Journal of the Society for Cardiovascular Angiography & Interventions 1 (2022) 100401

Contents lists available at ScienceDirect

Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: www.jscai.org

Editorial

The Impact of the Medical Device Directive to Medical Device Regulation Transition on Early Clinical Testing of Cardiovascular Devices

Adam J. Prince, MD, Emily P. Zeitler, MD, MHS, Aaron V. Kaplan, MD *

The Heart and Vascular Center, Dartmouth-Hitchcock Medical Center, and The Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire

Background

On May 26, 2021, the European Union (EU) updated its regulatory requirements for medical devices by implementing the Medical Device Regulations (MDR).[1] Although the change to the MDR system was driven by important shortcomings in the EU regulatory system, the transition has been chaotic and has a large impact on cardiovascular devices in development as well as on approved devices. This manuscript examines the background behind these changes and their impact.

Before the 1980s, regulation of medical devices throughout Europe was inconsistent, with each country having its own laws and regulations. In the 1990s, laws were enacted to create a uniform approach throughout the EU, which was designated "essential requirements." Though this system strives to create consistency across the medical device markets among EU member countries, differences in health care delivery systems, including discrepancies in coverage and reimbursement for new technologies, add market variation even after receiving the Conformitè Europëenne (CE) mark. These essential requirements, which later became known as general safety and performance requirements, focused on manufacturing standards and clinical performance, with less emphasis on clinical outcomes. The legal and regulatory framework was known as the Medical Device Directive (MDD). Concerns regarding the ability of the MDD system to assure the safety of commercially available devices surfaced with 2 high-profile scandals.[2]

The first scandal involved breast implants manufactured by Poly Implant Prothèse (PIP).[3] In the 1990s, PIP manufactured silicone implants that were available in Europe but not in the United States due to a moratorium on silicone implants in place since 1992 because of safety concerns. PIP also developed saline breast implants that were available in Europe and briefly in the United States, but these came under additional United States scrutiny when the entire class of devices was required to provide additional safety data around the year 2000. The PIP saline implants did not receive US Food and Drug Administration (FDA) approval based partially on the advice of an independent expert panel. Furthermore, among other deficiencies, an FDA manufacturing audit found that PIP was using a cheaper, industrial-grade (rather than medical-grade) silicone in breast implants. By 2009, an increased rupture rate began to attract the attention of the European popular press and politicians. The PIP implants were recalled in Europe the following year, with a recommendation from some health ministries for prophylactic removal. The scandal ultimately affected hundreds of thousands of patients and has been linked to instances of breast cancer and death. In this case, the FDA's higher regulatory threshold identified PIP's substandard manufacturing practices and protected Americans from exposure to an unsafe device that was available for more than 10 years in Europe.[4]

Deficiencies in the MDD system were further exposed by the metal-on-metal hip prostheses scandal.[5] In this case, metal-on-metal hip prostheses were introduced primarily based on preclinical and minimal clinical testing. The metal-on-metal interactions between the prosthetic femoral head and acetabular cup resulted in microparticle generation, leading to local inflammation and pain, as well as prosthesis loosening and fracture. These events led to market withdrawal, as well as the need for surgical removal, which impacted tens of thousands of patients.

The PIP and metal-on-metal hip prostheses scandals highlighted deficiencies in the MDD system, leading to calls for changes in the medical device approval and oversight processes in the EU. These efforts led the EU to design a new set of MDR, culminating in the MDR system, which was approved in May 2017, with full implementation in May 2022.

The European regulatory system is administered by the government of each member state through a designated agency, known as the competent authority, which is responsible for implementing EU-wide regulations. In addition, competent authorities extend their authority to notified bodies (NBs), which are independent private entities that administer the regulatory process for medical devices. NBs work directly with device manufacturers to evaluate devices to ensure that general safety and performance requirements are met. When these requirements are met, device approval is granted in the form of the CE mark. The issuance of a CE mark allows the medical device to be commercialized in

This editorial summarizes the session focused on the MDD-MDR transition at the Dartmouth Device Development (3D) Symposium held September 23-24, 2021, in Woodstock, Vermont.

Keywords: CE mark; medical device; medical device directive; medical device regulatory policy.

* Corresponding author: aaron.v.kaplan@hitchcock.org (A.V. Kaplan).

https://doi.org/10.1016/j.jscai.2022.100401

Received 13 April 2022; Received in revised form 9 June 2022; Accepted 11 June 2022

Available online 12 July 2022

all EU member countries, representing a market of nearly 500 million people. The NB is also required to ensure adequate postmarket surveillance and retains the ability to restrict, suspend, or withdraw the device's CE mark. Under the MDD, before the implementation of MDR, there were ~50 certified NBs, which introduced a high degree of variability into the regulatory process. This variation resulted in different requirements for market entry for similar devices and allowed medical device manufacturers the opportunity to "shop" for the NB presenting the fewest barriers to the market.

The standard for device approval is different between the United States and Europe. In the United States, market authorization for a medical device requires a demonstration of *safety* and *effectiveness*, with the threshold variable depending on the risk of the device and available alternatives. In Europe, a standard of *safety* and *performance* is required. Both systems require "preclinical" evaluation, eg, in vitro, sterility, and, sometimes, animal testing. For a first-in-class high-risk cardiovascular device, CE mark approval may require clinical data to demonstrate device *performance*, ie, demonstration that the device will perform in the intended fashion. These data are typically generated by observational studies and, rarely, by randomized clinical trials. On the other hand, FDA approval requires data demonstrating *safety* and *effectiveness*. For some high-risk interventional/structural cardiology devices, meeting this standard may require an adequately powered randomized controlled trial with sophisticated infrastructure with centralized data collection, core laboratory assessment, clinical events committee event adjudication, and safety monitoring by a data and safety monitoring board. The difference between the European performance standard and the United States effectiveness standard can be appreciated by examining data required for approval of first-generation transcatheter aortic valve replacement (TAVR).

The first-generation Edwards SAPIEN TAVR received a CE mark in Europe in 2007 with registry data assembled from a number of studies including <500 participants with performance demonstrated by a reduction in the aortic valve gradient.[6] In comparison, the initial FDA approval of the Edwards SAPIEN TAVR was based on data from a randomized controlled trial with 358 participants with an effectiveness end point of death or repeat hospitalization[7] compared with optimal medical therapy in patients ineligible for the contemporary standard of surgical valve replacement.[7] The safety and effectiveness end points were met, and upon initial approval, the device was only indicated for the small subset of the population with aortic stenosis represented in the trial. A series of subsequent randomized trials starting with a group of 699 high surgical risk participants compared TAVR outcomes to surgery and led to an expansion of approved indications for this class of devices.[8]

Though the scope of changes in the MDR is extensive, this manuscript will focus on 3 areas: NBs, clinical data required for initial approval, and review of previously approved devices.

Notified bodies

The MDR is designed to improve NB rigor by requiring recertification and changes in how NBs work with medical device developers. This recertification requirement has led to a marked reduction in the number of certified NBs from ~50 to 26.[9] Thus, there is a smaller number of NBs responsible for providing regulatory oversight using a more rigorous and intensive process. This has led to a profound shortage of MDR-certified NBs, making it difficult for device developers to enter the regulatory process. This shortage is particularly problematic for startup companies with a single product, which must compete with large established medical device manufacturers with much larger product portfolios, existing relationships with regulators, and greater resources to dedicate to regulatory activities. Undoubtedly, the more rigorous and consistent performance of NBs is important. However, the implementation of MDD, including a drastic reduction in NB capacity, has introduced a new and significant barrier to the introduction of novel medical devices to the European market as well as established medical device technologies.

Understanding requirements for approval

Adding to the problem, the new standard is not yet well understood by NBs and restricts providing direct guidance to regulated device manufacturers.[1] A clear and specific understanding of the clinical data required for approval is critical for device developers. Clinical trial planning to meet medical device regulatory standards is highly nuanced, time-sensitive, and benefits from detailed discussions between the medical device developer and the NB. In the United States, this is accomplished by a "presubmission" process in which device companies can discuss a clinical development plan with the FDA and receive direct feedback. Unfortunately, the combination of new standards with a reduced number of NBs working under poorly defined rules has made it difficult for device developers to obtain a clear understanding of the data required for CE mark approval for a new medical device.

These uncertainties, along with efforts by countries outside of Europe to streamline the regulatory process, have led to changes in trends where initial clinical evaluations for cardiovascular devices are taking place. In the 2010s, Europe was the default venue for initial clinical testing of high-risk cardiovascular devices. Europe's dominance in early clinical testing reflected a regulatory environment that enabled companies to work with highly skilled sites with a long history of excellence in performing these studies. However, the difficulty in linking early studies to device approvals reduces the value of performing studies at European sites and has led to a dramatic shift away from Europe. This shift is well illustrated by comparing the initial TAVR experience in the 2000s, where nearly all the first-generation valves were initially tested in Europe, to the more recent experience with transcatheter mitral valve replacement, for which initial clinical testing was most commonly carried out in the United States. This is not just frustrating for European clinician investigators and patients; it also limits the "ecosystem" from benefiting from this important well-developed resource.

Previously approved devices

The transition from MDD to MDR has implications beyond those for devices in development because the MDR calls for review and recertification of previously approved devices. This change requires manufacturers to generate dossiers conforming to the new MDR standard for every device in their product portfolio. This includes all devices regardless of risk, including those marketed for years with a well-defined and proven performance record. The resultant increase in work for both the device manufacturers and NBs, combined with a reduction in certified NBs, has added to the challenges for device developers to get meaningful review and understanding of what will be required for recertification.

Conclusions

Regulating medical devices requires governments to balance the benefits of new technology with the risks of a new therapy. The complexity of the clinical environment and the need for device developers to refine designs makes this a difficult and nuanced task requiring a regulatory infrastructure with adequate staff and resources. Though there were clear deficiencies in the MDD system, the implementation of the MDR has introduced new uncertainties which present barriers to getting devices to the global market.

Declaration of Competing Interest

Dr Kaplan is a Founder and Director of Conformal Medical, Inc, a venture-backed company developing next generation left atrial appendage closure technology. Dr Kaplan reports research support from Boston Scientific and the 3D Symposium support from Abiomed, Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Zeitler reports consulting services for Medtronic Inc, Biosense Webster, Boston Scientific, and Sanofi; research support from Boston Scientific and Biosense Webster; and travel support from Medtronic. Dr Prince has no conflicts of interest to report.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. European Medical Devices Regulation (EU 2017/74). Accessed July 12, 2022. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745
2. European Medical Devices Directive (93/42/EEC). Accessed July 12, 2022. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF
3. Greco C. The Poly Implant Prothèse breast prostheses scandal: embodied risk and social suffering. *Soc Sci Med.* 2015;147:150–157. https://doi.org/10.1016/j.socscimed.2015.10.068
4. Reuters. Staff. Timeline: A short history of breast implants. Reuters Jan 26, 2012. Accessed March 13, 2022. https://www.reuters.com/article/us-france-implants-pip/timeline-a-short-history-of-breast-implants-idUSTRE80P12V20120126
5. Scientific Committee on Emerging and Newly Identified Health Risks. The Safety of Metal-On-Metal Joint Replacements with a Particular Focus on Hip Implants. Adopted this Opinion at the 7th plenary of 24-25 September; 2014. Accessed July 12, 2022. https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_042.pdf
6. Edwards Lifesciences. Receives CE mark for Edwards SAPIEN transcatheter heart Valve. Press release Sept 5, 2007. Accessed July 12, 2022. https://www.edwards.com/ns20070905
7. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597–1607.
8. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *N Engl J Med*. 2011;364(23):2187–2198.
9. Medical EEC. Devices Europa. LIST OF BODIES NOTIFIED UNDER. Directive : 93/42/EEC Medical devices). Accessed March 13, 2022. https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.pdf&refe_cd=93%2F42%2FEEC&requesttimeout=900