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Medical Device White Paper Series

Software as a medical device

A comparison of the EU's approach with the US's approach

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1. Introduction

The International Medical Device Regulators Forum (IMDRF) aims to accelerate international medical device regulatory convergence. It comprises representatives from the medical device regulatory authorities of Australia, Brazil, Canada, China, the EU, Japan, the Russian Federation, Singapore, South Korea and the US. Through the IMDRF, regulators reached consensus on what software is considered a medical device. Regulators call it 'software as a medical device' (SaMD).[1] As SaMD might be regulated in one country but not in another (see Figure 1), this is an important consideration for manufacturers' go-to-market strategies and for the availability of SaMD across the world. This paper provides a comparison of how SaMD is regulated in the US and in the EU.

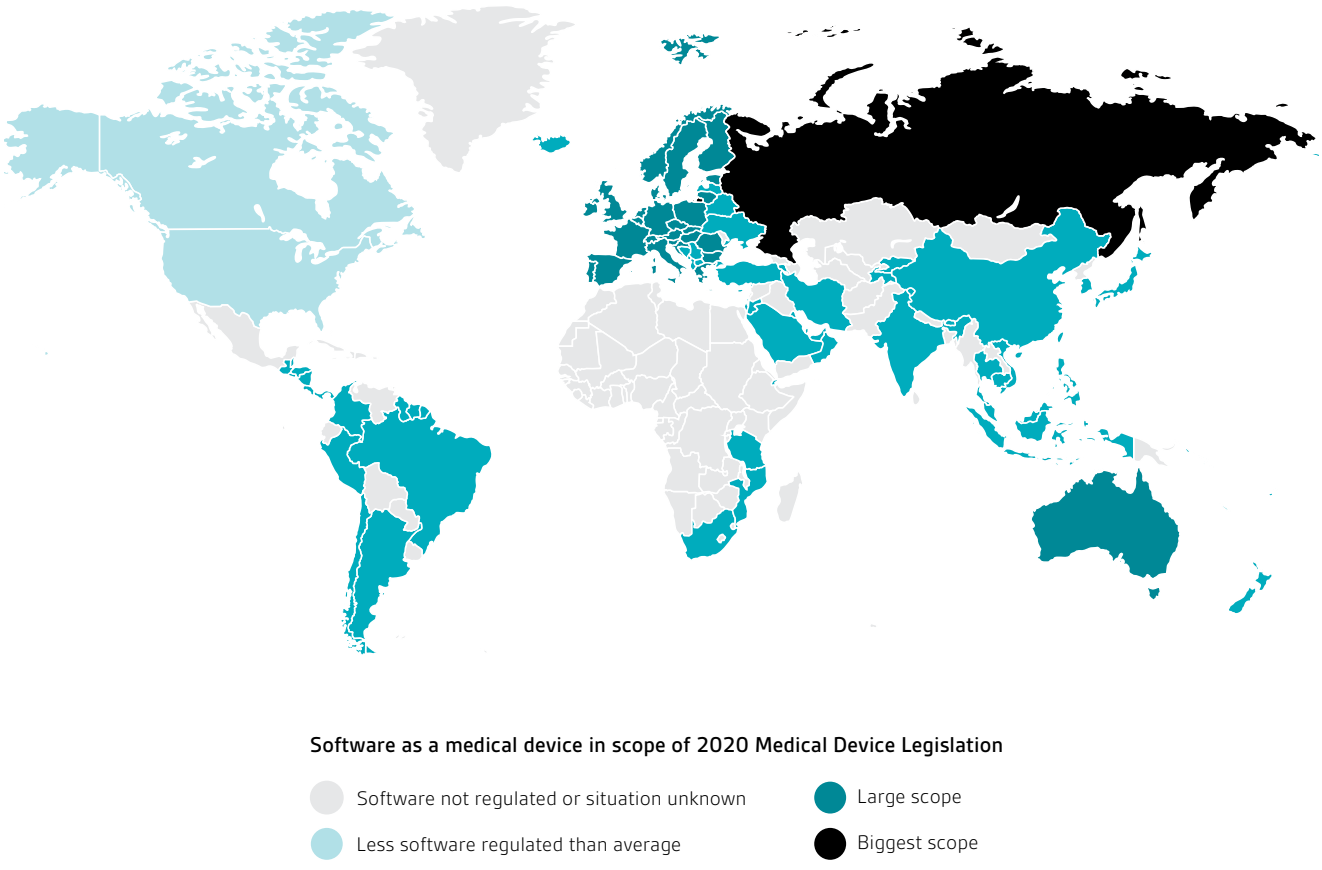


Figure 1 Regulatory fragmentation of software as a medical device. Analysis of software guidance issued by competent authorities from across the world reveals differences in what software one country qualifies as a medical device versus another country. For example, a symptom checker app might be considered a medical device in Russia and Europe but not in the US or Canada. (Cobbaert, 2020)

History

In 2007, the Swedish Medical Products Agency, Läkemedelsverket, analysed the top 10 incidents in health care. It noticed that software was often the root cause[2] – for example medical data being lost from a temporary database, medication being assigned to the wrong patient, the wrong dose being calculated, failure to caution that a patient is allergic to an active substance, etc. In several cases, software had caused the death of a patient. Läkemedelsverket investigated and found that a lot of the software used in health care qualified as a medical device but had not undergone a conformity assessment and did not carry CE marking. Even though EU regulators had long considered that software-only products could be subject to medical device legislation, it had not been very clear to people that the term 'device' could also be applicable to something intangible like software.

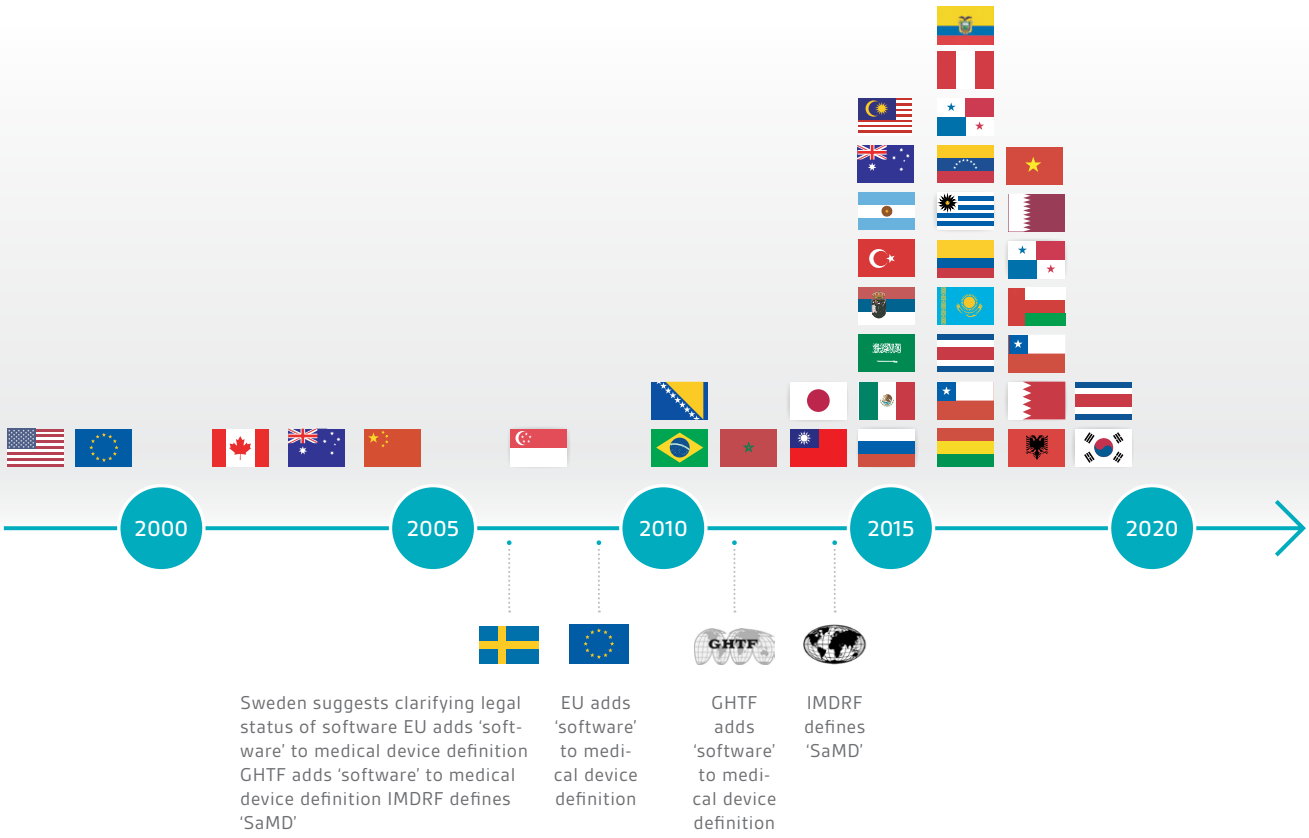


Figure 2 Date as of which countries recognized that software-only products could be medical devices. (Cobbaert, 2020)

Sweden took the issue forward when it held the presidency of the Council of the European Union. In 2009, it convinced other regulators to add the word 'software' to the EU definition of 'medical device'. In 2011, the Global Harmonization Task Force (GHTF), the predecessor of the IMDRF, also changed its definition. This caused a ripple effect across the world (see Figure 2). Following the direction of the World Health Organization (WHO), other countries started putting in place medical device legislation and leveraged the new GHTF definition for 'medical device', in effect regulating SaMD. Later, in 2013, IMDRF published its guidance to clarify what software it considers to be a medical device.

Software as a medical device

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'. The IMDRF provides clarification through notes, further supplemented by U.S. Food & Drug Administration (FDA) guidance.[3] An important clarification is that the italicized term does not refer to the physical location from where the software is running but to the regulatory status of the software. Software can run on general-purpose IT equipment in 'the cloud' but also on the computing platform of a hardware medical device and still be SaMD. When the hardware medical device needs the software to achieve its intended medical purpose – for example because it drives the hardware or fulfils a purpose claimed for the hardware device – then the software is not SaMD but part of the medical device in the regulatory meaning of the term. For example, consider software for automatic nerve detection intended to run on the computing platform of an ultrasound device. A manufacturer can place such software on the market as SaMD or as part of the ultrasound device, depending on whether the manufacturer wants to assign the nerve detection claim to the ultrasound device or just to the software. Software that does not fulfil a medical purpose on its own, on the other hand, is not SaMD. For example, software intended to solely drive an ultrasound transducer can be placed on the market as an integral part of the ultrasound device or as an accessory of the ultrasound device.

Placement on the market

Software can be qualified and placed on the market as:

- a medical device or in vitro diagnostic (IVD) medical device (the focus of this paper)
- an accessory for a medical device or for an IVD medical device (accessories by definition do not fulfill a medical purpose on their own)
- a part or a component of a medical device, IVD medical device or Annex XVI device (Annex XVI devices have no medical purpose but are in scope of the EU Medical Device Regulation (MDR[4])).

If the software is none of the above, it is not subject to the EU MDR, the EU In Vitro Diagnostic Regulation (EU IVDR)[5] or FDA regulations, unless it is placed on the EU market as part of a system – that is a combination of products, either packaged together or not, that are intended to be interconnected or combined or to achieve a specific medical purpose, in which case it is subject to the EU MDR. Connectivity alone is not sufficient for it to be considered a system,[6] because there is a third condition: the system must be placed on the market as one unit – for example it is sold under a single sales catalogue number.

EU MDR and EU IVDR Article 6 imply that software not placed on the European market might still have to comply with the EU MDR if offered, directly or through intermediaries, to a person established in the EU. Think of software offered as a download or as a service through web portals and application interfaces. If such software operates on servers based outside the EU, then such software might nevertheless be subject to the EU MDR or EU IVDR if it is accessible through, for example, website subscription to a person residing in the EU. Two years after publication of the EU MDR, the FDA clarified that, in the US, software as a service might be regulated as a medical device.[7]

SaMD that is not regulated

For the purpose of this paper, 'software' is defined as 'a set of instructions that processes input data and creates output data'. Software that does not meet this definition is 'inactive' – for example digital libraries, medical models and orthopaedic templates. Even if such software has a medical purpose, it is generally not subject to the regulation unless it is placed on the market as a part of or a component of a medical device, IVD medical device or Annex XVI device; as an accessory for a medical device or IVD medical device; or as part of a system. Such software is not in scope of this paper.

The FDA uses the fault lines provided by the IMDRF SaMD risk framework [8] to clarify what software is not in scope of its regulation, whereas the EU uses functional exemptions instead.

In the EU, SaMD with functionality that is limited to storage, communication, lossless compression or simple searching is not regulated.[9]

'Communication' refers to the transfer of data, data parsing (i.e. converting a string of data from one syntax to another, e.g. from a proprietary syntax to HL7), converting units (e.g. pound to kilogramme), and altering representation of information for embellishment or compatibility purposes.

'Lossless compression' refers to a compression procedure that allows the exact reconstruction of the original data.

'Simple searching' refers to the retrieval of records by matching record metadata against record search criteria or retrieval of information. Pattern detection and detecting whether a parameter is within bounds do not constitute simple searching.

In the US, SaMD to inform clinical management is not regulated if it is intended for a health care professional to independently review and understand the basis of the software recommendation on condition that the software does not perform signal or image acquisition, processing or analysis. Consequently, the EU regulation has a larger scope than that of the US, including significantly more clinical decisions support software intended to inform clinical management, such as drug–drug interaction and allergy checkers[10] (see Figure 3).

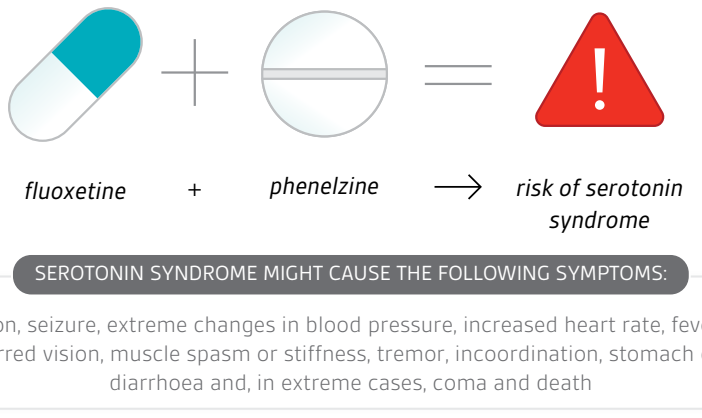


Figure 3 Example of the output of a drug–drug interaction checker. Drug–drug interaction and allergy checkers are used as part of drug prescription software. These checkers use information from pharmacopoeia and the electronic patient file to issue warnings related to possible adverse reactions when prescribing a drug that is contraindicated for a drug already taken by the patient or to which the patient is allergic. Such software is regulated in the EU9 but not in the US.11 (Cobbaert, 2020)

Finally, the EU and the US also do not regulate SaMD intended for conducting clinical investigations or population and epidemiological studies, because such software is not intended for providing diagnosis or treatment information for an individual, even though such software might use data from individuals – for example software to map the spread of COVID-19 in a country.

Regulatory requirements: FDA

The FDA has published multiple guidance documents regarding the regulation of software, including SaMD. Some types of software are regulated as medical devices, whereas other types of software are not regulated, and a third type of software is subject to 'enforcement discretion' – technically, the product is regulated but the FDA will not actively pursue enforcement unless there is a reason to.

Types of medical software

The FDA has defined stand-alone medical software in the Preamble Section AA Special Requirements for Stand-Alone Software—Final § 801.50 of the Unique Device Identification (UDI) System Regulations as 'medical software that is itself a medical device and is not a component, part, or accessory of a medical device'. [12]

The FDA has also published additional guidance documents about specific types of software that are used in health care that might be regulated. For example, 'Medical Device Data Systems' (MDDS) are defined as:

> ... hardware or software products intended to transfer, store, convert formats, and display medical device data. A MDDS does not modify the data or modify the display of the data, and it does not by itself control the functions or parameters of any other medical device. MDDS may or may not be intended for active patient monitoring.[13]

These applications might or might not be regulated, depending on other functions of the application. In general, if the software is solely intended to transfer, store, convert and display, then it is not subject to regulation. Examples include software that stores patient data for review at a later time, software that converts data into a format that can be printed and software that displays a previously stored electrocardiogram for a patient.

Note that the software does not modify the data and the software does not control the functions or parameters of a device. If the software has those features, it is likely to be a device. For example, software intended to generate alarms or prioritize patient-related information on a display would likely be considered a medical device. Similarly, software that detects and highlight abnormalities (computer-assisted detection (CADe)) or software that assesses associated disease severity (computer-assisted diagnosis (CADx)) is considered a device by the FDA and is subject to regulatory focus.

Similarly, 'clinical decision support' (CDS) software is defined as follows:

> Clinical decision support (CDS) provides clinicians, staff, patients or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care. CDS encompasses a variety of tools to enhance decision-making in the clinical workflow. These tools include computerized alerts and reminders to care providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support, and contextually relevant reference information, among other tools.[14]

Because of the variety of CDS applications, as well as an evolving regulatory landscape, some CDS software might be regulated by the FDA, other CDS software might be regulated by the FDA but under 'enforcement discretion', and some CDS software might not be regulated as medical devices. Although the FDA released draft guidance[3] on this topic in September 2019, final guidance has not been published.

Factors that affect whether or not the CDS software is regulated include:

- Is the intended user a health care provider (HCP)?
- Can the user independently review the basis of the CDS software information?
- What is the state of the health care situation or condition (is the patient state non-serious, serious or critical)?

Table 1 from the draft CDS guidance shows how these factors affect the device regulation:

		Intended user is HCP	Intended user is Patient or Caregiver
IMDRF Risk Categorization	Can the User Independently Review the Basis?*	FDA Regulation	FDA Regulation
Inform x Critical	Yes	Not a Device	Oversight Focus
	No	Oversight Focus	
Inform x Serious	Yes	Not a Device	
	No	Oversight Focus	
Inform x Non-Serious	Yes	Not a Device	Enforcement Discretion**
	No	Enforcement Discretion**	Oversight Focus

* "Can the User Independently Review the Basis?" asks whether the function is intended for the purpose of enabling the user to independently review the basis for the recommendations so that it is not the intent that user relies 436 primarily on any such recommendation (part of criterion (4)).

** "Enforcement Discretion" indicates that, based on our current understanding of the risks of these devices, FDA does not intend at this time to enforce compliance with applicable device requirements.

Table 1 Summary of regulatory policy for CDS software functions

Source: Table 3 from Clinical Decision Support Software Draft Guidance for Industry and U.S. Food & Drug Administration Staff, September 2019

The draft FDA guidance provides a large number of examples of the application of this table.

Finally, there are a number of software applications that run on people's phones or tablets. The FDA published mobile medical apps (MMA) guidance in 2013, which was updated in 2015 and again in 2019.[7] Like other products, whether or not a mobile application is a regulated device depends on the product's intended use. If the software is intended to perform a medical device function, then it is a medical device, regardless of the platform.

In addition to the guidance document, the FDA has created several web pages[15, 16] that discuss MMA and include various examples.

Regulatory requirements: EU

The EU uses the term 'medical device software' (MDSW) instead of SaMD. It defines MDSW as software that is intended to be used, alone or in combination, for a purpose as specified in the definition of 'medical device' in the MDR or IVDR.[9]

The EU uses a different term because:

1. it does not regulate SaMD with functionality that is limited to storage, communication, lossless compression, or simple searching or that is intended for the benefit of populations rather than individuals and

2. contrary to SaMD, software that fulfils a medical purpose but that is also intended to drive or influence the use of a medical device is still considered to be MDSW, whereas, according to the IMDRF notes, SaMD cannot drive a medical device. Qualification as MDSW is regardless of:

    - its location – for example operating in the cloud, on a computer, on a mobile phone or as an additional functionality on a hardware medical device

    - whether the software, in addition, also drives or influences the use of a (hardware) medical device.

If the software is solely intended to drive or influence the use of a hardware medical device, without by itself creating information for a medical purpose, then it is not considered MDSW but nevertheless is covered by the regulation as an accessory for a medical device or IVD medical device or as an integral part or component of a medical device or IVD medical device.

MDSW operates on computing platforms using operating systems and other platforms to access databases, workflow engines, dynamic link libraries, rules engines, etc. Such platforms usually do not qualify as MDSW, except if they contain functionality that qualifies it as a medical device. Consider an image management platform intended to store and communicate images within a hospital network. Such a platform is not considered MDSW if it only stores and communicates information. If, however, the platform contains an application programming interface (API) to provide third-party modules with access to platform tools – for example to segment tubular and sigmoid structures so they can extract vascular trees and detect tumors – then the platform qualifies as a medical device if its toolkit comes with tool-type claims relating to specific medical purposes.

It is noteworthy that the IMDRF, FDA and EU use different definitions for 'medical device'. Despite these differences, the practical interpretation largely overlaps if one ignores the functional and CDS exemptions applied in the two regions. Consider, for example, fertility and contraception apps and apps to support women during pregnancy. Such apps are in scope of the EU definition,[9] as the purpose refers to 'support and control of conception'. The IMDRF definition[1] refers to 'control of conception' only, but it acknowledges through its notes that some jurisdictions also consider medical devices to be products used for in vitro fertilization or assisted reproduction technologies. The FDA does not refer to any such purpose in its definition of 'medical device', [17] but, through its jurisprudence, it has indicated considering contraception apps to fall under its scope. In 2018, the FDA granted clearance to a mobile app that calculates when a woman is likely to be fertile, and therefore acts as a contraceptive.[18]

A case apart are accessibility apps to help people with visual, auditory or speech impairments to engage with the outside world. Such apps are subject to EU MDR, but they are not considered a medical device in the US, nor are such apps considered SaMD, as they do not meet the definition of the IMDRF. Nevertheless, the IMDRF acknowledges through its notes that some jurisdictions regulate *aids for people with disabilities*.[1]

In vitro diagnostics

IVD medical devices are a special kind of medical device. They examine specimens derived from the human body – for example to predict treatment response or reactions. Only software in combination with hardware can examine specimens. Most countries consider SaMD that processes information from an IVD to be a normal medical device, rather than an IVD. This is different in the EU, which for historical reasons considers that some SaMD can be considered an IVD medical device. The IMDRF supports this position.

In 2007, the European Commission and the Member States published a consensus paper[19] on IVD kits measuring parameters, which can be used for evaluating the risk of trisomy 21. These kits measure blood markers. They rely on software-only products that are accessories to these kits. Only when used *in combination* with the software could a claim for the detection of trisomy 21 be assigned to the kit.

Over time, this focus on the software as an accessory of the kit was lost and the scope expanded to include certain independent software such as IVD medical devices. This was eventually 'carved into stone' with the new definition for 'IVD medical device', which refers to software used *alone* for the examination of specimens.[20] MDCG guidance tells us that we need to consider the intended purpose and the source of the input data to make the medical device or IVD medical device determination. As many of the purposes listed for medical devices and IVD medical devices overlap – for example 'diagnosis' (medical device) versus 'information concerning a physiological or pathological process or state' (IVD medical device) – and as the source of the input data can be variable (see Figure 4), this creates a rather nebulous legal status for SaMD using IVD input data in the EU.

Figure 4 Example of different medical device/IVD medical device input data used for providing diagnostic information. Traditionally, diabetic patients measured their blood glucose level through a finger prick using an IVD hardware device to analyse the sample. Nowadays, many use medical devices rather than IVD medical devices because they are less cumbersome. Either they wear a monitoring patch on their upper arm or they squeeze a small radio-wave instrument between their fingers. A manufacturer of SaMD that uses blood glucose as input data can no longer be sure whether the data originates from a medical device or an IVD medical device. As the source of the input data is a deciding criterion, this creates legal uncertainty regarding whether the software is a medical device or an IVD medical device. (Cobbaert, 2020)

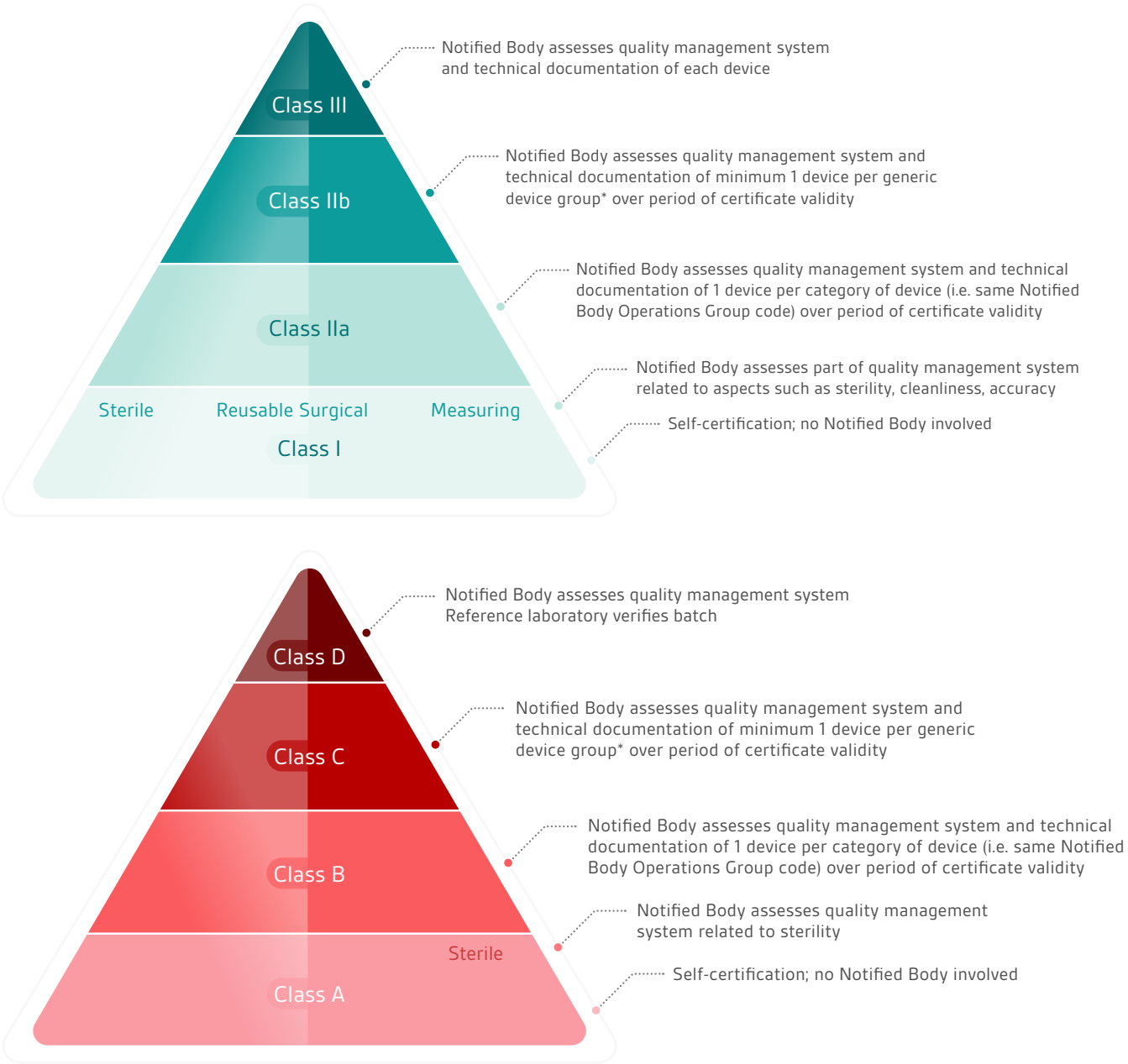
This situation is not future-proof. Increasingly, clinical decision support systems are being deployed using all kinds of information found in the electronic patient record where it is not clear whether it was derived through a medical device or an IVD medical device and, if it is information from an IVD medical device, to what extent it substantially influences the artificial intelligence (AI) decision for a particular patient. The distinction is important because medical devices and IVD medical devices follow a different regulation in the EU and might require a different Notified Body.

Classification

In the US, a manufacturer typically classifies its SaMD by browsing through FDA databases[21] to determine the applicable product code and matching device class. If no code appears to fit, the manufacturer can submit a request for information to the FDA[22] – a straightforward approach that leads to Class I, II or III classification, requiring, respectively, a registration, a 510(k) submission/De Novo submission or a Premarket Assessment (PMA).

Classification in the EU is more complex. The EU MDR distinguishes Class I, IIa, IIb and III, whereas the EU IVDR uses letters to distinguish the classes: Class A, B, C and D. The MDR also makes a distinction for Class I devices that contain a measuring function, are reusable surgical instruments or are sterile. Only Class I devices that are not sterile, not reusable surgical instruments, and do not contain measuring functionality and Class A IVDs do not require a Notified Body. The class also affects the Notified Body sampling frequency (see Figure 5) and the type and frequency of reporting. In addition, all medical devices require a clinical evaluation[23] or a performance evaluation.[24]

Many devices and almost all Class III devices and Class IIB implantable devices will require a clinical investigation. Not carrying out a clinical investigation requires a documented justification.



*generic device group: a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics

Figure 5 Illustration of extent of Notified Body review for increasing device classification. In the EU, a Notified Body increases the technical documentation sampling frequency for higher-class devices. (Cobbaert, 2020)

Classification according to EU IVDR is relatively straighforward, as the classification rules act as a waterfall mechanism (see Figure 6) with relatively few terms that require interpretation. Classification according to EU MDR, on the other hand, is more complex, especially when software is involved.

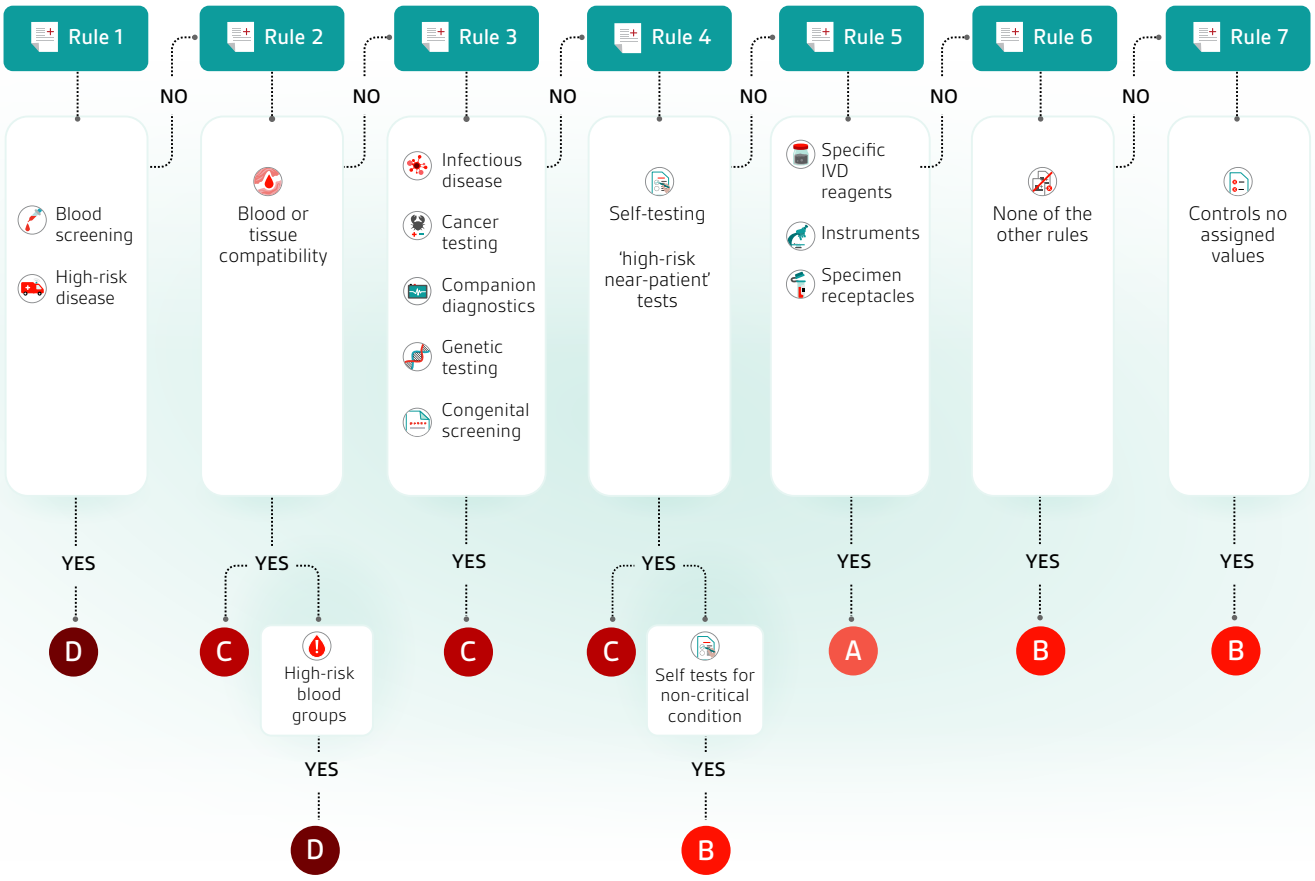


Figure 6 EU IVDR classification system. The EU IVDR classification rules are ordered from high to low class, making them usable as a waterfall mechanism, in that the first rule that applies to your device will provide for the highest class. This is in contrast to the EU MDR, where, for example, the last rule (i.e. Rule 22) leads to the highest class, Class III. (Cobbaert, 2020)

Under the EU MDR, MDSW is classified through classification Rules 11, 15 and 22, unless it is intended to drive or influence a hardware medical device, in which case other classification rules come into play (outside of the scope of this paper). Note that under the EU MDD, Rules 9 and 10 have also been used to classify independent MDSW, but the MDCG guidance,[9] by not describing these identically worded rules in the EU MDR, hints at regulators not considering them applicable to independent MDSW under the EU MDR.

Rule 15 applies to contraception apps and leads to Class IIb. Rule 22 leads to Class III and applies to active therapeutic devices with an integrated or incorporated diagnostic function, which significantly determines the patient management. To our knowledge, no SaMD currently exists on the market that is subject to Rule 22, although we expect future digital therapeutics with an integrated diagnostic function (see Figure 7).

Figure 7 Digital doc.[25] The avatar will see you now. Virtual therapists used the video game 'Second Life' to reach patients. Although the game involved humans behind the avatar, technology could be developed to make the avatars fully autonomous, similar to personal digital assistants like Siri and Alexa. (Wootton, 2010)

Contrary to Rules 15 and 22, all SaMD in scope of EU MDR is subject to classification Rule 11. The following (italicized) text is verbatim text from the EU MDR. For the purposes of identification in this white paper, the paragraphs have been assigned 'a', 'b', and 'c'. These do not appear in the EU MDR.

> *[Rule 11a] Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:*
>
> *— death or an irreversible deterioration of a person's state of health, in which case it is in class III; or*
>
> *— a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.*
>
> *[Rule 11b] Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.*
>
> *[Rule 11c] All other software is classified as class I.*

Rule 11a refers to software intended to provide information that is used to take decisions. These decisions can be made by the software itself, by other software, by hardware or by humans. Rule 11a is applicable not only to software that provides diagnosis or therapy by itself but to all MDSW if this software provides information for a specific medical purpose, as listed in the definition of 'medical device':

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state …

Rule 11a does not apply to firmware needed to provide the output of a thermistor in a digital thermometer. That firmware is neither SaMD nor MDSW, as it does not in itself create information for medical purposes (unless the software creates, for example, an alert when fever occurs; such an alert is considered information for medical purposes and such software is considered SaMD and MDSW). Rule 11a also does not apply to fertility apps. Fertility apps are intended to *support conception,* a purpose that qualifies for a medical device, but that is not listed in the definition of 'medical device' as a specific medical purpose. Although they are not described in the MDCG guidance,[9] it could be argued that accessibility apps intended *to alleviate or compensate for a disability* are not subject to Rule 11a because such apps provide information for very different purposes than specifically medical (see Figure 8). Fertility and accessibility apps are subject to Rule 11c, leading to Class I, unless other rules apply.

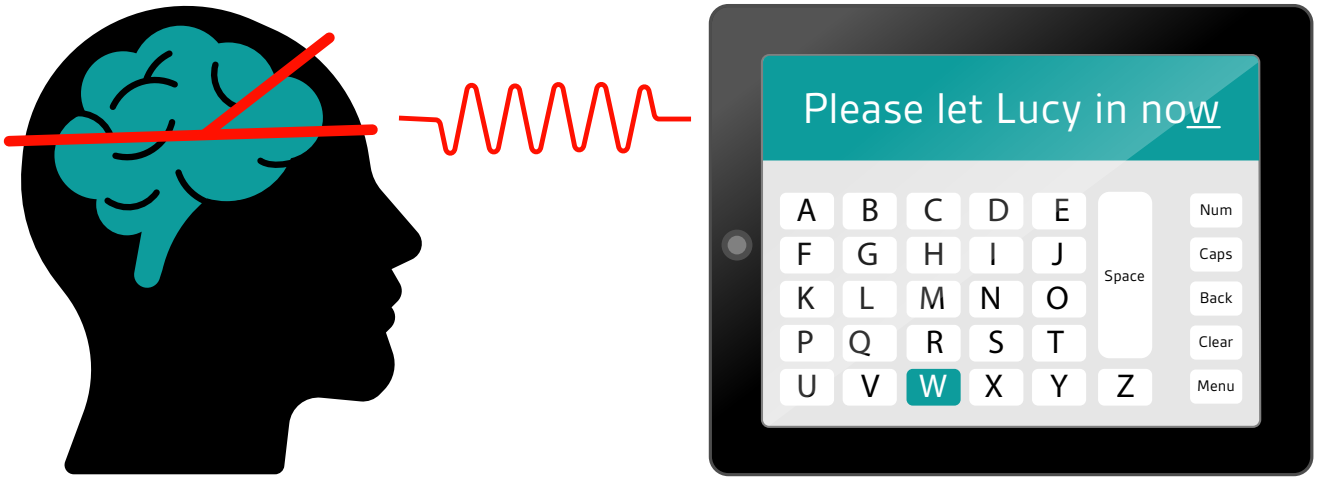


Figure 8 Illustration of an application intended to alleviate or compensate for a disability. The app uses brainwaves to allow patients with locked-in syndrome to communicate with the outside world. Locked-in syndrome is a state of wakefulness and awareness with quadriplegia and paralysis of the lower cranial nerves, resulting in inability to show facial expression, move, speak or communicate, except by coded eye movements or through these apps. (Cobbaert, 2020)

If Rule 11a is interpreted literally, all SaMD is Class III because it is always possible, with some imagination, to think of a situation where the information provided by the software leads to death, no matter how unlikely. Instead, regulators advise interpreting Rule 11a using the IMDRF SaMD risk framework, which relies on the significance of the information and the criticality of the disease, condition or intervention (see Figure 9 and Figure 10).

			Significance of Information		
			• Treat • Provide therapy to a human body • Diagnose disease/ condition • Detect disease/ condition • Screen disease/ condition	• Aid in treatment • Provide enhanced support for safe and effective use of medicinal products or medical device • Aid to make a definitive diagnosis • Triage or identify early signs of a disease or condition	• Inform of options for - Treatment - Diagnosis - Prevention • Aggregate relevant clinical information
Disease Type Patient Condition	**Intervention Type**		Treat or Diagnose	Drive Clinical Management	Inform Clinical Management
• Life-treating	• Requires major therapeutic interventions • Sometimes time critical • Accurate and/or timely diagnosis vital to: avoid death; serious deterioration of health or to mitigate public health risk	Critical	III Type IV.i	IIb Type III.i	IIa Type II.i
• Moderate in progression • Often curable	• Does not require major therapeutic interventions • Not expected to be time critical • Vital to avoiding unnecessary interventions	Serious	IIb Type III.ii	IIa Type II.ii	IIa Type I.ii
• Slow with predictable progression of disease state • Minor chronic illnesses or states • May not be curable	• Can be managed effectively	Non-Serious	IIa Type II.iii	IIa Type I.iii	IIa Type I.i

Figure 9 Illustration of how EU MDR Rule 11a maps on the IMDRF SaMD risk framework. (Cobbaert, 2020)

The second paragraph (Rule 11b) refers to software for monitoring of physiological processes (not just vital physiological processes!).

'Monitoring' refers to monitoring over time or verifying whether a signal is within range – that is checking against limits. As monitoring is a specific medical purpose, MDSW for monitoring of physiological processes is subject to both Rule 11a and Rule 11b.

			Significance of Information		
			• Treat • Provide therapy to a human body • Diagnose disease/ condition • Detect disease/ condition • Screen disease/ condition	• Aid in treatment • Provide enhanced support for safe and effective use of medicinal products or medical device • Aid to make a definitive diagnosis • Triage or identify early signs of a disease or condition	• Inform of options for - Treatment - Diagnosis - Prevention • Aggregate relevant clinical information
Disease Type Patient Condition	**Intervention Type**		Treat or Diagnose	Drive Clinical Management	Inform Clinical Management
• Life-treating	• Requires major therapeutic interventions • Sometimes time critical • Accurate and/or timely diagnosis vital to: avoid death; serious deterioration of health or to mitigate public health risk	Critical	- image-based stroke detection - melanoma detection - paediatric meningitis detection - screening of mutable pathogen	- virtual colonoscopy - melanoma tracking	- stroke prediction - identifying genetic predisposition to develop sepsis in general population
• Moderate in progression • Often curable	• Does not require major therapeutic interventions • Not expected to be time critical • Vital to avoiding unnecessary interventions	Serious	- sleep apnoea detection - tinnitus sound therapy - diagnoses Parkinson's disease based on data captured by vibration/position sensors	- heart arrhythmia detection - cardiovascular surgical planning - guide for diagnosis of kidney function disorders and cardiac risk - insulin dose calculator	- data collection to guide exercise-based treatment or cardiac rehabilitation patients - prediction of asthma episode
• Slow with predictable progression of disease state • Minor chronic illnesses or states • May not be curable	• Can be managed effectively	Non-Serious	- skin lesion tracking to diagnose or rule out eczema	- Nystagmus and other eye movement disorder detection	- provides options for diagnosing seasonal allergic rhinitis vs. common cold - alert doctor of potential triggers indicative of cholesterol management issues - advise on eff seasonal allergy drug

Figure 10 Examples of SaMD mapped against IMDRF risk framework. These (abbreviated) examples are provided by IMDRF and the FDA[11]. (Cobbaert, 2020)

As Rule 11a is applicable to nearly all MDSW and leads to Class IIa, IIb or III, but not Class I, the implication is that the vast majority of MDSW is Class IIa or higher and requires a conformity assessment by a Notified Body. In addition, under the EU IVDR, the vast majority of MDSW now requires conformity assessment carried out by a Notified Body. This is in stark contrast to the situation under the existing EU Medical Devices Directives, where only a small fraction of software requires a Notified Body.

Possible future directions

In the US, the FDA is examining alternative regulatory pathways for software. For example, the FDA has proposed a software 'Precertification (Pre-Cert) Program', which is intended to be a regulatory model that is more streamlined and efficient, resulting in getting product to market and to patients faster than existing methods.

This Pre-Cert Program[26] involves focusing primarily on the product developer, instead of focusing primarily on the product itself. If the developer can demonstrate a culture of quality, excellence and responsiveness, then the FDA believes that a streamlined approval process could be allowed.

The FDA is piloting this program exclusively on SaMD products so that the focus can be on software development excellence. The current model proposal includes:

- Excellence Appraisal – the FDA evaluates the software development team for organizational excellence, which would include excellence principles of product quality, patient safety, clinical responsibility, cybersecurity responsibility and proactive culture
- Review Determination – a model where lower-risk devices have a streamlined or perhaps no premarket review requirements
- Streamlined Review – the FDA identifies what would be included in a streamlined review
- Real-World Performance – leveraging performance data to support the regulatory status.

AI and machine learning (ML) systems have the potential to significantly improve health care. Some of these systems even have the ability to learn and improve themselves over time. Just like how people learn from experience, 'adaptive' ML systems can increase their performance as they collect and analyse real-world data about their past performance.

This brings a great opportunity but also a great challenge – how to manage timely changes to software that impact product performance? How change of AI during runtime relates to its conformity assessment is a domain in which IMDRF should provide further guidance. The FDA has already published a discussion paper that focuses on this very issue, and cites the Pre-Cert Program as a possible regulatory pathway.

Conclusion

Marc Andreessen, Co-Founder of Netscape, an American company famous for its now obsolete web browser, once said that software is eating the world. He meant that an awful lot of successful technology companies find themselves in a different market than the one they started out in. Today they realize that in order to survive they need to turn themselves into a software company.

Placing SaMD on the market has become significantly harder in the EU, whereas the US has removed some of its 'red tape'. In the EU, SaMD classification has become complex, whereas in the US it is very straightforward.

The health care field is moving faster than it has in the past, and new applications might make us pause and go back to our fundamental goals of assuring safety and effectiveness and discovering alternative paths to reach those goals. The shift from a purely product focus to a product+process viewpoint is a new pathway for the FDA, through which it converges towards the quality management system approach used within the EU.

Product developers are innovators. With the explosion of wearables and objects that are part of the Internet of Things (IoT), health and wellness information and technology can be found everywhere. Such apps could run on the computing platform of your mobile phone but also on your fridge or your car. Technology surrounds us to the point that we suggest that humanity has entered an era of 'everywhereables', and this technology will vastly improve our understanding of the human body. Most of these innovations will be driven by software, and most of that software will be SaMD.

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