	Particles (micro and nano)	N.A.	N.A.	N.A.	The device does not cointain these particles	N.A.	N.A.	N.A.
		IR: N.A.				**IRR: N.A.**		
22	Solvents	3	1	3	Prescriptions about cleaning	1	1	2
		IR: afap				**IRR: acc.**		
23	Cleaning and disinfecting agents	3	1	3	Prescriptions about cleaning	1	1	2
		IR: afap				**IRR: acc.**		
24	Not correct functions (alarms)	3	1	4	Safety system of the SW: alarms and error messages	2	1	2
		IR: **afap**				**IRR: acc.**		
25	Lost or reduced functions	2	1	4	Alarms and error messages	1	1	2
		IR: afap				**IRR: acc.**		
26	Errors of attention	2	3	3	Prescriptions about use by qualified personnel	1	1	2
		IR: **afap**				**IRR: acc.**		
27	Errors related to experience, violation of procedures	3	1	3	Prescription about use by qualified personnel	1	1	2
		IR: afap				**IRR: acc.**		
28	Incomplete IFU	3	1	3	Usability test	1	1	2
		IR: **afap**				**IRR: acc.**		

H	Hazards	IG	IPN	IPF	Control measures	IG	IPN	IPF
29	Inadequate description of performance characteristics	3	1	3	Description of technology used	1	1	2
		IR: afap				**IRR: acc.**		
30	Inadequate description of the intended use	4	1	3	Indications about the intended use	1	1	2
		IR: afap				**IRR: acc.**		
31	Inadequate provision of limitations	4	1	3	Indications about contraindications and side-effects	2	1	2
		IR: afap				**IRR: acc.**		
32	Inadequate description of accessories to be used with the device	5	1	3	Usability test	1	1	2
		IR: **afap**				**IRR: acc.**		
33	Inadequate description of preliminary controls before use	5	1	4	Usability test	1	1	2
		IR: not acc.				**IRR: acc.**		
34	Complicated IFU	2	1	3	Usability test	1	1	2
		IR: acc.				**IRR: acc.**		
35	Side effects	4	1	4	Warnings about contraindications and side effects	2	1	2
		IR: **afap**				**IRR: acc.**		

H= hazard; IG= index of gravity; IPN= index of probability in normal conditions; IPF= index of probability in a single fault condition; IR= index of risk evaluation; IRR= index of residual risk evaluation; acc.= acceptable; afap= as far as possible, not acc.= not acceptable; N.A.= not applicable.

5.2.3 Conclusion of the Risk Analysis

The following considerations about the risk analysis are for both the laser and the lipolysis devices.

Report acceptability

- RR in the **acceptable** area: all the single RR are acceptable.
- RR in the **afap** area: No RR.
- RR in the **not acceptable** area: No RR.

The overall RR is acceptable.

The risk analysis has a **positive** evaluation.

5.3 Clinical Evaluation

5.3.1 Clinical Evaluation Report for the Laser

Medical field concerned

Dermatology.

Overview of the problems

Hirsutism

Hirsutism is a condition characterized by excessive growth of hairs. Women suffering from hirsutism (5-10% of the female population) may have endocrine disorders. Among the main causes, there are elevated androgen levels or polycystic ovary syndrome [42].

Diagnosis of hirsutism

It is commonly diagnosed visually, using the modified Ferriman-Gallway scoring system. A score between 0 and 4 is assigned to each of the nine androgen-sensitive body areas. Hirsutism is present when the sum of the scores is greater than 8/9. A sum higher than 25 indicates severe hirsutism [43].

Treatment of hirsutism

Hirsutism can be treated with pharmacological agents and/or other methods.

- The choice of the pharmacological agent depends on the medical history of the subject. One possible solution is the use of oral contraceptives in case of endocrine problems.
- Hair removal methods are described in Tab. 12 [43].

Table 12. Advantages and disadvantages of hair removal methods.

Hair removal method	Advantages	Disadvantages
Shaving	Not expensive	It must be done frequently
Chemical depilatory agents	Not expensive	Irritation of the skin and possible dermatitis
Waxing	Effective	Painful. It can provoke scarring and folliculitis
Laser photoepilation	Long-lasting hair removal	Not recommended for subjects of black skin. Not effective in blond and white-haired women. Side-effects are erythema, edema, and hyperpigmentation.

Studies

The scores attributed to the studies A.1 and A.2 [20], [21] regarding suitability criteria and data contribution criteria are reported in Tab. 13.

Table 13. Scores attributed to the data from the studies [20], [21].

REQUIREMENT	A.1	A.2	Average score
SUITABILITY CRITERIA			
Appropriate device	1	1	1.00
Appropriate device application	2	2	2.00
Appropriate patient group	2	2	2.00
Acceptable report/data collation	2	2	2.00
DATA CONTRIBUTION CRITERIA			
Data source type	1	1	1.00
Outcome measures	1	1	1.00
Follow-up	1	1	1.00
Statistical significance	1	1	1.00
Clinical significance	1	1	1.00
Total score	12	12	12.0

Demonstration of equivalence

Demonstration of equivalence for the study A.1 (Tab. 14)

Table 14. Technical, biological, and clinical considerations to prove the equivalence of the device from the study A.1 with the laser under evaluation [19], [20].

Technical, biological, and clinical considerations The device:	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Pulsed diode laser with a spot size of 12x16 mm	Long-pulsed diode laser with a spot size of 9x9 mm	NO, the spot size does not influence the principle of functioning
has similar specifications and properties	Wavelength: 808 nm Fluence: max 40 J/cm^2	Wavelength: 800 nm Fluence: 25 or 40 J/cm^2	NO Fluence is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	Diode laser technology performing selective photothermolysis	Diode laser technology performing selective photothermolysis	NO
uses the same materials in contact with the same human tissues	Anodized aluminium and inorganic glass	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For hair removal	For hair removal	NO This requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, independently of body parts, distant from the orifices	through tegumentary apparatus. In this specific case, it is used on pits but the device can be used in any body part, distant from the orifices	NO
is used in a similar population	In adult population	In women between 20 and 60 years	NO

Demonstration of equivalence for the study A.2 (Tab. 15)

Table 15. Technical, biological, and clinical considerations to prove the equivalence of the device from the study A.2 with the laser under evaluation [19], [21].

Technical, biological, and clinical considerations **The device:**	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Pulsed diode laser with a spot size of 12x16 mm	Long-pulsed diode laser with 2 different spot sizes: one of 10x10 mm and the other of 10x30 mm	NO, the spot size does not influence the principle of functioning
has similar specifications and properties	Wavelength: 808 nm Fluence: max 40 J/cm^2	Wavelength: 805 nm Fluence: 25÷33 J/cm^2	NO Fluence is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	Diode laser technology performing selective photothermolysis	Diode laser technology performing selective photothermolysis	NO
uses the same materials in contact with the same human tissues	Anodized aluminium and inorganic glass	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For hair removal	For hair removal	NO This requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, independently of body parts, distant from the orifices	through tegumentary apparatus. In this specific case, it is used on pits but the device can be used in any body part, distant from the orifices	NO
is used in a similar population	In adult population	In women between 24 and 50 years	NO

Additional considerations to demonstrate the equivalence

The devices coming from the literature have the following similar characteristics with the laser under evaluation.

- They are used under **similar conditions of use** in aesthetic studios.
- They are in **contact with intact skin** for a few minutes.
- They do **not release** any substance.

- They are used by **qualified personnel**.
- They do not present any relevant critical performance [19].

Final considerations about the equivalence

The equivalence of the devices from the studies with the laser under evaluation is confirmed because there are **NO significant different characteristics** between the mentioned devices that can affect clinical performance and safety.

Results from the studies

Results from the study A.1

Performance: the following scale was used to score the improvement obtained with three sessions: 0= no improvement; 1= <25% improvement; 2= 25-50% improvement; 3= 51-75% improvement; 4 = >75% improvement.

The laser working at 25 J/cm^2 got a mean of 3.3.

The laser working at 40 J/cm^2 got a mean of 3.0.

Good results were maintained during follow-up [20].

Safety: Erythema and little inflammation after the treatment. Only pain was experienced. Two subjects with dark skin experienced hyperpigmentation and one patient blistering [20].

Results from the study A.2

Performance: the efficacy was measured in terms of hair clearance (number of removed hairs over number of initial ones). After the first session, the mean hair clearance with D1 (handpiece with smaller spot) and D3 (handpiece with larger spot) was 62.1% and 62.3%, respectively. The mean hair clearance after the third session was 65.5% with D1 and 77.4% with D3. At 3 month follow-up, the mean hair clearance was 38.7% and 50.1% with D1 and D3, respectively [21].

Safety: in a Visual Analog Scale (VAS) from 0 (no pain) to 10 (intolerable pain), the mean VAS was 3.1 with D1 and 4.3 with D3. One subject experienced post-inflammatory hyperpigmentation. No other side effects [21].

Conclusions to the CER

The laser is an **effective and safe methodology to remove hairs**, given the positive outcomes from the literature studies [20], [21]. The laser is considered safe since,

except for pain, no serious side-effect is experienced after treatments. Erythema and hyperpigmentation are minor contraindications, resolvable in a short period.

5.3.2 Clinical Evaluation Report for the Lipolysis Devices

Medical field concerned

Dermatology.

Overview of the problems

Cellulite and skin laxity

Cellulite appears like orange peel and cottage cheese texture. It is present mainly on the buttocks and upper posterior thighs, but it can also affect the abdomen and upper arms. About 80%-90% of women suffer from cellulite.

One of the causes is attributed to the fibrous structure. Fibrous connective cords tether the skin to the muscles and in the middle there is fat. When these cords shorten due to the accumulation of adipose tissue, they pull the skin down, resulting in typical depression. Also, hormonal factors and genetics contribute to developing cellulite [44].

Cellulite severity

One classification discriminates cellulite into mild, moderate, and severe. The scale of Nürnberger and Müller identifies 5 features to be scored from 0 to 3, where 0 means absence of cellulite and 3 refers to the most severe cellulite evidence. The final sum ranges from 0 to 15 [44].

Treatments

Methods to face cellulite are reported in Tab. 16.

Table 16. Advantages and disadvantages of cellulite's treatments.

Methods for treatment	Advantages	Disadvantages
Creme application	Not expensive	Not effective
Cosmetic surgery	Effective	Invasive
Laser therapy	Non-invasive	Not able to reach deep structures
Bipolar Radiofrequency	Minimal skin damage Non-invasive	Limited working area Not so effective as surgery
Monopolar radiofrequency	Minimal skin damage Non-invasive	Not so effective as surgery

Photoaging

Photoaging, which is the acceleration of skin aging, is a physiological state typical of old people. Photoaging appearance is characterized by wrinkles, rough texture, and decreased elasticity. It worsens by exposure to sunlight.

Venous and lymphatic insufficiency

Venous and lymphatic insufficiency underlines a circulatory issue. Standing challenges the circulatory system, increasing venous pressure in the legs and feet and compromising venous return and the lymphatic system. These conditions also occur when the lymphatic system cannot handle the difference between filtration (from capillaries to interstitium) and reabsorption (from interstitium to capillaries) and edema can be experienced.

Treatments

Precautions to preserve the physiological venous return and lymphatic functioning are listed below.

- Physical activity helps to reduce fluid retention.
- Avoiding standing for a long period helps to prevent edema.
- Massages.
- Surgery is suggested for severe cases.
- Pressotherapy is a technique that consists in applying external pressure to the limbs to alleviate fluid retention (Fig. 31) [31].

Figure 31. Pressotherapy using leggings and abdomen applicators [17].

Studies

The scores attributed to the studies [22]–[31], regarding suitability criteria and data contribution criteria, are reported in Tab. 17.

Table 17. Scores attributed to the data from the literature studies [22]–[31].

R	RFc	RFr	EP	EST	LLLT	PS.1	PS.2	US	CV	PT	Aver.
S.C.											
Appropriate device	2	1	2	2	2	2	2	2	2	1	1.8
Appropriate device application	2	2	2	2	2	2	2	2	2	2	2.0
Appropriate patient group	2	2	2	2	2	2	2	2	2	2	2.0
Acceptable report/data collation	2	2	2	2	2	2	2	2	2	2	2.0
D.C.C.											
Data source type	1	1	1	1	1	1	1	1	1	1	1.0
Outcome measures	1	1	1	1	1	1	1	1	1	1	1.0
Long period follow-up	0	0	0	0	0	0	1	0	0	0	0.1
Statistical significance	1	1	0	1	1	1	1	1	0	1	0.8
Clinical significance	1	1	1	1	1	1	1	1	1	1	1.0
Total score	12	11	11	12	12	12	13	12	11	11	11.7

R=requirement; S.C.= suitability criteria; D.C.C.= data contribution criteria; RFc= capacitive radiofrequency; RFr= resistive radiofrequency; EP= electroporation; EST=electrostimulation; LLLT= low-level laser therapy; PS= photobiostimulation; US= ultrasound; CV= cavitation; PT= pressotherapy; aver.= average.

Demonstration of equivalence

Demonstration of equivalence for the study RFc (Tab. 18)

Table 18. Technical, biological, and clinical considerations to prove the equivalence of the device from the study RFc with the technology under evaluation [19], [22].

Technical, biological, and clinical considerations **The device:**	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Monopolar capacitive RF device at 455 kHz	Capacitive RF device at 550 kHz	NO, they have similar output

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
has similar specifications and properties	Working frequency: 455 kHz	Working frequency: 550 kHz	NO The working frequency is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	Capacitive RF generates endogenous heat through the Joule effect	Capacitive RF generates endogenous heat through the Joule effect	NO
uses the same materials in contact with the same human tissues	Polymer Rilsan	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For cellulite reduction	For cellulite reduction	NO This requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, mainly on gluteal and abdomen area, distant from vital nodes of the nervous system	through tegumentary apparatus, on gluteal area	NO
is used in a similar population	In adult population	In women between 25 and 50 years	NO

Demonstration of equivalence for the study RFr (Tab. 19)

Table 19. Technical, biological, and clinical considerations to prove the equivalence of the device from the study RFr with the technology under evaluation [19], [23].

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is of similar design	Multipolar resistive RF	Combination of multipolar RF and pulsed electromagnetic field	NO, they have similar RF output

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
has similar specifications and properties	Working frequency: 455 kHz	Working frequency for RF: 1 MHz Working frequency for PEMF: 15 Hz	NO The working principle and output are the same. The working frequency of RF is a little bit different
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	Resistive RF generates endogenous heat through the Joule effect	Resistive RF generates endogenous heat through the Joule effect + PEMF produces an electrical current around the cell membrane changing the electric potential of the receptors	NO, they both use RF technology
uses the same materials in contact with the same human tissues	Stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For skin laxity improvement	For facial skin laxity improvement and photoaging improvement	NO, this requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, distant from the vital node of the nervous system	through tegumentary apparatus, on the face, distant from the vital node of the nervous system	NO
is used in a similar population	In adult population	In women of mean age of 45.2 ± 5.9 years	NO

Demonstration of equivalence for the study EP

Considerations: The device under evaluation that exploits EP technology (modulated frequency 1.6÷2.1 kHz, maximum output current 3 mA) is compared to several equivalent devices using the same technology [24]. The principle of functioning and the intended purpose are the same, thus demonstrating that there

are **no significant different characteristics** between the technologies which can affect clinical performance and safety.

Demonstration of equivalence for the study EST (Tab. 20)

Table 20. Technical, biological, and clinical considerations to prove the equivalence of the device from the study EST with the technology under evaluation [18], [25].

Technical, biological, and clinical considerations The device:	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Device emitting alternating current (Russian current-Kotz)	Device emitting alternating current (Russian current Kotz)	NO, they have similar output
has similar specifications and properties	Working frequency: 2.5 kHz modulated at 75 Hz Max output current: 5 mA	Working frequency: 2.5 kHz modulated at 75 Hz Max output current: 6 mA	NO The working frequency is the same
uses similar deployment methods where relevant	Electrodes	Electrodes	NO
has similar principles of operation and critical performance requirements	Russian current (Kotz) to stimulate muscle contraction	Russian current (Kotz) to stimulate muscle contraction	NO
uses the same materials in contact with the same human tissues	Applicators made of stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For electrical muscle stimulation	For electrical muscle stimulation	NO, this requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus on knee extensors, but it can be applied in other body parts, distant from the vital nodes of the nervous system	NO
is used in a similar population	In adult population	In the male population aged between 23 and 48 years	NO

Demonstration of equivalence for the study LLLT (Tab. 21)

Table 21. Technical, biological, and clinical considerations to prove the equivalence of the device from the study LLLT with the technology under evaluation [19], [26].

Technical, biological, and clinical considerations **The device:**	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Low-level laser therapy	Low-level laser therapy	NO, they have similar output
has similar specifications and properties	Wavelength: 635 ÷ 760 nm	Wavelength: 635 ÷ 680 nm	NO The wavelength is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	LLLT emits light at a specific wavelength providing a non-thermal effect	LLLT emits light at a specific wavelength providing a non-thermal effect	NO
uses the same materials in contact with the same human tissues	PVC	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	For body contouring	For body contouring	NO, this requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus, on the waist but it can be used on any body part distant from the vital nodes of the nervous system	NO
is used in a similar population	In adult population	In the adult population of an average age of 48 years	NO

Demonstration of equivalence for the study PS.1 (Tab. 22)

Table 22. Technical, biological, and clinical considerations to prove the equivalence of the device from the study PS.1 with the technology under evaluation [19], [27].

Technical, biological, and clinical considerations **The device:**	**Device under evaluation**	**Equivalent device**	**Differences (YES or NO)**
is of similar design	Phototherapy	Phototherapy	NO, they have similar output

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
has similar specifications and properties	Red light: wavelength 635 nm; Max irradiance: 2.5 mW/cm^2 Blue light: wavelength 456 nm; Max irradiance 4.5 mW/cm^2	Red light: wavelength 660 nm; Irradiance: 2.67 mW/cm^2 Blue light: wavelength 415 nm; Irradiance 4.23 mW/cm^2	NO The wavelength is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	Biostimulation with blue and red light	Biostimulation with blue and red light	NO
uses the same materials in contact with the same human tissues	Stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	To face acne issue	To face acne issue	NO, this requirement is necessary for the clinical data selection process)
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus, distant from the vital nodes of the nervous system	NO
is used in a similar population	In adult population	In population from 14 to 50 years	NO

Demonstration of equivalence for the study PS.2 (Tab. 23)

Table 23. Technical, biological, and clinical considerations to prove the equivalence of the device from the study PS.2 with the technology under evaluation [19], [28].

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is of similar design	Phototherapy	Phototherapy	NO, they have similar output
has similar specifications and properties	Yellow light: wavelength 590 nm; Max irradiance: 1.0 mW/cm^2	Yellow light: Wavelength 590 nm; Fluence: 0.1 J/cm^2	NO The wavelength is the same
uses similar deployment methods where relevant	Applied parts	Applied parts	NO

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
has similar principles of operation and critical performance requirements	Biostimulation with a light source	Biostimulation with a light source	NO
uses the same materials in contact with the same human tissues	Stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	To improve photoaging	To improve photoaging	NO, this requirement is necessary for the clinical data selection process)
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus, on the face, distant from the vital nodes of the nervous system	NO
is used in a similar population	In adult population	In adult population	NO

Demonstration of equivalence for the study US (Tab. 24)

Table 24. Technical, biological, and clinical considerations to prove the equivalence of the device from the study US with the technology under evaluation [19], [29].

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is of similar design	US device	US device	NO, they have similar output
has similar specifications and properties	Working frequency: 1 MHz modulated (max intensity 3 W/cm^2)	Working frequency: 1 MHz (max intensity of 0.4 W/cm^2 and 0.08 W/cm^2 respectively for continuous and pulsed ultrasound type wave)	NO The working frequency is the same
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	US waves are absorbed by human tissues, provoking a thermal effect responsible for vasodilation	US waves are absorbed by human tissues, provoking a thermal effect responsible for vasodilation	NO

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
uses the same materials in contact with the same human tissues	Stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	To improve endothelial function	To improve endothelial function	NO, this requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus, over the brachial artery	NO
is used in a similar population	In adult population	In the adult population (age between 18 and 35 years old)	NO

Demonstration of equivalence for the study CV (Tab. 25)

Table 25. Technical, biological, and clinical considerations to prove the equivalence of the device from the study CV with the technology under evaluation [19], [30].

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is of similar design	Low-frequency US device at 40 kHz	Low-frequency US device at 33 kHz ± 3 kHz	NO, they have similar output
has similar specifications and properties	Working frequency: 40 kHz	Working frequency: 33 kHz ± 3 kHz	NO The working frequency is similar
uses similar deployment methods where relevant	Applied parts	Applied parts	NO
has similar principles of operation and critical performance requirements	CV creates microbubbles inside the interstitial liquid which implode, destroying adipocytes	CV creates microbubbles inside the interstitial liquid which implode, destroying adipocytes	NO
uses the same materials in contact with the same human tissues	Stainless steel	The material is not specified	It is not possible to say if the materials are different or not
is used for the same clinical condition or purpose	To reduce excessive localized fat	In this specific case to reduce lipomas (composed of lobules of adipocytes)	NO, this requirement is necessary for the clinical data selection process

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is used at the same site in the body	through tegumentary apparatus, distant from the vital nodes of the nervous system	through tegumentary apparatus, on lipomas	NO
is used in a similar population	In adult population	In adult population (average age 48 years old)	NO

Demonstration of equivalence for the study PT (Tab. 26)

Table 26. Technical, biological, and clinical considerations to prove the equivalence of the device from the study PT with the technology under evaluation [19], [31].

Technical, biological, and clinical considerations The device:	Device under evaluation	Equivalent device	Differences (YES or NO)
is of similar design	Sequential pneumatic compression through applied parts (leggins for lower limbs with 8 chambers)	Sequential pneumatic compression through applied parts (leggins for lower limbs with 3 chambers)	NO, they apply external pressure on limbs
has similar specifications and properties	Max pressure: 120 mmHg per area (10 levels of pressure)	Pressure: From 65 to 45 mmHg in a distal to proximal direction	NO They exploit the same principle of functioning
uses similar deployment methods where relevant	Applied parts for lower limbs, arms and abdomen	Applied parts for lower limbs	NO
has similar principles of operation and critical performance requirements	Pneumatic compression increases the shear stress of vessels which stimulates nitric oxide production to enhance venous return. The compression is sequential to emulate the physiological fluid direction	Pneumatic compression increases the shear stress of vessels which stimulates nitric oxide production to enhance venous return. The compression is sequential to emulate the physiological fluid direction	NO
uses the same materials in contact with the same human tissues	Synthetic fabric	The material is not specified	It is not possible to say if the materials are different or not

Technical, biological, and clinical considerations **The device:**	Device under evaluation	Equivalent device	Differences (YES or NO)
is used for the same clinical condition or purpose	To improve venous return and lymphatic drainage	To improve venous return and lymphatic drainage	NO, this requirement is necessary for the clinical data selection process
is used at the same site in the body	through tegumentary apparatus, on the limbs and abdomen, distant from the vital nodes of the nervous system	through tegumentary apparatus, on the lower limbs, distant from the vital nodes of the nervous system	NO
is used in a similar population	In adult population	In adult population (average age 41 years old)	NO

Additional considerations to demonstrate the equivalence

The devices coming from the literature studies have the following similar characteristics with the technologies under evaluation.

- They are used under **similar conditions of use** in aesthetic studios.
- They are **in contact with intact skin** for a few minutes.
- They do **not release** any substance.
- They are used by **qualified personnel**.
- They do not present any relevant critical performance [19].

Final considerations about the equivalence

The equivalence of the devices from the studies with the lipolysis devices under evaluation is confirmed because there are **NO significant different characteristics** between the mentioned devices that can affect clinical performance and safety.

Results from the studies

Results from the study RFc

Performance: around 25% reduction of collagen fibrous thickness was observed after RF treatment. Thus, RF guarantees improvement of cellulite appearance [22].

Safety: comfortable temperature during RF treatment [22].

Results from the study RFr

Performance: improvement of skin texture in almost all the patients. Skin laxity improved in four patients, nasolabial fold in one of them, and facial contour in three of them [23].

Safety: At week 1 of treatment, three patients experienced face redness; at weeks 2 and 3 one patient experienced erythema. Thereafter, no other side-effects [23].

Results from the study EP

Performance: new aqueous pathways are created within the stratum corneum or/and existing ones are enlarged through the application of electrical current. The skin resistance drops by several orders of magnitude. Transdermal transport occurs through localized transport regions (LTR). The size and number of LTR increase linearly with the number and duration of pulses [24].

Safety: marks left by the electrodes (applicators) disappear after a few minutes. The main unpleasant sensation is due to muscle contraction. No skin irritation, only rise of skin temperature (due to the Joule effect) [24].

Results from the study EST

Performance: during the electrical muscle stimulation (EMS) sessions, the torque output increased to 30% maximal voluntary isometric contraction strength (MVC) in the first 15 contractions. The skin temperature of the stimulated leg raised about 2°C, reflecting the increased blood flow due to vasodilation induced by the electrical current [25].

Safety: Just discomfort. Muscle soreness was evaluated under half of a VAS at 48 hours post-EMS and then disappeared after 96 hours [25].

Results from the study LLLT

Performance:

- 0.4-0.5 cm loss in waist girth after each treatment;
- a reduction of 2.15 cm in waist girth after 4 weeks.

Safety: No adverse event after the treatment [26].

Results from the study PS.1

Performance: the mean improvement was 45% and 58% in comedones and 63% and 76% in inflammatory lesions, using blue light and combined blue-red light

radiation, respectively [27].

Safety: minor side-effects, such as flare-up of acne, dryness, facial rash, and headaches were experienced by a small percentage of patients [27].

Results from the study PS.2

Performance: signs of photoaging were reduced in 90% of subjects. Smoother texture and reduced peri-orbital rhytids, erythema, and pigmentation. After 4 months of treatments, elastosis and redness improved. Ten patients showed increased collagen in the papillary dermis.

Safety: No side-effect. No pain [28].

Results from the study US

Performance: The mean hyperaemic diameter of the brachial artery was 3.99 mm and 4.05 mm with pulsed ultrasound type wave (PUT) and continuous ultrasound type wave (CUT) respectively, compared to 3.89 mm of the baseline. The flow-mediated dilation was around 14% and 15% with PUT and CUT respectively, compared to the basal value of 11% [29].

Safety: US energy absorbed by human tissues provokes a thermal effect contributing only to vasodilation. The rise of body temperature can be disregarded. No other side-effect [29].

Results from the study CV

Performance: CV destroys the adipocytes localized in a mass, such as lipoma. The average initial dimension of the lipoma was 54.85 mm, which became 41.68 mm one month after the treatment [30].

Safety: No contraindication. During the treatment, the rise of skin temperature around the lipoma was well tolerated [30].

Results from the study PT

Performance: the pre-and post-treatment outcomes are reported in Tab. 27 for the control and experimental groups. Both groups showed improvement in venous blood velocity after the therapy, but the improvement was higher in the experimental group who received also the sequential pneumatic compression (SPC) treatment [31].

Table 27. Pre- and post- treatment measures for control and experimental group [31].

Measure	**Pre**		**Post**	
	CG	EG	CG	EG
Maximum BV (cm/s)	10.3 ± 2.54	10.6 ±3.57	15.6 ± 3.33	19.0 ± 3.93
Mean BV (cm/s)	5.6 ± 0.97	6.2 ± 1.26	9.5 ± 3.25	11.3 ± 2.31

CG= control group; EG= experimental group; BV= blood velocity.

Safety: No serious side-effect. SPC is painless [31].

Conclusions to the CER

The positive outcomes associated with the equivalent devices [22]–[31] from the literature prove that the lipolysis devices under evaluation are **effective**. The technologies are also **safe** since no relevant side-effects occurred. After the treatments, minor complications such as erythema, redness, and rashes could occur but they are resolvable in a short time.

CHAPTER 6
DISCUSSION

6.1 Technical Documentation

The technical documentation reported for the laser and the lipolysis devices according to Annex II of Regulation 2017/745 provides the information to be supplied by manufacturers for the conformity assessment procedure [1].

The technical documentation includes the most important information related to the device, from the general description with the scope, intended users, and target groups to the detailed technical characteristics. Both Epil808 2.0 and family eCosmo are active electrical devices intended for professional use; this means that only qualified beauticians who received the proper training are authorized to use them. These devices have different principles of functioning: the laser operates through selective photothermolysis, whereas the family eCosmo exploits several different technologies. The laser emits monochromatic light energy which, hitting the human tissues, is mainly absorbed by the melanin of hair follicles, causing hair removal. Instead, the family eCosmo has many principles of functioning:

- resistive and capacitive RF exploit an electric field inducing a current which generates heat at the human tissue level through the Joule effect. In the resistive RF, there is a direct coupling between the applied part and the human tissues; instead, in the capacitive RF, there is a separating dielectric.
- US consists of acoustic pressure waves inducing a hyperthermic effect through a working frequency of 1 MHz and a cavitation (mechanical) effect through a working frequency of 38 kHz.
- Photobiostimulation induces intracellular photochemical reactions through light energy irradiated towards chromophores [28].
- LLLT emits light energy and acts through photochemical reactions to promote micro-pores formation in the adipocytes' membranes [26].

- PT consists of pressure waves generated by a pneumatic pump to perform a massage from the peripheral limbs to the proximal direction.
- EP uses electrical pulses to open aqueous channels within cellular membranes to inoculate substances.
- EST exploits alternating electrical current to stimulate motor neurons for muscular contraction.

The risk class of the devices is a crucial point because it determines the level of risk for the human body but also the correct conformity assessment procedure to be followed. The devices are classified according to rule 9 of Annex VIII because they are active and provide energy to the human body [1]. However, the difference is that eCosmo and Slim pAct fall within class IIa; instead, the laser belongs to class IIb given the high-intensity light energy emitted and the possible harms that can be experienced in case of overexposure. Due to the risks connected to the laser beam, manufacturers are obliged to affix warning labels on the device and in the environment intended for use [2].
However, the risk class of the devices of the current study may change if novelties will be introduced with the official publication of CS. The definition in Rule 9 contains the statement “therapeutic devices” [1] which is appropriate for MD, not for devices without a medical intent. Thus, manufacturers are waiting for clarifications regarding this issue.

From a functional point of view, all devices have the display unit with the CPU and the applicators to provide the treatments (Fig. 22, 28, 29). The laser has also the hydraulic case (Fig. 22) which contains the circuit to cool the laser diode. The presence of the pedal in Epil808 2.0 and eCosmo (Fig. 22, 28) guarantees that the treatments are provided only under the user’s authorization. Given its higher risk class, the laser has additional safety elements: the button on the laser handpiece, the interlock connector, and the emergency stop button legally required (Fig. 22) [2], [38]. Slim pAct has a safety system that can be actuated by the subject under treatment, the wired remote control (Fig. 29). The devices are driven by software and the user sets up the parameters through the touch-screen (Fig. 24, 30). The manufacturers usually provide a table where they indicate how to correctly combine

the parametric values to achieve effective results, considering the different physiology of the subjects. For the laser epilation, the efficiency depends on the hair and phenotype characteristics, whereas when using lipolysis devices, the results depend on the anatomical characteristics, including the body mass index and metabolic characteristics, and treated areas [2].

The values of the technical characteristics following the Italian Law related to the electromechanical devices of the aesthetic environment [14] have been reported in Tab. 5, 7, 8. Some of these parameters, like the working frequency and fluence, were also considered when choosing the literature studies about equivalent MD to perform the clinical evaluation.

Since the devices are electrical, they are mains-operated and cannot be connected to a power supply not compliant with Community Laws [38]. Moreover, users have to observe precautions in terms of electromagnetic compatibility and they cannot use the devices together with other electrical equipment, otherwise, interferences might cause hazardous situations for the subjects.

The accessories are provided together with the device and they are necessary for its correct use and maintenance [2]. Epil808 2.0, which falls within class IV (Tab. 5) according to the international classification of lasers, can emit scattered radiations and burns can be provoked if the laser beam intensity is not controlled. Thus, goggles for the patients and the users, included in the accessories, are fundamental for eye protection [2].

The materials of the functional elements were discussed in detail in sections 5.1.1 and 5.1.2, giving particular attention to the materials of the applicators which were the subjects of the biological evaluation. The physicochemical characterization, the manufacturing processes, and the use in the medical field were analyzed for the materials in contact with the subjects [12]. These materials have to be compliant with the harmonized standard ISO 10993-1:2018 and they have to pass the biological tests specific for a certain type and duration of contact (Tab. 6, 9) [12]. As an alternative, strong rationals for not performing the tests have to be provided. For this study, the tests regarding toxicity, sensitization, irritation, and intracutaneous reactivity [12] were not performed. The reason is that the materials used to make the applicators were the same (same chemical and physical

characteristics) already applied in the medical field under similar conditions of use, like the inorganic glass (in contact with intact skin for a limited period), or were the same used for more invasive applications, such as polyoxymethylene and stainless steel. Given these justifications, the materials were considered biocompatible for their intended purposes.

The documentation related to the design, manufacture, and validation processes following the standard about the QMS of MD shall be submitted for the conformity assessment evaluation [45]. In addition, information about special manufacturing processes has to be included if they are performed [1]. Nevertheless, these documents are missing in sections 5.1.1 and 5.1.2 as well as the labels and IFU. For all the devices, the IFU shall include prescriptions about the operating environment, indications on cleaning and disinfection of the devices, and a list of warnings and contraindications to ensure safe use. The IFU for the laser shall also contain indications about the minimum and maximum radiation intensity, duration, frequency, and spot size [1], [2].

To pass the conformity assessment, devices have to comply with GSPR and for this reason, manufacturers or expert external laboratories shall conduct tests to validate the devices. In addition, the harmonized standards applied have to be indicated [1]. In this case, the tests conducted by Elits Group to validate the devices concern the electrical safety in compliance with EN 60601-1 [38] and the electromagnetic compatibility in line with EN 60601-1-2 [39]. Considering the several different technologies, also other standards had to be observed:

- CEI EN 60601-2-22 for the laser equipment [40];
- CEI EN 60601-2-10 for muscular stimulators [46];
- CEI EN 60601-2-5 for ultrasonic physiotherapy equipment [41];
- CEI EN 60601-2-57 for non-laser light source equipment [47].

Furthermore, usability tests and tests to validate the software were performed by the manufacturers and their documentation has to be included.

Since the devices do not belong to risk class I, all the technical documents have to be analyzed by a NB together with the documentation related to the QMS. Also, the

documentation concerning PMS (according to Annex III), which is not reported in this study, has to be included [1].

6.2 Risk Management

The current risk analysis is included in the technical documentation to be provided for the conformity assessment evaluation [1]. The results were reported in Tab. 10 and Tab. 11 respectively for the laser and the lipolysis devices and analyzed only some possible hazards and hazardous situations which could be experienced.

Rationales for the assignment of values to IG, IPN, and IPF before adopting control measures (Tab. 10, 11) are provided in the following paragraph. However, a quantitative evaluation (Tab. 10, 11) was not possible because many hazards were not experienced but just foreseen. Moreover, the harm severity may depend on the physiological characteristics of the subjects, treatment intensity, and treated areas [2]. To discuss the risk evaluation, it is important to remind that the case of a single fault condition does not refer only to a device defect or malfunction, but it also refers to the lack of IFU's observation.
The argumentation about the values of IG, IPN, and IPF after implementing control measures is not relevant because all indexes assumed similar values and the risks became all acceptable. For this reason, an analysis of risks/benefits was not carried out afterwards.

Electromagnetic energy

- 1 - 2. Mains voltage and leakage current. They are the most harmful hazards which can provoke electric shock and lead to people's death (IG=6).
- 3 - 4. Electric and magnetic fields. The devices are electrical and can be subjected to these types of hazards which could lead to a lesion that requires medical intervention (IG=4). The issue of magnetic interference is still present (IG=2) even after the adoption of control measures.
- 5. Electric discharge. This hazard is responsible for causing minor electric shocks. Similar considerations as the hazard number 4 can be done. In this

case, the probability of occurrence of the harm is higher if the device is not used in a suitable environment (IPF=3).

These hazards related to electromagnetic energy were controlled by tests carried out in conformity with the standard related to the basic safety of electrical medical equipment [38]. Measures of leakage currents and patient auxiliary currents were performed as well as protective earth connections were adopted. Moreover, these devices belong to the safety electrical class I (Tab. 5, 7, 8) and have type BF applied parts [38], which are floating with respect to the main electric circuit.

Radiations

- 6. Ionizing radiation. These devices do not emit this type of radiation.
- 7. Not ionizing radiation. The gravity is greater for the laser radiations whose intensity, if not controlled, can cause permanent lesions (IG=5).

Thermal energy

- 8. High temperature. Given its high-intensity light emission, the laser can rise a patient's body temperature and provoke burns (IG=5) in case of overexposure (IPF=5). For this reason, this last one has to be avoided as IFU indicate.
- 9. Low temperature. This hazard mainly refers to the violation of temperature of use and storage (IPF= 3). Not to damage the devices, the equipment has to be stored under suitable environmental conditions, as indicated in the IFU. In addition, not to provoke discomfort for the patients, treatments have to be performed in aesthetic studios with the suitable temperature of use.

Mechanical energy

- 10. Falling objects. This situation could happen if the blocks of the laser are not correctly assembled and installed (IPF=3) or in case the applied parts of the devices accidentally fall from the user's hands during the treatment.

Potential energy

- 12. Gravitational force. This hazard is independent of a single fault condition and it can be associated with the possibility of falling of the entire device during its displacement because the devices are transportable.

Acoustic energy

- 14. US energy. This hazard regards only the US technology of eCosmo. The US induces hyperthermic effects in human bodies and, in case of overexposure, relevant side-effects may be provoked (IG=4).

Biological hazards

- 15. Bacteria, fungi, viruses. Without a correct cleaning of the applied parts in contact with the subject (IPF=3), the patient can be infected and may need medical treatments to recover (IG=4). Even following correct cleaning procedures, there is still the remote possibility that micro-organisms cause infections as well.

Immunological agents

- 16. Allergens. The allergic reaction (IG=4) caused by the use of not biocompatible materials is independent of a fault condition. This hazard is connected with the choice of materials that have to pass the biological evaluation [12].
- 17. Irritating substances. The possibility to compromise the skin (IG=3) augments in case the cleaning prescriptions are not followed (IPF= 3).

Chemical hazards

- 19. Exposure of respiratory tracts to acids, alkalines, and oxidants. If residues left by cleaning are not correctly removed, there is the probability to provoke relevant side-effects (IG=4).
- 22. Solvents. The same consideration as 19.
- 23. Cleaning and disinfecting agents. The same consideration as 19 & 22.

Functioning

- 24. Not correct functions (alarms). The IG is higher for the laser. The probability of harm occurrence increases in the case of a single fault

condition (IPF=5). Two different safety systems exist for Epil808 2.0 and the family eCosmo and ensure that in case of malfunctions, only uncomfortable situations could verify and not serious harms. The laser has a redundant safety system on the HW part. Instead, messages of errors and alarms are provided via software for the family eCosmo.

- 25. Lost or reduced functions. The hazard is due to a fault condition (IPF=5), but the issue is just the lack of treatment and the severity is negligible (IG=2).

Errors of use

- 26. Errors of attention. This hazard is independent of a normal or fault condition because it depends on the user's attention. The severity of the harm may be higher for the laser (IG=4) because there is the possibility to direct the laser beam towards the eyes and cause sight damage.
- 27. Errors related to experience and violation of procedures. Similar considerations as 26.

Labels

- 28 - 29. Incomplete IFU and Inadequate description of performance characteristics. In case indications in the IFU are missing, the probability that side-effects occur is higher (IPF=3) than in normal conditions. The severity of a possible injury is a little bit higher for the laser (IG=4) than for the lipolysis devices because the first one belongs to a higher risk class.
- 30 - 31. Inadequate description of the intended use and Inadequate provisions of limitations. The risks related to these hazards are evaluated in the same way for all the devices because independently of the kind of treatment if they are performed on not eligible subjects, they can provoke severe lesions (IG=4).

Operative instructions

- 32 - 33. Inadequate description of accessories to be used and Inadequate description of preliminary controls before use. In case the devices are used with the wrong accessories or without the proper preliminary controls,

severe damages could be provoked (IG=5). An example may be connecting the devices with other power cables with respect to the ones provided by the manufacturers or not controlling the integrity of the parts before performing the treatments.

- 34. Complicated IFU. The problem is that the user may operate without following the IFU (IPF= 3) due to the difficulty to interpret them. However, the problem is not relevant (IG=2) because he received the training for the use.

Warnings

- 35. Side-effects. If the contraindications reported in the IFU are not taken into account (IPF= 4), relevant side-effects can be experienced (IG=4).

Finally, after implementing the control risk, all the single RR were acceptable and the same for the overall RR. This means that the risk analysis got a positive evaluation. However, a risk management review has to be done before the devices are placed on the market [2].

Additional considerations for the hazards which got higher scores are provided.

- The hazard related to the **electric shock** is monitored through the choice of a power supply compliant to the international standard of basic safety for MD [38] and through the tests regarding electrical safety performed by the internal or external laboratories.
- **Allergenicity** of materials in direct contact with the subjects is controlled through the choice of biocompatible materials according to ISO 10993-1:2018 [12].
- The hazards related to the **principles of functioning** are accepted because these technologies are established and applied by people who have the proper knowledge and follow the IFU. Despite the higher risk class of the laser technology, the safety redundant control on HW and the emergency stop button are additional elements that minimize any possible risk.

The risk management file was developed for Epil808 2.0 and the family eCosmo, but this document needs to be updated during the life cycle of the devices with the information coming from PMS concerning new risks and incidents [2].

6.3 Clinical Evaluation

Epil808 2.0 and the family eCosmo were examined in the current clinical evaluation. To demonstrate the performance and safety of the devices, both favourable and unfavourable data were chosen from literature studies [20]–[31]. Specifically, favourable data had to show the benefits of the technologies, instead unfavourable data had to provide minimal side effects.

Firstly, the problems faced by the different technologies were described. The information found in Pubmed mainly refers to the causes, diagnosis, and treatment methods for hirsutism, cellulite, photoaging, and venous insufficiency. For what concerns the solutions to the hirsutism issue (Tab. 12), they are just temporarily effective, except the laser technology which guarantees long-lasting epilation. Regarding the methods to face cellulite (Tab. 16), even if surgery is the most effective one, it is invasive. Thus, RF technologies are preferred because they are non-invasive and allow to reach optimal results in terms of adipose tissue reduction. As far as concerns venous insufficiency, tips to face the problem are physical activity, massages, and PT [31].

The data chosen to perform this clinical evaluation came from CE marked MD from the literature [20]–[31]. All the data got a total high positive score (Tab. 13, 17), meaning that they provide good evidence to prove the performance and safety of the technologies under evaluation. The benefits were supported by clinical and statistical significance (Tab. 13, 17). A negative remark can be done for the studies about the equivalent MD to the technologies of the family eCosmo because they did not provide outcomes in the follow-up period (Tab. 17).

The equivalence of the MD from literature studies [20]–[31] with the examined devices was demonstrated in terms of similar technical, biological, and clinical

characteristics (Tab. 14,15, 18-26) [19]. The most important features to prove the equivalence were:

- similar design of the devices;
- similar properties;
- similar working principles;
- same intended purpose;
- similar materials in contact with the patient;
- similar intended target group and users [19].

Since the previous characteristics were verified without relevant differences between the MD from the studies and those under evaluation, the equivalence was confirmed. On the contrary, in case of impossibility to demonstrate the equivalence, clinical investigations had to be performed [2].

From the results about **performance** and **safety** reported in sections 5.3.1 and 5.3.2, it was possible to conclude that the technologies analyzed in the current CER are effective and safe for their intended purposes. In particular:

- the laser guarantees long-term hair removal;
- RF is able to face cellulite and skin laxity;
- EP can inoculate active principles in cutaneous layers;
- EST can maintain muscular tropism;
- US promotes vasodilation;
- CV and LLLT reduce localized fat;
- PT aids venous return.

The chosen data were also good to prove that benefits overcome possible risks. In fact, as the studies [20]–[31] demonstrate, all the treatments were performed without causing severe side effects to the subjects. Only negligible and transitory contraindications could be experienced, which did not compromise the person's health status and, for this reason, they can be accepted.

The CER needs to be regularly updated with a frequency that depends on new information coming from PMS and on the level of risks the device can introduce [13]. In this case, since the technologies are established and require a NB for the

conformity evaluation, the CER can be updated when the NB reviews the manufacturers' documentation if no relevant incident occurs during the use.

6.4 Devices Without an Intended Medical Purpose

Epil808 2.0 and family eCosmo belong respectively to the high-intensity electromagnetic radiation emitting equipment and to the equipment intended for lipolysis [2]. They represent only small categories of Annex XVI devices because there are many others covered by Regulation 2017/745.

Devices of Annex XVI have to comply with CS and MDR will definitely apply to these devices after CS application [2]. Even if this legislation has not been already published, manufacturers of these products have begun to adjust the manufacturing and production phases to comply with MDR. In fact, the New Regulation imposes the same legal dispositions of MD to devices without a medical intent and manufacturers have to:

- prepare the technical documentation according to Annex II and III;
- classify their devices according to the New Risk Classification;
- register to Eudamed;
- provide the information for the unique identification of their devices;
- comply with GSPR;
- establish and document a QMS interconnected with PMS and risk management;
- conduct a clinical evaluation;
- carry out a clinical investigation in case of impossibility to demonstrate the equivalence with analogous devices with a medical purpose [1].

Actually, the main issue is the uncertainty of dispositions contained in the CS. Despite draft CS are circulating and can be consulted by manufacturers, they are still not definitive and modifications may appear in the next official release. By the way, CS are expected to be released in the first half of 2022 and once CS will be published, manufacturers of Annex XVI devices will start the European certification procedure.

If the device belongs to class I, manufacturers have to carry out a self-conformity assessment and afterwards, they can place their device on the market with the CE marking affixed on it. Instead, if their device falls within higher risk classes (mainly class IIa or IIb), manufacturers have to sign an agreement with the NB to conduct a QMS and technical documentation assessment. Once they achieve the certificates of conformity, they place their CE marked product on the market under MDR [1].

To conclude, the documents developed in the current work were only an attempt in view of the next certification procedure under Regulation 2017/745. In the meantime, these aesthetic devices are still placed on the market in conformity with the Italian Law concerning electromechanical devices of the aesthetic environment [14].

CONCLUSIONS

In conclusion, the technical documentation provided in the current work according to MDR, including risk management and the CER, was developed for aesthetic Annex XVI devices [1]. Specifically, this study applied to aesthetic devices designed, manufactured, and produced by the company Elits Group that is waiting for the official release of CS to carry out the certification procedure under Regulation 2017/745.

References

[1] European Commission, “Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices,” *Off. J. Eur. Union*, 2017.

[2] European Commission and Medical Device Coordination Group, “Draft Common Specifications for the groups of products without an intended medical purpose listed in Annex XVI of Regulation (EU) 2017/745,” 2022.

[3] European Commission, “Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices,” *Off. J. Eur. Union*, 2020.

[4] N. Clemens, “The New European Medical Device Regulation 2017/745: Main Changes and Challenges,” *Res. Gate*, no. January, pp. 1–26, 2017.

[5] N. Clemens, “The European Medical Device Regulation 2017/745/EU: Changes and Impact on Stakeholders,” *J. Clin. Res. Best Pract.*, vol. 14, no. 9, 2018.

[6] European Commission, “Medical devices change of legislation. What you need to know!,” 2020.

[7] Medical Device Coordination Group, “MDCG 2021-6 Regulation (EU) 2017 / 745 – Questions & Answers regarding clinical investigation,” 2021.

[8] BSI GROUP, “Comparison of the articles of the European Medical Devices Directive (93/42/EEC) and the Medical Devices Regulation (2017/745),” *BSI White Pap.*, pp. 1–7, 2017.

[9] BSI GROUP, “The European Medical Devices Regulations - What are the requirements for vigilance reporting and post-market surveillance?,” *BSI White Pap.*, 2017.

[10] Medical Device Coordination Group, “MDCG 2021-24 Guidance on classification of medical devices,” 2021.

[11] European Commission, "Draft Functional specifications for the European Database on Medical Devices (Eudamed) - First release," no. 1. 2019, pp. 1–91.

[12] International Electrotechnical Commission, "International Standard ISO 10993-1 Biological evaluation of medical devices- Part 1 Evaluation and testing within a risk management process," 2018.

[13] European Commission, “Guidelines on Medical Devices - clinical evaluation: a guide for manufacturers and notified bodies under Directive 93/42/EEC and 90/385/EEC,” 2016.

[14] Ministry of Economic Development and Ministry of Health, "Italian Decree number 206 of 15 October 2015 on electromechanical equipment for aesthetic activities", 2015.

[15] "Notified Bodies Nando," *European Commission official website*, [https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=34].

[16] European Commission, "Regulation (EC) No 765/2008 of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products," *Off. J. Eur. Union*, 2008.

[17] Elits Group, "Elits Group - devices, equipment, and products for aesthetic studios." [https://elitsgroup.it/].

[18] Technical Commitee 62 about electrical equipment for medical use, "CEI UNI EN ISO 14971. Medical devices - Application of risk management to medical devices", 2019.

[19] Medical Device Coordination Group, "MDCG 2020-5 Clinical Evaluation - Equivalence," 2020.

[20] C. Handrick and T. S. Alster, "Comparison of Long-Pulsed Diode and Long-Pulsed Alexandrite Lasers for Hair Removal," *Dermatologic Surg.*, vol. 27, no. 7, pp. 622–626, 2001.

[21] S. J. Jo, J. Y. Kim, J. Ban, Y. Lee, O. Kwon, and W. Koh, "Efficacy and Safety of Hair Removal with a Long-Pulsed Diode Laser Depending on the Spot Size: A Randomized, Evaluators-Blinded, Left-Right Study," *Ann. Dermatol.*, vol. 27, no. 5, pp. 517–522, 2015.

[22] R. M. Valentim Da Silva et al., "Effect of capacitive radiofrequency on the fibrosis of patients with cellulite," *Dermatol. Res. Pract.*, vol. 2013, 2013.

[23] Y. B. Lee, Y. S. Eun, J. H. Lee, M. S. Cheon, B. K. Cho, and H. J. Park, "Effects of multi-polar radiofrequency and pulsed electromagnetic field treatment in Koreans: Case series and survey study," *J. Dermatolog. Treat.*, vol. 25, no. 4, pp. 310–313, 2014.

[24] A. R. Denet, R. Vanbever, and V. Préat, "Skin electroporation for transdermal and topical delivery," *Adv. Drug Deliv. Rev.*, vol. 56, no. 5, pp. 659–674, 2004.

[25] A. Aldayel, M. Jubeau, M. McGuigan, and K. Nosaka, "Comparison between alternating and pulsed current electrical muscle stimulation for muscle and systemic acute responses," *J. Appl. Physiol.*, vol. 109, no. 3, pp. 735–744, 2010.

[26] V. K. Caruso-Davis, Mary K. Guillot, Thomas S. Podichetty, "Efficacy of Low-

Level Laser Therapy for Body Contouring and Spot Fat Reduction," *Obes. Surg.*, 2011.

[27] P. Papageorgiou, A. Katsambas, and A. C. Chu, "Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris," *Br. J. Dermatol.*, vol. 142, no. 5, pp. 973–978, 2000.

[28] R. A. Weiss, D. H. McDaniel, R. G. Geronemus, and M. A. Weiss, "Clinical trial of a novel non-thermal LED array for reversal of photoaging: Clinical, histologic, and surface profilometric results," *Lasers Surg. Med.*, vol. 36, no. 2, pp. 85–91, 2005.

[29] M. Hauck et al., "Comparison of the effects of 1 MHz and 3 MHz therapeutic ultrasound on endothelium-dependent vasodilation of humans: a randomised clinical trial," *Physiother. (United Kingdom)*, vol. 105, no. 1, pp. 120–125, 2019.

[30] S. Verardi *et al.*, "The use of stable cavitation in non-invasive treatment of localized lipomas," *J. Plast. Dermatology*, vol. 5, no. 2, pp. 157–161, 2009.

[31] A. Yamany and B. Hamdy, "Effect of sequential pneumatic compression therapy on venous blood velocity, refilling time, pain and quality of life in women with varicose veins: A randomized control study," *J. Phys. Ther. Sci.*, vol. 28, no. 7, pp. 1981–1987, 2016.

[32] Schott, "Technical Safety Information about inorganic glass," 2015.

[33] "ABS Technical data sheet," 2014.

[34] T. C. F. De Oliveira, S. D. F. S. Rocha, D. G. Ramos, C. G. Ramos, M. V. D. A. Carvalho, and M. G. Ramos, "Effects of Multipolar Radiofrequency and Pulsed Electromagnetic Field Treatment for Face and Neck Rejuvenation," *Dermatol. Res. Pract.*, vol. 2017, 2017.

[35] RG gomma s.r.l., "Rilsan Data sheet," 1993.

[36] Polyedra SPA, "PVC Data sheet," 2014.

[37] Lederplast S.p.a., "Technical data sheet LEDERTEX COSMOS 45-130."

[38] Technical Commitee 62 about electrical equipment for medical use, "CEI EN 60601-1 Medical electrical equipment Part 1: General requirements for basic safety and essential performance," 2006.

[39] Technical Commitee 62 about electrical equipment for medical use, "CEI EN 60601-1-2: Medical electrical equipment. General requirements for basic safety and essential performance. Collateral standards: Electromagnetic disturbances. Requirements and Test," 2015.

[40] Technical Commitee 62 about electrical equipment for medical use, "CEI EN

60601-2-22 Medical electrical equipment Part 2: Particular requirements for basic safety and essential performance of surgical, cosmetic, therapeutic and diagnostic laser equipment," 2013.

[41] Technical Commitee 62 about electrical equipment for medical use, "CEI EN 60601-2-5 Medical electrical equipment Part 2: Particular requirements for basic safety and essential performance of ultrasonic physiotherapy equipment." 2015.

[42] E. Matheson and J. Bain, “Hirsutism in women,” *Am. Fam. Physician*, vol. 100, no. 3, pp. 168–175, 2019.

[43] N. K. Agrawal, “Management of hirsutism,” *Indian J. Endocrinol. Metab.*, vol. 17, 2013.

[44] G. Casabona and G. Pereira, “Microfocused Ultrasound with Visualization and Calcium Hydroxylapatite for Improving Skin Laxity and Cellulite Appearance,” *Plast. Reconstr. Surg. - Glob. Open*, vol. 5, no. 7, pp. 1–8, 2017.

[45] Technical Commitee 62 about electrical equipment for medical use, "CEI UNI EN/ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes." 2016.

[46] Technical Commitee 62 about electrical equipment for medical use, "CEI EN 60601-2-10 Medical electrical equipment Part 2: Particular requirements for basic safety and essential performance of nerve and muscle stimulators," 2015.

[47] Technical Commitee 62 about electrical equipment for medical use, "CEI EN 60601-2-57 Medical electrical equipment Part 2: Particular requirements for the basic safety and essential performance of non-laser light source equipment intended for therapeutic, diagnostic, monitoring and cosmetic/aesthetic use," 2011.

Acknowledgements

I would like to extend my sincere thanks to my advisor, professor Laura Burattini, for her availability and the opportunity of doing the internship within a company.

I would like to offer my special thanks to Andrea Santi, the chief executive officer of Elits Group, for his assistance and letting me make this training experience in the medical device industry and to Mauro Veroli, my company tutor, for his technical support. I would like to thank also Sandro Crocelli, the technical consultant of Elits Group, for the advice concerning the medical device regulatory framework.

I wish also to extend my special thanks to all the company Elits Group for the support and welcome received.

Certainly, I appreciate all the support I received from my family and my friends over the academic years.