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Current Perspectives on Medical Devices and the Quest for Clinical Data to Support their Marketing Authorization: A Short Overview

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Abstract

The need to collect clinical data in the EU market authorization process of medical devices (MDs), commonly known as CE marking, arises from the requirement to demonstrate that a device meets the "Essential Requirements", namely that it is safe, that it performs as intended by the manufacturer, and that any risks are acceptable when weighed against the benefits of the device. These data may come from scientific literature or be the result of clinical studies, called Clinical Investigations (CIs) in the case of Medical Devices (MDs). The aim of this article is to describe methodology and role of CIs on MDs in EU. In particular, this paper centers on the change occurring in the role of CIs following the full application on May 26, 2021, of the Medical Devices Regulation (MDR) (EU) 2017/745 and the repeal of Directives 93/42EEC on MDs (MDD) and 90/385 EEC on the Active Implantable Medical Devices (AIMD).

Keywords: Medical Device; Clinical Investigation; Clinical Evaluation; Marketing Authorisation

Abbreviations: MDs: medical devices; CIs: Clinical Investigations; AIMD: Active Implantable Medical Devices; MRD: Medical Devices Regulation; PMCP: Post-market clinical follow-up; MeSH: medical subject headings; EC: European Commission; ISO: International Organization for Standardization; CEN: Committee for Standardization; GCP: Good Clinical Practice

Introduction

The European market of MDs accounts for one quarter of the worldwide market, with a turn-over of about 100 billion Euros, and more than half million employees. The EU "Big Five" (Germany, France, Italy, UK and Spain) make up the lion's share with about 70% of the market. MDs include products that are very different in term of technology and potential risk for the patients. Just to give an example, a plaster or a heart stent are both MDs. To allow for this difference, MDs are categorized into four regulatory classes, namely, Class I, IIa, IIb and III based on increasing risks associated with their intended use [1]. According to the ISO 14971 standard, MDs manufacturers must perform a benefit-risk analysis of their products as part of the certification procedure [2]. Rules are established by the MDR which came into full application on May 26, 2021, and repealed the MDD and the AIMD. The core elements of the MDD are maintained in the MDR. However, there are important differences between the two regulatory frameworks. This difference is already evident in the definition of MD that now has been broadened to include non-medical and cosmetic devices not previously regulated. Examples include products for cleaning, disinfection or sterilization of devices as well as contact lenses, liposuction equipment, or epilation lasers.

Terminology and writing have also been expanded and updated

The current definition of MDs coincides to a certain extent with the one present in the MDD but for the fact that the terms "prediction" and "prognosis" playing a fundamental role in modern clinical practice have been now inserted. In turn, the term "handicap" has been replaced by "disability", better reflecting today's social policy. Moreover, MDs for the support of conception have been included within the scope of the definition [3]. The most important change, however, concerns the requirements for obtaining CE marking, more stringent than before [4]. In the MDD these were termed 'essential requirements', while in the MDR they are referred to as 'general safety and performance requirements' [3,5-7]. This paper illustrates concisely how the approach to CIs is changing due to the full application on May 26,

2021 of the Medical Devices Regulation (MDR) (EU) 2017/745 and the repeal of Directives 93/42EEC on MDs (MDD) and 90/385 EEC on the Active Implantable Medical Devices (AIMD).

The overall picture

To demonstrate that a MD meets the "essential requirements", i.e., that it is safe, that it works as intended by the manufacturer, and that any risks are acceptable when compared to the benefits of the MD, it is necessary to collect clinical data and perform a clinical evaluation. However, sometimes, a non-clinical assessment can also be used to establish the benefits of an MD: e.g., usability testing, computer modelling and simulations, and cell-based testing [8]. The clinical evaluation of this data must follow a well-defined and methodologically sound procedure based on the following key aspects:

a) Critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the MD, where the following requirements are met:

i. Documented evidence that the MD subject to clinical evaluation for the intended purpose is equivalent to the MD to which the data relate.

ii. Data adequately demonstrate compliance with the relevant general safety and performance requirements.

b) Critical evaluation of the results of all CIs

c) Critical evaluation of the combined clinical data provided by scientific literature and by CIs.

Every MD sold in Europe, regardless of its classification, must have a Clinical Evaluation Report in its technical file. The MDR sets out detailed requirements regarding CIs in comparison with the MDD. Clinical Evaluation must be based on clinical data not only in the case of implantable devices and devices in Class III (high risk), as prescribed previously, but for all MDs. The option (a) mentioned above is commonly used by manufacturers for the CE marking of low- to medium-risk devices (Class I, IIa and IIb) for which safety and performance can be adequately demonstrated by a combination of nonclinical data (i.e., bench testing and animal testing) and clinical data that already exists on the MDs (published or unpublished) or by analogy with published data generated on an equivalent device [9,10]. In the case of implantable devices and class III devices, CIs shall be performed, except if (as reported verbatim by the MDR):

i. the device has been designed by modifications of a device already marketed by the same manufacturer

ii. the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, and this demonstration has been endorsed by the notified body

iii. the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

Moreover, article 61 [5] of MDR gives certain manufacturers an exemption from having to perform CIs by demonstrating equivalence to other companies' products provided that the following conditions are fulfilled in addition to what is required above:

i. the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device to have full access to the technical documentation on an ongoing basis, and

ii. the original clinical evaluation has been performed in compliance with the requirements of the MDR and the manufacturer of the second device provides clear evidence thereof to the notified body [3].

Furthermore, Article 120 (2) of the MDR states that certificates issued in accordance with the MDD will remain valid until 27 May 2024 at the latest. It is crucial emphasize that medical device companies are responsible for the safety and effectiveness of their products throughout the entire medical device life cycle, creating a need for rigorous pre-market trials and post market surveillance activities to monitor the performance of medical devices.

Methods to conduct CIs are also progressively changing.

As part of the transition from the MDD to the MDR, the old MEDDEV documents (a group of guidelines concerning MDs. that applied under the MDD) are gradually being replaced by the Medical Device Coordination Group (MDCG) guidance documents under the MDR. The aim of these guidelines is to promote a common approach to be followed by manufacturers and notified bodies that are involved in conformity assessment procedures [11].

MEDDEVs are not legally binding. However, since their publication is the result of a consultation process between all the stakeholders (including experts from competent authorities), it is strongly recommended that the guidelines be followed.

The European guidance documents regarding CIs are:

a) MEDDEV 2.7/1 Rev. 4 on Clinical evaluation by manufacturers and notified bodies

b) MEDDEV 2.7/2 Rev 2 on clinical investigation validation and assessment by competent authorities

c) MEDDEV 2.7/3 Rev. 3 on Serious Adverse Events (SAE) reporting

d) MEDDEV 2.7/4 on the need for, and general principles of, clinical investigations [12,13].

In particular, MEDDEV 2.7/1 Rev. 4 guidelines are those dedicated to the evaluation of the risk-benefit profile, a fundamental requirement of clinical evaluation [14]. The MDCG was established because of the need to provide the

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methodological details for conducting CIs in accordance with the MDR. The European Commission awarded a Horizon 2020 grant to a consortium led by the European Society of Cardiology and the European Federation of National Associations of Orthopedics and Traumatology, with the aim of examining clinical investigation methodologies, providing advice on study designs and developing recommendations for aggregating data from registries and other real-world sources. The so-called Coordinating Research and Evidence for Medical Devices (CORE – MD) project will run until March 2024.

The MDCG guides for the implementation of the MDR, are not also legally binding, but their use is generally expected. They implement Article 105 of the MDR, in which they are intended to contribute to, among other things, the "effective and harmonized implementation of the Regulation". The MDCG was established by the MDR in the first place. It consists of at least one, and at most two, experts from each member state and a maximum of two deputies, all of whom are experts in the field of medical devices and in vitro diagnostic MDs and are appointed for a period of three years. Currently, there are still some guidance documents of the MEDDEV and more and more guidance documents of the MDCG that are resorted to. Especially new topics like UDI and EUDAMED database are only addressed by the MDCG guides [11,15].

In 2020, seven additional documents were published only on the subject of Clinical Investigation and Evaluation, to provide guidance to manufacturers. The guides mentioned above are the following:

MDCG 2020-5 Guidance on clinical evaluation – Equivalence

MDCG 2020-6 Guidance on sufficient clinical evidence for legacy devices

MDCG 2020-7 Guidance on post-market clinical follow-up (PMCF) plan template

MDCG 2020-8 Guidance on PMCF evaluation report template

MDCG 2019-9 Summary of safety and clinical performance

MDCG 2020-10/1 Appendix: Clinical investigation summary safety report form

MDCG 2020-10/2 Guidance on safety reporting in clinical investigations

MDCG 2020-13 Clinical evaluation assessment report template [12,16,17]

There are also topics for which the MEDDEV or MDCG guides can be used indiscriminately. For example, the guidance document MDCG 2020-5 and MEDDEV 2.7/1 rev 4 have distinctly identified criteria for evaluating an equivalent device to be used as clinical evidence [18].

In addition to providing guidance for the harmonized implementation of the MDR, the Coordination Group is also involved in the monitoring of technical progress, the further development of norms and standards and the assessment of Notified Bodies and the assistance to competent authorities in a wide range of regulatory areas [17]. The MDR specifically requires CIs to be conducted according to GCP with direct reference to the ISO 14155 standard. The third edition of this standard, developed by the ISO technical committee ISO/TC 194, was released in July 2020. The ISO 14155 standard "Clinical Investigation of MDs for human subjects - Good clinical practice" is an international guidance document that addresses good clinical practice insofar as the design, conduct, recording and reporting of CIs carried out on human subjects are concerned. Moreover, the above-mentioned standard specifies general requirements aimed to ensure the rights, safety, and well-being of human subjects, supports the scientific conduct of CIs and provides documented evidence for the credibility of experimental results. In addition to this, ISO 14155 defines the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of MDs [19].

Literature search

A number of papers published on this subject matter over the past few years (January 2016 to date) were selected with no claim to completeness. Basically, MEDLINE and PubMed databases were scanned for retrieving relevant articles. The author used medical subject headings (MeSH) to identify synonyms of keywords and studies relating to the scope of this review. The terms of interest were combined in different ways using Boolean operators "Medical Devices" AND "Clinical Investigations". CIs were also searched on the Website ClinicalTrials.gov using the advanced search strategy and the above-mentioned keywords with Boolean operators. In particular the websites of the European Commission (EC) and the Italian Ministry of Health were visited for retrieving information on regulations and guidelines. For economic data on MDs industry the main sources were the website of the EC and the reports of the Italian Association of Medical Device Manufacturers (AMDM) (Assobiomedica from 2016 to 2020).

Conclusions

At point 64 (L 117/9), MDR states: "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…" [1]. Therefore, ISO 14155 provides guidance and requirements for the design, conduct, recording and reporting of CIs in accordance with the MDR and the ethical principles set out in the Declaration of Helsinki. In the previous regulatory framework, no mention was made on the use of the ISO 14155:2011 standard for conducting CIs. The explict reference made in the MDR to the said standard has maked it more strongly binding. This can pave the way to more harmonized procedures for conducting CIs thus facilitating the exchange of experimental results among

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EU Member States and countries outside the EU as well [20]. Meanwhile, the International Organization for Standardization (ISO) in collaboration with the European Committee for Standardization (CEN), in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement), prepared ISO14155: 2020.

This third edition cancelled and replaced the second edition (ISO 14155:2011), which has been technically revised. That revision resulted in the adoption of the harmonised standard EN ISO 14155:2020 on CIs of MDs for human subjects, the references of which have been published by Implementing Decision (EU) 2020/438. [21,22]. This third edition is also not legally binding. Although, compliance with a harmonised standard confers a presumption of conformity with the corresponding essential requirements. The biggest update in ISO 14155:2020 is the strong emphasis on the role of clinical evidence, as presented in the European Medical Device Regulation (MDR), the application of ISO 14971 risk management principles across all stages of clinical investigations, and the improved guidance on clinical study design. The previous version of ISO 14155 only maked reference to ISO 14971 in terms of "investigational device risks", and to support risk-benefit assessments to meet clinical investigation design rationale requirements [23]. Now all stakeholders involved, primarily Sponsors, Ethics Committees, Competent Authorities have the tools to improve the safety and performance of MDs.

They were initially granted 3 years of transition, then extended to 4 years due to the COVID-19 pandemic. During these 4 years, compliance with MDR requirements was voluntary. On May 26, 2021, the MDR came into full application and the MDD was repealed [9]. Manufacturers should have already adopted the aforementioned standard and implemented all applicable procedures and practices, as it will reflect the state of the art in Good Clinical Practice (GCP) for CIs of MDs. In addition, the device's life-cycle approach supported by data, required by MDR, implies also the continuous need of expertise and involvement from the scientific community to guarantee safety and performance related to the adopted technologies. Therefore, the key elements to improve the safety and effectiveness of the devices are the full awareness and application of the new regulatory framework and the active collaboration between the various actors involved. The osmosis between the different actors is fundamental for the creation of a fruitful and solid basis to support technological evolution and the application of rules [23]. Awareness of regulatory requirements can improve the innovation process and its efficiency in terms of both social and ethical impact. This process is still underway and should be further fostered in the years to come.

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