Regulatory Framework of Software as Medical Device

Artificial intelligence (AI) and machine learning (ML) based technologies have the potential to transform healthcare by deriving new and important insights from the vast amount of data generated during the delivery of healthcare every day. The ability for AI/ML software to learn from real-world experience and improve its performance makes these technologies uniquely situated among software as a medical device (SaMD) and a rapidly expanding regulations by different Health Authorities.

To overcome the challenges while interpreting software product fits into the Medical Device framework, IMDRF has developed different guidance including Risk based categorization to determine possible level of premarket reviews.
Medical device software is software that is intended to be used, alone or in combination, for a medical purpose as specified in the definition of a “medical device” in the medical devices regulations under concern.

- Article 2(1) of EU MDR Regulation (EU) 2017/745
- Section 41BD of the Therapeutic Goods Act 1989
- Section 201(h) of the Food, Drug, and Cosmetic Act

» Software for the following intended purposes is considered to be a medical device:

- Diagnosis of an individual’s disease or condition
- Monitors an individual’s disease or condition
- Provides therapy to an individual
- Controls other medical devices
- Is an accessory to a medical device
- Recommend or specify a treatment or intervention specific to an individual
- Software used to generate virtual anatomical or physiological models

- When Software that does not meet the definition of a medical device (i.e. software that is not SaMD) but is intended by the manufacturer to be an accessory for a medical device, falls under the scope of regulation.
- Software products that are not intended to have a therapeutic purpose fall outside the scope of the definition of a medical device. Software would not be considered a medical device; Examples
    - Educational or general information purposes
    - Displaying of recording information
    - Managing data
    - Enabling communication
    - Encouraging a healthy lifestyle

Regulatory Approach - Recent Regulatory Reforms

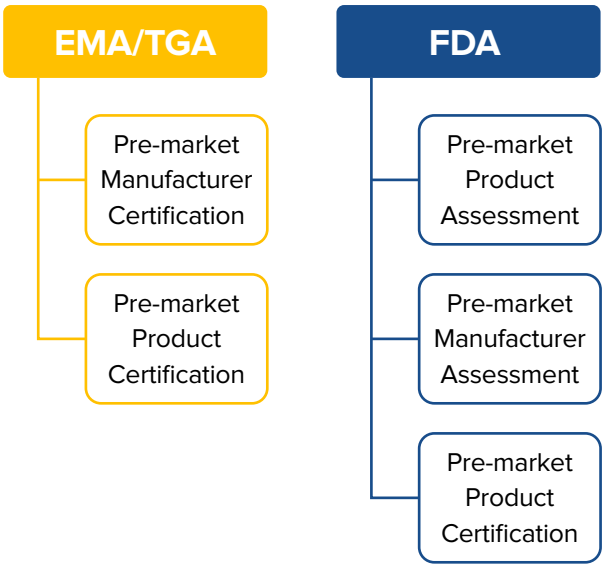
The US FDA, EU and Australia TGA have additionally specified that general platforms, on which such medical software may run or be distributed, are not intended by their manufacturer to be used for therapeutic purposes would not be regulated as a medical devices.

TGA
- Risk based classification system
- Conformity assessment (CA) procedures
- Inclusion in the ARTG
- Post-market monitoring & reporting

EU
- Classify Medical Device Software (MDSW)
- Define Conformity Assessment route
- NB Assessment
- CE Certification

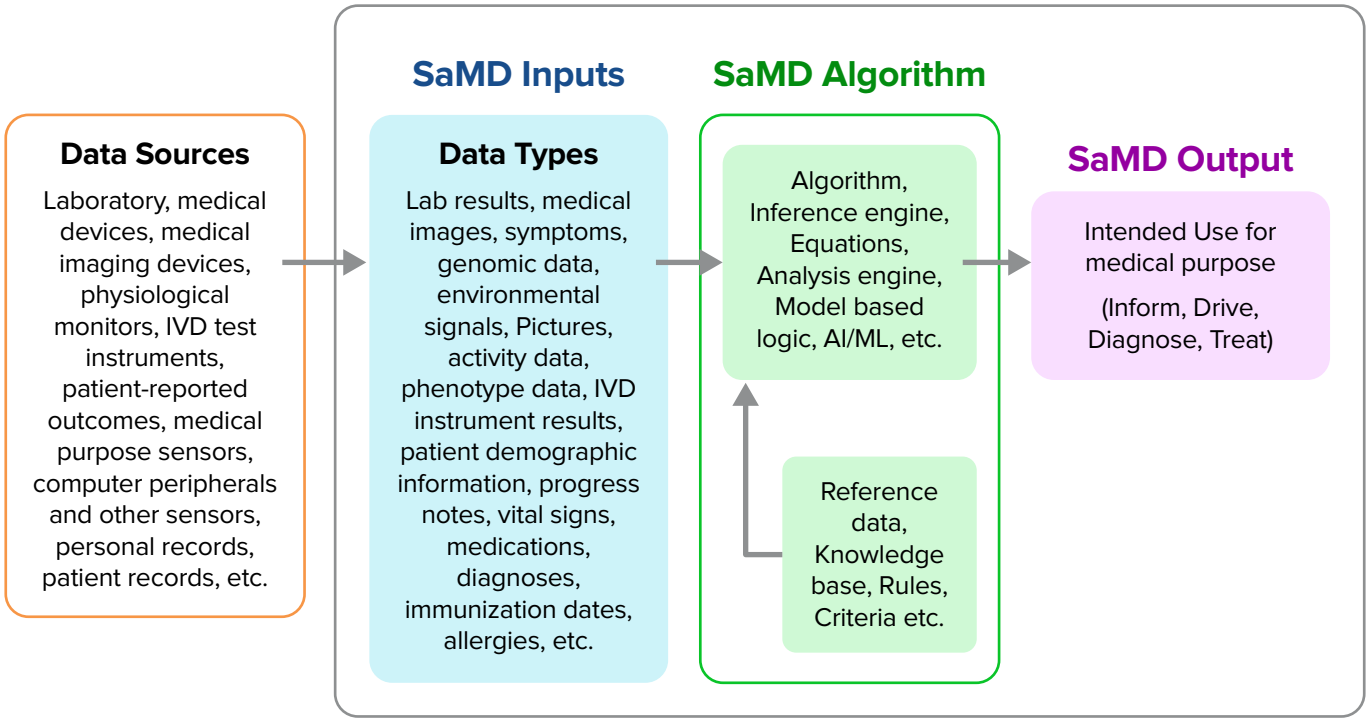
FDA
- Pre-Cert De Novo
- Review Determination Pre-Sub
- Submit Pre-Cert 510(k)
- Real-world Performance

Difference in Regulatory Schemes



General Principles and Context of SaMD

- A SaMD can best be described as software that utilizes an algorithm (logic, set of rules, or model) that operates on data input (digitized content) to produce an output that is intended for medical purposes as defined by the SaMD manufacturer.
- The risks and benefits posed by SaMD outputs are largely related to the risk of inaccurate or incorrect output of the SaMD, which may impact the clinical management of a patient.



SaMD Basic Programming Model

Clinical Evaluation

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STAGE 1

Valid Clinical Association

Is there a valid clinical association between your SaMD output and your SaMD's targeted clinical condition?

STAGE 2

Analytical/ Technical Performance

Does your SaMD correctly process input data to generate accurate, reliable, and precise output data?

STAGE 3

Clinical Performance

Does use of your SaMD's accurate, reliable and precise output data achieve your intended purpose in your target population in the context of clinical care

Global Approach to Software as a Medical Device and Classification

IMDRF Risk Categorization framework allows the manufacturers and regulators to identify the risk categories of SaMD based on the output of a SaMD (inform clinical management, drive clinical management, or treat or diagnose) and the state of healthcare situations and conditions (non-serious, serious or critical) used for healthcare decisions.

		High (Treat or Diagnose)	Medium (Drives clinicalManagement)	Low (Informs clinical Management)
Critical situation or Patient condition	IMDRF	Category IV	Category III	Category II
	EU[1]	Class III	Class IIb	Class IIa
	FDA[2]	Class III	Class III	Class I or II
	TGA[1]	ClassIII	Class IIb	Class III
Serious situation or patient condition	IMDRF	Category III	Category II	Category I
	EU	Class IIb	Class IIa	Class IIa
	FDA	Class II or III	Class II or III	Class I or II
	TGA	Class IIb	Class IIa	Class IIb
Non-serious situation Or patient condition	IMDRF	Category II	Category I	Category I
	EU	Class IIa	Class IIa	Class IIa
	FDA	Class I or II	Class I or II	Class I or II
	TGA	Class IIa	Class I	Class IIa (may cause harm) Class I (any other case

Note: This table does not take into account Class I for EU; 1 Rules-based device classification; 2 Product Code-based classification

Evidence of Compliance and Documentation

Recommend that you describe the role of the software in causing, controlling, and/or mitigating hazards that could result in injury to the patient or the operator.

- QMS
- Version Control
- Release management
- Software Description
- Device Hazard Analysis and Risk management (Benefit must outweigh the risks)
- Software Specifications
- Hardware Requirements
- Software Performance and Functional Requirements
- Software Development
- Software Environment Description
- Software maintenance
- Problem resolution
- Configuration management
- Design Verification and Validation
- Clinical evidence
- Bug/Defects reporting and correction

Standards for Compliance

Standards related to Software for Medical Devices are to be followed:

- **IEC 62304 -** Medical device software - Software life cycle processes
- **ISO 13485 -** Medical devices - Quality management systems - Requirement for regulatory purposes for process-oriented approach, not just in the development.

- **ISO 14971** - Medical devices - Application of risk management to medical devices
- **IEC 62366** - demands, that the usability of medical devices using a "usability-oriented development process" be followed.
- **IEC 60601-1** - obliges manufacturers of programable electrical medical systems (PEMS) to follow a life cycle process.
- **IEC 80002-1** - Medical device software — Part 1: Guidance on the application of ISO 14971 to medical device software

EU MDR- Qualification of Software in Regulation (EU) 2017/745 – MDR

Considerations on Placing on the Market

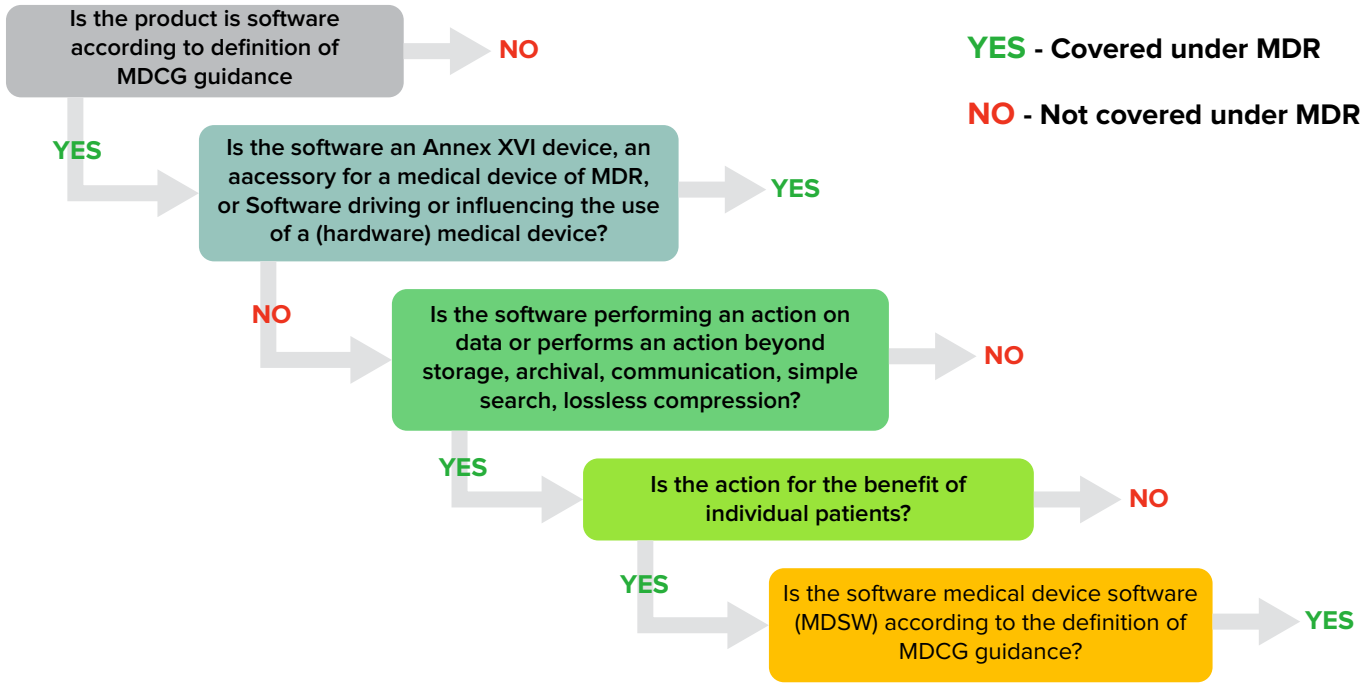
- Medical Device Software (MDSW) can be placed on the market in two different ways:
  - Option 1: as a medical device in its own right
  - Option 2: as an integral component/part of a device

Note: MDSW could be independent under both scenarios described above, despite the presentation in which it is placed on the market.

- Modules: Some of these modules have a medical purpose, some not. The modules which are subject to the EU MDR must comply with the requirements of the regulations and must carry the CE marking. It is the obligation of the manufacturer to identify the boundaries and the interfaces of the different modules.

Decision steps for qualification of software as MDSW

The qualification of MDSW, either as a device or an accessory, is independent of the software's location or the type of interconnection between the software and a device. There are five steps for the qualification of MDSW



TGA - Consultation: Scope of regulated software-based products

In early 2019, the TGA conducted a public consultation on the Regulation of software, including Software as a Medical Device (SaMD).

Three key changes to the regulatory framework were proposed as part of the Consultation:

1. Classify SaMD products according to the potential harm they could cause to patients;
2. Requiring SaMD to be included in the ARTG- Changes to exclude SaMD products from the personal importation exceptions and require them to be included in the Australian Register of Therapeutic Goods (ARTG) and will require an Australian sponsor; and
3. Changes to the essential principles- include clear and transparent requirements for demonstrating the safety and performance of SaMD and other regulated software

The changes introduced by the amendment commence on 25 August 2020 and will potentially make existing SaMD subject to more stringent regulation.

New rules have been introduced for the classification of programmed and programmable medical devices, and software that is a medical device (PPSMD). The new rules cover software-PPSMD used for:

- Diagnosing and screening for a disease or condition
- Monitoring the state or progression of a disease, condition, etc.
- Specifying or recommending a treatment
- Providing therapy (via provision of information)
- Patient images and anatomical models (introduced as part of the personalised medical device reforms)

Lifestyle and fitness-based software such as that used in fitness trackers and pedometers generally falls outside this framework as it is not used for therapeutic purposes.

Proposed carve-out principles by TGA: specified in consultation document, not yet been implemented in the Regulations

- it can be demonstrated that there are already adequate (or similar) alternative mechanisms in place for oversight for software-based products;
- any risks associated with their use and performance (e.g., risk of misdiagnosis or inappropriate treatment) can be appropriately mitigated

Organizational arrangements needed to meet the proposed changes: are variable and highly dependent upon

- The type and structure of the company;
- The type of technology requiring initial regulatory assessment (or reclassification);
- The capabilities of in-house regulatory counsel; and
- The availability of specific industry regulatory consultants who are up to speed and able to service industry demand.

FDA - Total product Lifecycle approach (TPLC) of the Software Pre-Certification Program

- Types of premarket submissions for software devices, include:
  - 510(k) Notification including Traditional, Special, and Abbreviated submissions
  - Premarket Approval Application (PMA)
  - De Novo Application
- The FDA offers TPLC approach that would allow for the evaluation of organizations and their SaMD products throughout the lifecycle of the organization and products (from its premarket development to postmarket performance), so that patients, caregivers, and other users have assurance of the safety of those products.

- The product types that may benefit from precertification might include all software that meets the definition of a device in section 201(h)1 of the FD&C Act including SaMD, software in a medical device (SiMD), and other software that could be considered accessories to hardware medical devices.

- For the pilot program, the FDA selected nine companies from more than 100 that expressed interest: Apple, FitBit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool and Verily.

- FDA intends to perform testing of the Software Pre-Cert Program model prior to employing it and it is as an alternative premarket pathway for SaMD. There are four key program components:

    1) Excellence Appraisal
    2) Review Determination
    3) Streamlined Review
    4) Real-world Performance

- Uses IMDRF risk categories to determine possible levels of premarket reviews

- FDA 21 CFR Part 820 Quality System Regulation QSR Requirements for Medical Device

- FDA will assess the culture of quality and organizational excellence of a particular company and have reasonable assurance of the high quality of their software development, testing, and performance monitoring of their products to provide access to safe & effective AI/ML based SaMD:
    - Establish clear expectations on quality systems and good ML practices (GMLP)
    - Conduct premarket review for those SaMD
    - Expect manufacturers to monitor the AI/ML device and incorporate a risk management approach and other approaches outlined in Guideline.
    - Enable increased transparency to users

Key Points to be remembered

- Apply medical device definition to software based on Intended Use and criteria specified.
- Key IMDRF guidance and ISO standards provide help with interpretation and adoption of SaMD in the regulatory framework.
- QMS controls and lifecycle management are essential (e.g. ISO 13485 and IEC 62304). Implement Design QMS processes early in software development life-cycle.
- Must consider data security and privacy requirements (HIPPA, GDPR, SOC, etc) and reimbursement requirements.
- Level and type of Clinical Evidence should be based on the significance of information provided by the SaMD.
- Continuous post-market monitoring and responding to changes is required (cybersecurity, platform changes, changes to third party software etc.)

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