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Regulation and Its Impact on Innovation in Healthcare: SAMD Case

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Abstract

Digitalisation in healthcare can transform the industry, thus a new product development shall be supported and promoted by stakeholders. Healthcare is also a heavily regulated industry to ensure safety of the end-users – the patients.

The aim of this article is to analyse regulation of software as a medical device (SAMD) in Europe in the light of recently introduced Regulation (EU) 2017/745 (MDR). The analysis starts with defining what SAMD is and how it is classified, as well as how the classification has changed according to the new regulation. As the new rules significantly change the classification for most of the SAMDs, their impact on the innovation process is explored from the perspective of the innovators and the market. Furthermore, the regulation of AI solutions in the medtech industry is also explored.

The analysis also covers how the SAMD can launch updates to be compliant with the regulatory requirements. Several obstacles in the innovation process have been identified and explored.

Keywords: AI solution, machine-learning solution, Medical Device Regulation, medtech, Software as a Medical Device.

Introduction

Digitalisation is inevitable and the healthcare industry sees a growing number of various solutions available in the market every day, being used for both medical and non-medical purposes. The COVID-19 pandemic has also catalysed the creation and adoption of various digital health solutions. There are no signs of returning to the old practices, but rather the exponential growth in demand and offer of newly developed digital solutions. The promise of each of those is to make a process more efficient, be it quicker or more precise diagnosis or a cheaper and more user-friendly patient appointment management system. Whichever the solution it is, the patient is always at the center of the development.

Currently, there are more than 33,000 medtech companies in Europe. The leader is Germany with the largest number of medtech companies, followed by Italy, the UK, France, and Switzerland. 95 % of those companies are small or medium-sized with less than 50 employees (The European Medical Technology Industry in figures, 2021). Since November 2019, Germany is also the first European country to reimburse the costs of certain digital health solutions under its Digital Healthcare Act. One could challenge the benefits of the Act on the healthcare industry, as there are several limitations to be reimbursed (Gerke *et al*., 2020); nevertheless, it is the first official recognition of digital healthcare solutions at the state level. Germany was later followed by Belgium, and soon France will launch a reimbursement scheme similar to the Germany's (Lovell, 2022). Recently, Latvia has also taken a step forward to reimburse digital healthcare tools (Asare, 2021), and most probably more and more countries will follow the lead.

The rapid growth of digital healthcare tools is supported also by recent statistics: 47 % of apps in 2020 are focused on health condition management rather than wellness management, up from 28 % in 2015 (Digital Health Trends, 2021). This is the proof that the role of the regulatory framework will not diminish but rather grow.

The healthcare industry is regulated on an international and state level. In the European Union, the regulatory texts are formulated by the European Commission, and up until very recently, there were three most important directives regulating the market – the Active Implantable Medical Devices Directive 90/385/EEC (1990), the Medical Devices Directive 93/42/ EEC (1993) and the In Vitro Diagnostic Medical Devices Directive 98/79/EEC (1998).

Yet due to the rapid advancements in technologies, progress in science, interpretation risks, and other reasons "*a fundamental revision of those Directives is needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation*". The 2017/745/EU Regulation (MDR) replacing the existing directives "*aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products.*"

It is worth mentioning that the Poly Implant Prothese scandal has been credited for being one of the causes of the regulatory changes in the EU. The case is an example of how risks might be widely interpreted and wrongly managed without sufficient regulatory oversight (Greco, 2015) thus harming the human body.

The new MDR is intended to eliminate any safety concerns as it introduces increased requirements for the CE certification process, especially the documentation process, and the clinical tests are of greater importance. For most software products the MDR will also mean up-classification. The European Commission also expects that the MDR will increase industry transparency as the data about the devices will be

publicly available in the new EUDAMED database (Factsheet for manufacturers of medical devices, 2018). In comparison, the U.S. Food & Drug Administration (hereinafter – FDA) approved devices have had publicly available data summaries; while for the CE-marked devices, before introducing the new MDR, all the data have been confidential.

The changes will inevitably impact the innovation and medtech development process, as well as the time to bring new (and updated) medical devices into the market. While the strict standards promise increased safety and efficacy for the patients, keeping up with the regulatory standards will require extra personnel, financial resources, and time, which will be the biggest challenges to the small and medium-sized medtech companies, especially new start-ups which are often considered as innovation front-runners.

This paper includes analysis of the European regulatory framework for medical devices, as well as comparison to the U.S. regulatory framework. The paper explores the definition and classification of software as a medical device, separating AI (Artificial Intelligence) solutions and their specific regulatory framework.

1 Definition of SAMD

The recent 2017/745 regulation defines Medical Device (MD) as "*any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings, (...) and which does not achieve its principal intended action by pharmacological, immunological or metabolic means*", thus differentiating MD from drugs. The regulation officially states that software alone can be a medical device, in contrast to MDD 93/42/ EEC where software was not defined.

Another, yet similar definition is provided by The International Medical Device Regulators Forum (IMDRF), which is an international voluntary group of medical device regulators building grounds for standardised medical device regulations, including the EU Commission, the FDA, Health Canada to name a few. The IMDRF defines SAMD as "*software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device*" (Software as a Medical Device (SAMD): Key Definitions, 2013). This definition is promoted also by the FDA (Software as a Medical Device (SAMD)), and it clearly supports the same understanding as it is represented in the EU regulation 2017/745/EU.

When discussing digital solutions and software as medical devices, it should be considered that a significant part of computer science is Artificial Intelligence (AI). Its importance is growing as AI can potentially transform the industry. Therefore, a separate, more precise definition might be needed to distinguish and better describe such a solution. AI solution as per general definition is an evaluated and validated model consisting of computer algorithms to perform tasks that are usually executed by human intelligence. Machine learning (ML) is an AI technique that uses a large amount of training data with little human guidance to perform its task and achieve the goal.

While the EU regulation does not provide a separate definition, the IMDRF defines it as a Machine Learning-enabled Medical Device (MLMD) – *"a medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose*" (Machine Learning-enabled Medical Devices ...). Thus, by definition, MLMD is a medical device and a part of the SAMD group, but it is important to highlight that not all SAMDs are MLMDs. Most probably in the future, both these definitions will be used in the future to better separate the solutions, their complexity, and also the applicable regulation.

2 Intended Use of the Device

An inseparable part of the definition of MD is the intended use of the device. Article 2(1) of the Regulation states that medical purpose is:

1) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
2) diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
3) investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
4) providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations.

Any medical device shall be intended for at least one of the purposes above. Respectively, not all software used in healthcare are medical devices and shall not be treated like ones. Accounting, financial, patient appointment management, and other systems, which are not used for any purpose stated above shall not comply with the MDR rules and do not undergo the certification process.

However, if a non-medical software contains a module that has a medical purpose, such module might be classified as a medical device and thus is required to be certified.

3 Classification and Up-Classification

The new MDR introduces a new and definite classification for software, which was unspecified in the previous directives. While the fact of defining SAMD is welcome, the new rulings mean up-classification for most of the software to at least class IIa, while class I will be appropriate only for rare cases.

Rule 11 (Annex VIII, Chapter III, Article 6.2) states that "*software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class Iia*". If those decisions can cause a downturn in health conditions or even death, the software shall have a higher risk class. The same class IIa is assigned to software that monitors physiological parameters, except in cases when it could result in danger to the patient (class IIb). The other software that does not fall into these categories can be classified as class I.

Therefore, by comparing the rule 11 conditions to the definition of intended use, the rule can be applicable to almost all SAMDs, and the class I would be an exception. The Medical Device Coordination Group gives an example of a class I app which calculates a user's general fertility status based on the user's data input, predicting ovulation (Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR).

For most SMEs the up-classification will be a challenge. If up until the MDR the software could be self-declared (as in class I), according to the new rulings, the certification will require a considerably larger amount of resources for the complex certification process. In some cases, the software might fall into the higher class IIb or III, though further guidance would be needed to define the incidence of health deterioration for the device to be up-classified.

4 Changes in a Medical Device

Any medical device and especially software have various updates throughout its lifecycle. While some hardware might have no updates at all, software is dynamic and is updated regularly, sometimes it can be just a day between the versions. Therefore, the new MDR ruling can significantly impact product development.

According to the MDR Article 120 (2) and (3), the products which were certified under previous directives remain valid until the end of the certification period unless they have significant changes in the design or intended use. The Medical Device Coordination Group has created a guidance document on which changes are considered significant (Guidance on significant changes regarding the transitional provision under Article 120 of the MDR regarding devices covered by certificated according to MDD or AIMDD, 2020), yet the document is not an official position of the European Commission and is not legally binding. Thus, following the guidelines does not guarantee rightfulness in case of a dispute.

Nevertheless, the guidance document provides easy-to-follow steps to understand which changes are considered significant and shall be approved. Those range from changes in design or performance specifications to algorithm or architecture changes to new target audiences. E.g., a software that was classified in class I under MDD and is now up-classified under MDR (which happens in most cases) must undergo a full certification process to make the intended changes. Such requirement can jeopardise the innovation process.

When a medical device is already certified under MDR, the regulation sets the requirement to inform the Notified Body of the planned changes and then the body assesses if an audit is required. When developing a SAMD, the involvement of the body on a regular if not daily basis seems inevitable. While there are no specifics on which changes are considered substantial and thus need approval, one might consider the same guidelines mentioned above are applicable in these cases.

5 AI Solutions

AI solution is an evaluated and validated model consisting of computer algorithms to perform tasks that are usually executed by human intelligence. It would allow processing large data in short time and could be used in healthcare from diagnostics to personalised therapies to new drug development. For example, MIT researchers cooperating with Massachusetts General Hospital staff have developed an AI model to significantly improve cancer screening and its early detection, by far in tests outperforming existing practices. This would allow to improve patient outcomes, as well as minimise screening volume and costs (Yala *et al*., 2022). Another solution – the ML model facilitates the prediction process of how two proteins will attach, which could help to speed up the drug development process (Zewe, 2022). The two examples provide a potential insight of how AI solutions can drive healthcare development.

When it comes to AI product development, these solutions require more resources, namely financial, time and expertise, with the most crucial component being the data. The quality of a valid AI solution is interdependent on the quality of training data and lack of biases.

The new MDR does not provide any specifications or guidelines for AI solution development and certification in Europe, nor is there such a pathway in the USA. Yet, while in Europe there is no working initiative, particularly for medical device AI solutions, the FDA is currently working on and reviewing how those solutions could be regulated. The regulatory framework would include Predetermined Change Control Plan, Good Machine Learning Practice guidance, methodology for evaluating and improving algorithms, and other initiatives (Artificial Intelligence / Machine Learning (AI/ML)-Based Software as a Medical Device (SAMD) Action Plan, 2021), which shows that Europe is one step behind the US regulatory development. However, the European Union is working on general AI regulations which would also impact medical devices in the EU and beyond, introducing additional requirements on the use of AI (Proposal for a Regulation of the European Parliament and of the Council Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) And Amending Certain Union Legislative Acts, 2021).

6 Comparison Between European and U.S. Regulatory Framework

Researches also show that among the devices which have been approved both in the USA and Europe, in most cases those were approved in Europe first, naming the less rigorous and decentralised evaluation process for CE mark as one of the reasons, yet leading also to higher recall rates (Muehlematter *et al*., 2016). While an easier approval process benefits the developers, those devices can be associated with greater risk and might undermine safety of a patient. However, it should be noted that the research has been published up until the year 2021 when the new MDR with more strict rules has not been fully in place, thus the results of a similar research after 2021 most probably differs, using data about devices approved within the MDR framework.

7 Regulatory Agencies

In Europe, the regulatory approval process is decentralised, and the devices are audited and certified by Notified Bodies (except the lowest risk category allows self-declaration). Currently, there are 27 authorised organisations, with 7 bodies in Germany and Italy each (Nando Information System, 2022), which is not a surprise considering that those countries also host a vast number of med-tech companies. This number (27) is nearly a half of the number of authorised bodies compared to the number of bodies under the previous Directive 93/42/EEC-50. This means that the capacity is half of what it was before yet knowing that the process is more complex and more demanding, this clearly results in longer approval processes and slower innovation.

Meanwhile, many European countries do not have even a single body. Some countries with developed medical device industries do not host such bodies. For example, Denmark positions itself as a leading medtech hub in Europe with around 1000 companies operating in medtech, and more than 250 dedicated medtech companies which employ 15,000+ people (excluding contractors), thus being the fourth largest medtech employer in Europe per capita (Ministry of Foreign Affairs of Denmark, Invest in Denmark). Yet, Denmark does not host a Notified Body.

In the Czech Republic their Association of Manufacturers and Suppliers of Medical Devices represents 140 companies with 9000 employees, reaching 760-million-euro turnover a year (Peter *et al*., 2020). Nonetheless, currently they do not host a local Notified Body (the Czech Republic had 2 bodies designated under Directive 93/42/EEC).

None of the Baltic States host a Notified Body, thus a medtech company willing to undergo an audit and receive a CE mark shall turn to a body located in another European country. Fair to note, the medical device markets in these countries are significantly smaller. According to the data by the State Medicine Agency of Latvia (State Medicine Agency of Latvia, 2022), 32 devices have received CE marks within MDR framework, and all of those are in the lowest risk category (I), yet one being recalled afterwards. There is no detailed information if any of these medical devices is SAMD. If compared to other European countries, having a Notified Body in Latvia would be an extraordinary situation, and most probably it would serve as an example to many foreign companies.

Presumably having a Notified Body in a country might push the development of the medtech industry, although there is a lack of supporting evidence for this argument. The current shortage of Notified Bodies is a challenge for entire Europe, not a single country.

Conclusions

The number of medical devices is increasing, along with stricter certification rules, yet the number of notified bodies within the new MDR is half the number it was within the early directives creating a scarce gap. This raises a reasonable concern of possible complications for industry development and innovations. While the more complex requirements demand more resources from the developer companies, the small number of notified bodies prolongs and hinders the innovation launch in the market even more. There shall be some mechanisms introduced by the European Commission or on the state level to promote the arrival of new bodies and support innovation.

The new MDR also means up-classification for the most SAMD. If within the previous regulatory framework software were mostly class I and thus able to self-declare, now, according to the MDR, most will be at least class IIa, needing to undergo more complex procedures and audit. This will require more financial and time resources, which are less available to small companies (start-ups), and it is a setback to innovate.

Also, the requirement to approve most changes in SAMD is alarming; as a dynamic product, a software experiences a large number of updates, and the need for approvals definitely slows down the innovation, also taking into account the little number of Notified bodies. While the approval process ensures safety of the product, the current regulation might turn out to be overprotective and burdensome, especially for ML-based solutions.

A growing number of medical device software are AI driven, and those can have the most significant impact on healthcare industry development, especially as the AI discipline itself is developing at a tremendous speed. Yet, AI also brings increased risks, thus the regulatory framework development shall keep up with the development of the discipline so as not to lag and eventually undermine the product and patient safety.

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