

The Regulatory Framework of Medical Devices: From the 90s to Today

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ABSTRACT

In Europe the medical devices sector is yet little known, probably because of its fragmentation in several products extremely heterogeneous between them. However, that is a sector of great importance in healthcare, contributing to the improvement of the level of health protection through the development of innovative solutions for diagnosis, prevention, treatment and rehabilitation. This fragmentation is matched by an equally complex regulatory framework that has not undergone updates for more than twenty years. Finally, on May 26, 2017, the Regulation (EU) 2017/745 for medical devices and the Regulation (EU) 2017/746 for in vitro diagnostic medical devices respectively came into force. Their aim is to improve the safety of medical devices while allowing patients to benefit of innovative health care solutions in a timely manner. The stakeholders involved were originally granted a transition period of 3 years to comply with Regulation 2017/745 and of 5 years for Regulation 2017/746. Due to the COVID-19 pandemic, the first 3-year deadline has been extended to May 26, 2021. But this deadline is just around the corner and we are still in full pandemic.

Keywords: medical device, in vitro diagnostic medical device, classification, notified body, clinical investigation, ISO 14155: 2011.

INTRODUCTION

Until 25 May 2017, the core legal framework of medical devices (MDs) consisted of only three directives:

- 1) Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990).
- 2) Council Directive 93/42/EEC on Medical Devices (MDD) (1993).
- 3) Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMD) (1998).

The first two directives have been harmonized by Directive 2007/47/EC.

This legislation categorized MDs into four regulatory classes: Class I, IIa, IIb and III on the basis of increasing risks associated with their intended use, described in Annex IX of the Directive 93/42/EEC. The classification rules were based on criteria such as the duration of use, invasive nature, contact with critical parts of the body, biological effect and the supply of energy.

But first of all, it was clarified what is meant by a MD. According to Article 1 of Directive 93/42 and Directive 2007/47, MD means “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process, control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;” [1,2].

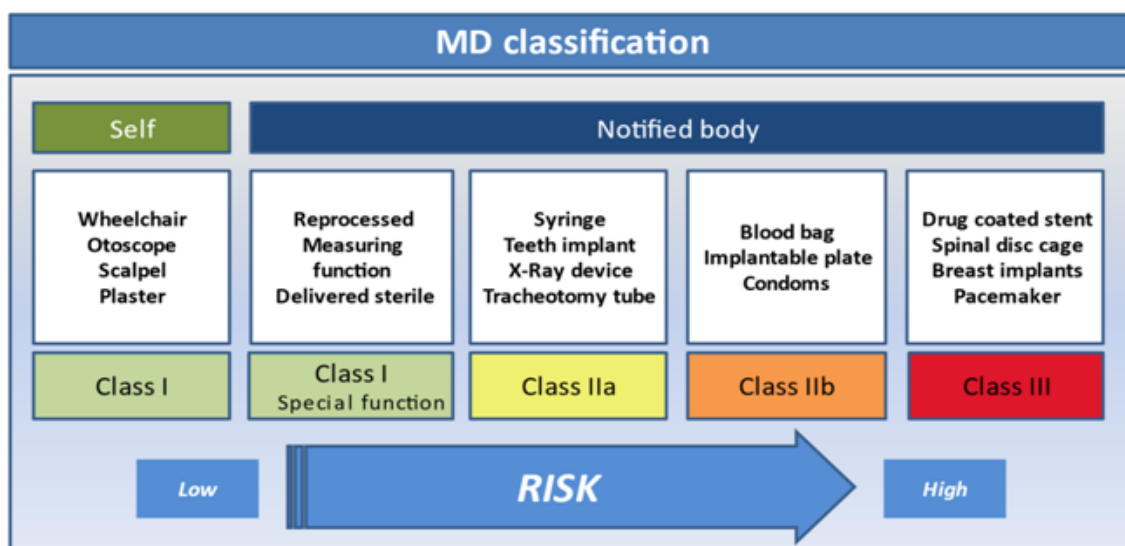


Fig 1. MD classification

So, a product may be considered as a medical device if it doesn't achieve one of the functions provided for in the definition by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

That definition covers a wide range of products that are very different in term of technology and potential risk for the patients. Matter of fact, thermometers for measuring body temperature, plasters, prophylactics, heart valves, pacemakers are all MDs. In Europe, it is estimated that there are at least half a million MDs with a total sales amount to 100 billion Euros, and more than half million employees [3]. It is a market accounts for one quarter of worldwide market and the EU “Big Five” (Germany, France, Italy, UK and Spain) occupy 70% of the EU market. The placing on the market of MDs is regulated on a Community basis. MDs must satisfy the “Essential Requirements” namely they shall be designed and manufactured in such a way that their use, during conditions of normal use, does not compromise the clinical condition or the safety of patients and users. This approach, carried out with the same mechanism throughout the European Economic Area (EFTA), is called "new approach". It was adopted by the European Union with the EU Council resolution of 7 May 1985 with the aim of removing technical barriers to trade in the internal market and of ensuring that MDs satisfy the same essential requirements in the different countries of the European Union. Consequently, the competent authorities of each Member State allow the circulation of MDs manufactured in other Member States on the basis of legal certainty of their equivalence. Moreover, the “new approach” forces each country not to

introduce, by means of national standards, restrictions on the free movement of MDs that have satisfied essential requirements. Regulations relating to the safety and performance of MDs in the EU were harmonized in the 1990s, following the New Approach on legislative principles. A fundamental characteristic of the “new approach” is that, unlike the legislation of drugs, MDs are not subject to any pre-market authorization by a regulatory authority but to a conformity assessment [4]. After 23 years from the Resolution of The Treaty of Rome in 1985, the European Council has defined that the compliance with the essential requirements laid down by Directives is demonstrated by the presence on the MD of the CE marking. Moreover, starting in the late 1990s, the European Union has reached bilateral agreements called “Mutual Recognition Agreements (MRAs)” with the objective to promote trade in goods between the European Union and third countries by providing easier access to conformity assessment and so facilitating market access. These countries are Australia, Canada, Japan, New Zealand, the USA, Israel and Switzerland [5]. In this system, the Manufacturer has a key role. It's his responsibility for ensuring that MDs meet the Essential Requirements (safety and performance) documenting it by providing a technical dossier defined “Technical File”. The matter includes documents related to the design of the MD, to risk management, to the manufacture, to possible test reports, to the labels, to the instructions for use and to the clinical evaluation. For low-risk MDs (Class I) such as a tongue depressor or colostomy bag,

the manufacturer is allowed to self-declare conformity with the Essential Requirements. For medium- to high-risk MDs (Class IIa, IIb, III), the manufacturer must call on Notified Bodies, independent companies that specialize in evaluating many products, including MDs, for CE marks and are designated by Competent Authorities to cover certain types of MDs. Lists of Notified Bodies can be searched on the NANDO (New Approach Notified and Designated Organizations) web site. The lists include the identification number of each notified body as well as the tasks for which it has been notified, and are subject to regular update [6]. First, a manufacturer of a MD selects a properly designated Notified Body in a country of the manufacturer's choosing. For approval by a Notified Body, MDs are subject to performance and reliability testing linked to the risks of their intended use. For most MDs, the standard is met if the MD successfully performs as intended in a manner in which benefits outweigh expected risks. The specific requirements for premarketing clinical studies are vague, and details of trials are typically not made available to the public. Although clinical data are required for high-risk MDs, guidelines for the nature of these studies are not binding on manufacturers or Notified Bodies.

MATERIALS AND METHODS

We conducted a systematic review of scientific literature, analysis of website of Competent Authorities, European Commission and Eurlex.

RESULTS AND DISCUSSION

This regulatory system has several limits. Notified Bodies are the first to be contested. They are private companies paid by the firms hoping to win approval, giving rise to fears over independence. In total, Europe uses 60 private firms, or “notified bodies”, that have contracts with makers. Each is overseen by a national regulator. The US system, overseen by one main regulator “Food and Drug Administration”, is seen as more rigorous. What I have just said it is demonstrated by several scandalous stories on medical devices. One of these, it is the ASR hip story considered one of the biggest disasters in orthopedic history.

The ASR Hip System, manufactured by a subsidiary of American giant Johnson and Johnson called DePuy, is a one-piece cup and socket that may be used either for total hip replacement (ASR XL) or hip resurfacing (DePuy ASR) On 24 August 2010 DePuy, after

receiving new information from the National Joint Registry of England and Wales reporting that “some” ASR patients were undergoing a second hip replacement surgery sooner than expected, acted quickly by voluntarily recalling its ASR (articular surface replacement) hip prostheses from the market. Moreover, the failing prosthesis had several pathological effects. Ions of cobalt and chromium, the metals from which the implant was made, were also released into the blood and cerebral spinal fluid in some patients. Both forms of the DePuy ASR came on to the market in Europe in 2003. At the time, resurfacing prostheses were classed as a class IIb device, which meant they didn't need to be tested in patients before entering the EU market. DePuy claimed to have conducted laboratory testing “including tests on simulators that evaluate how the device wears over time, the materials used in the device and device strength.” But exactly what information the company has submitted is not open to public scrutiny; the scientific rationale was held by the company and by the notified body that in this case was the British company BSI. In this regard, the UK Medicines and Health Products Regulatory Agency (MHRA) has stated that clinical trials may have been too small and short to detect problems for pre-market approval purposes. But even clinical trials with relatively short follow-up could have detected problems with ASR. The absence of any clinical studies of implants in patients before approval remains a cause for concern. There is a strong concern that no clinical trials of implants have been performed in patients prior to approval [7].

In 2012 following the discovery of the fraudulent use of non-medical grade silicone in breast implants manufactured by the company “Poly Implant Prothèse” (PIP), The European Commission and EU countries have taken joint action to tighten controls, provide a better guarantee for the safety of MDs, and restore confidence as part of the Joint Plan for Immediate Actions under existing Medical Devices Legislation (the so-called PIP Action Plan). It focused on four key areas: 1. the functioning of notified bodies; 2. market surveillance; 3. coordination as regards vigilance; 4. communication and transparency [8].

Following in 2012, the Commission adopted a package of measures on innovation in health and published two regulation proposals to revise existing legislation on general MDs and IVDMDs.

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The aim of the revisions was to ensure:

- a consistently high level of health and safety protection for EU citizens using these products;
- the free and fair trade of the products throughout the EU;
- that EU legislation is adapted to the significant technological and scientific progress occurring in this sector over the last 20 years.

Revisions included: the extension of the scope of legislation, better supervision of independent assessment bodies, clear rights for economic operators, and stronger requirements for clinical evidence [9].

On 5 April 2017, two new Regulations on MDs and IVDMDs establishing a modernized and more robust EU legislative framework to ensure better protection of public health and patient safety were adopted [10,11].

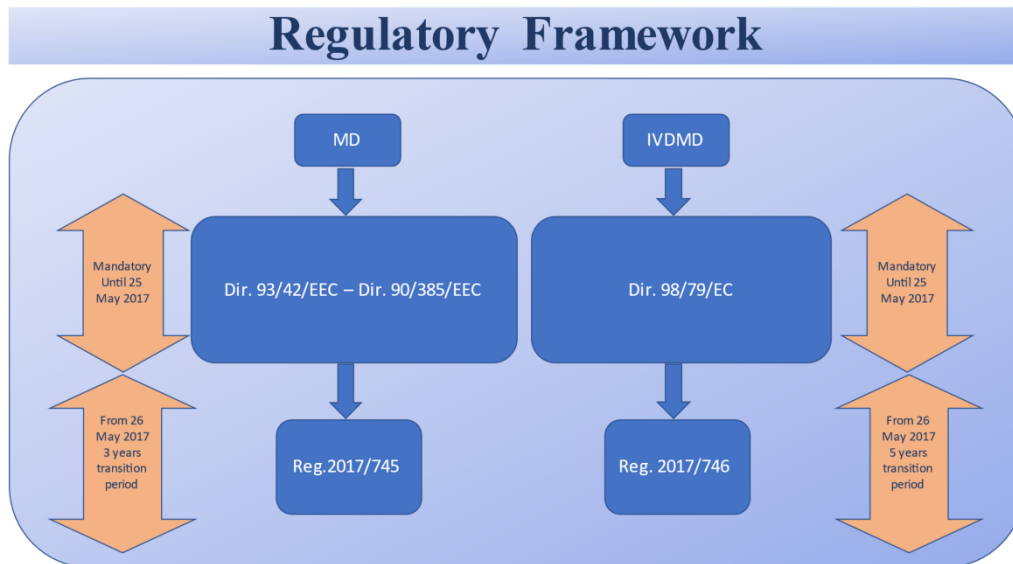


Fig2. MD and IVDMD Regulatory Framework

CONCLUSIONS

On May 26, 2017, Regulation (EU) 2017/745 came into force. It represents a true Copernican revolution in the field of clinical investigations. The entire chapter VI, which extends from article 61 to article 82, is dedicated to the topic in question. It describes in detail the requirements that a clinical investigation must meet even in emergency situations, the information that the informed consent must contain, the obligations of the Sponsor in conducting it and those of the Member State in evaluating the documentation attached to the application and assessing the reliability of the data generated during its conduct. The latter is great news. Indeed, under the previous regulatory framework the Member State had much lower obligations. Specifically, for the start of the clinical investigation the principle of tacit consent was valid, that is, for class III MDs and active implantable MDs, the clinical investigation could start only after 60 days from the notification to the Competent Authority; for all other MDs, the clinical investigation could begin immediately after notification.

On the contrary, Regulation (EU) 2017/745 imposes obligations on the Member State. In fact, the Member State, once the application has been received, must verify its completeness and notify the Sponsor within 10 days (period that can be extended to a further 5 days) from its receipt. Once this has happened, if the documentation is complete, for class III and active implantable MDs, the Member State will be required to evaluate the content of the documentation by giving a second notification to the Sponsor within 45 days from the date of validation of the application (period that can be extended of another 20 days for the purpose of consulting experts or suspending it for requests for clarifications). Only after receiving this second notification, the Sponsor will be able to begin the clinical investigation. For all other MDs the clinical investigation can begin immediately after the validation of the application (as long as the application is complete).

The real revolution is represented by point 64 of the Regulation (EU) 2017/745 which states the following: "The rules on clinical investigations

should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects and with the most recent version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects”.

In the previous regulatory framework, absolutely no mention was made of the use of this standard for conducting clinical investigations, therefore its use was not legally binding. Having made clear reference in Regulation (EU) 2017/745 to ISO14155: 2011 gives it a strong binding power. The objective of the reference to this standard is to harmonize the procedures used for conducting clinical investigations in order to facilitate the exchange of their results between EU Member States and countries outside the EU.

After all, it is important to underline that the requirements of this international standard are superimposable to those established by Regulation (EU) 2017/745.

Therefore, to comply with the standard ISO 14155:2011 means to comply with the requirements established by the above-mentioned Regulation.

Originally, all the stakeholders involved were granted 3 years of transition to comply with Regulation (EU) 2017/745. During this three-year period, compliance with requirements imposed by this Regulation would have been voluntary.

In response to the COVID-19 pandemic, on 23 April 2020 the European Parliament and the Council adopted Regulation (EU) 2020/561 which defers by one year the date of application of Regulation (EU) 2017/745, precisely on May 26, 2021 [12].

But this deadline is just around the corner and we are still in full pandemic.

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