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Regulatory approach for the approval of Artificial intelligence/ Machine language (AI/ML) Based Software as medical devices (SaMD)

D. Avinash*, Madhu Gudipati, and Rama Rao Nadendla

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences (Autonomous), Lam, Guntur-522 034, Andhra Pradesh, India.

ABSTRACT

Artificial Intelligence and Machine Language (AI/ML)-Based medical technologies has the potential to change the medical care by determining new and significant experience from the huge measure of information produced during the conveyance of medical care each day. The capacity for AI/ML programming to gain from certifiable criticism (preparing) and improve its presentation (variation) makes these advancements particularly arranged among programming as a clinical gadget (SaMD) and a quickly extending territory of innovative work. Our vision is that with fittingly customized administrative oversight, AI/ML-based SaMD will convey protected and powerful programming usefulness that improves the nature of care that patients get. Different types of medical devices and various documentation procedures for the approval of the AI/ML based SaMD was discussed and the modifications or the updates regulatory approach to the SaMD were clearly mentioned for the easy approval considering the IMDRF, GMLP, TPLC and FD&C regulations. The future trend and the current approved SaMD were discussed.

Keywords: AI/ML, SaMD, IMDRF, GMLP, TPLC, FD&C Act

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Corresponding Author

Name: D. Avinash

Email: madhugudipati7@gmail.com

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INTRODUCTION

Artificial intelligence and Machine Language (AI/ML)-Based medical technologies. **Artificial intelligence:** Mc Carthy has defined AI as, the science and engineering of making machines, especially intelligent computer programs.^(1,6)

The AI/ML based study in health care study has raised since 2010. The extent of usage of AI has spread over through the several branches of medical studies right from diagnosis to the treatment. AI is not simply a single technology rather it is a summation of

different field studies like statistical analysis of data, expert decisions they are mostly on if-then statements and machine learning. The patient care was well developing with a peer interaction with AI and the patient. It already occupied over humans in various domains of patient's health care. AI based Medical devices are now the helping hand in the care of the patient's daily activity.^(1,2,7,8)

Machine Learning: It an AI technique that is used to design and train software algorithms to and act simultaneously on the given data. ML might be a Locked which means the given algorithm does not change over time based on new data, while adaptive software can change its behaviour over time based on new data.^(3,8) All the structure of AI is made up of software. Software that is intended to make a device or used for the maintenance of the device like testing, source coding management, servicing etc., is not considered as software for the medical purpose, generally software with a medical purpose consists of:

Key Definitions:

Software as a Medical Device (SaMD): The International Medical Device Regulators Forum (IMDRF) has defines "SaMD as a software based medical device the is intended to be used for one or more medical purposes the perform these purposes without being part of a hardware medical device".⁽²⁾

Medical device: 'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease.⁽¹⁾

In Vitro Diagnostic (IVD) medical device

It is a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.^(1,4)

Software as a Medical Device (SaMD): The International Medical Device Regulators Forum (IMDRF) has defines "SaMD as a software based medical device the is intended to be used for one or more medical purposes the perform these purposes without being part of a hardware medical device"⁽²⁾ FDA also considers these medical devices as the purposes are included to treat, diagnose, cure, mitigate, or prevent disease or other conditions. They also have the potential to adapt and optimize device performance in real-time to improve patient health care continuously. AI/ML technologies stood among SaMD (Software as a Medical Device) because of its good ability to learn and get updating by the recent feedbacks from various sources and adapting it according to the circumstances and need. Learning, adaptation and optimization are the main attribute of AI/ML based SaMD.^(9,10)

Traditionally medical devices are reviewed by FDA through a premarket pathway, FDA and EMA strived to develop the regulations of SaMD but FDA brought a tailored guideline for the development and approvals of the SaMD to reach the users safe and effectively.⁽³⁾ Before marketing the medical software or hardware the parent company has to submit it for FDA approval. The regulatory body has to review and provide clearance under 3 levels.

1. SaMD 510(k) notification,
2. de novo pathway and
3. premarket approval.

510(k) clearance: A 510(k) clearance for an AI/ML is granted when the device has shown as a safe and effective that is substantially equivalent to a legally marked device (section 513(i)(1)(A) FD&C act) Which is called as "PREDICATE". to get a clearance, the submitter must have provided substantial equivalence proof with one or more other legally marketed products in their application. Without an approval of being substantially equivalent to the other algorithm, it cannot be legally marketed.^(6,11)

Premarket approval: Premarket approval is FDA procedure for evaluating the safe and effectiveness for Class III medical devices. Class III medical devices

are those that have a large impact on human health and may present a potential unreasonable risk of illness. and for such devices the evaluation must undergo more thorough scientific and regulatory processes to determine their safety and effectiveness where general and special controls are no suitable for evaluation. In order to approve an application, the FDA determines that the device's safety and effectiveness is supported by satisfactory scientific evidence. Upon approval, the applicant can proceed with marketing the product.⁽¹²⁾

de novo pathway: Regarding the de novo classification, it is used to classify those novel medical devices for which there are no Predicate device for showing the Substantial equivalence, but which offer adequate safety and effectiveness with general controls alone/ general and special controls. The de novo classification is a risk-based assessment of the device before approval and allowing the device to be marketed. The devices which are cleared with a denovo classification request may be classified into class I and class II and used in future as a predicate in pre-market notification submissions.⁽¹³⁾

This traditional paradigm of medical devices approval by FDA is not applicable to adaptive AI/ML technologies.as for every change in software, a pre-market review is needed for safety and effect issues.

For any change is the software that was cleared under 510(k), FDA's center for devices and radiological health has published guidelines (Deciding when to submit a 510(k) for a software change to an existing device.^(2,5)

The 510K software modifications guidance focuses on the risk to the users upon updating the initial algorithm. Categories of software modifications:

- a change the introduces a new risk or modifies an existing risk that could result in significant harm
- a change to risk controls to prevent significant harm, and
- a change that significantly effects clinical functionality or performance specifications of the device.⁽⁵⁾

When the above changes are applied to the SaMD they would again require a premarket submission to FDA for reviewing the performance, safety and effectiveness as referred in 21 CFR 807.81(a)(3) supplement application is to be submitted at the time of reviewing for any change to the initial performance characteristics. We can't even imagine an approach for the pre-market review for each and every small change in the algorithm. But a reasonable and assured approach is need for maintaining the safety guidelines while giving a path to the software of continuous learning on the patient care.⁽⁵⁾

Till date the FDA has approved only SaMD /AI that has “locked” algorithm (an algorithm that provides the same result each time the same input is applied to it and does not change) prior to the marketing and a compulsory review is required for the changes included in the algorithm.⁽³⁾ The power of the AI to change or evolve upon the adaptation from the real-world feedback lies in the ability to learn and the wide distribution of the devices. On continuous learning the AI/ML may give outputs that are different from the initially approved device that performed on the same inputs. Due to the monotonous adaptive nature of these devices FDA has started “a total product lifecycle-based regulatory framework for these technologies that would allow for modifications to be made from real-world learning and adaptation, while still ensuring that the safety and effectiveness of the software as a medical device is maintained”⁽²⁾

This type of approach enables the rapid improvement without effecting the safeguards. Thus, TPLC is based on the digital health software precertification (pre-cert) program which allows continuous validation and evaluation.⁽¹⁴⁾

This approach assures that the changes are made according to pre-specified objectives, and uses a proper validating procedure that execute the same effectiveness and safety of the initially cleared device and also include the real-world monitoring. This framework makes the manufacturers to keep an eagle eye on the safe and effective. Which makes the manufacturers and FDA easy for approvals and in turn it benefits the patients. This approach rehearses from the current premarketing programs and mostly depends on IMDRF’s risk categorization rules, the FDA’s benefit – risk framework, risk management principle also.

FDA introduces a “predetermined change control plan” in the premarket review itself which describes the antedate changes that could be possible which is described in “Software as Medical Device Pre-specification” and also defines the methodology used for implementation of the changes in algorithm that mages the patient’s risk which is defined in “algorithm change protocol”.⁽¹⁵⁾

The FDA, expects a responsibility from producers on the genuine execution of the predetermined change control plan for algorithm modification in AI based clinical gadget from the approves pre- specifications. Both FDA and manufactures have an eagle eye on the AI/ML device right from the premarketing to the post marketing performance for assuring the patient safety.

A mentioned before the rules for risk management of these devices were drawn from the IMDRF the risk categorization is as below:

- 1) **Significance of information provided by the SaMD to the healthcare decision**, which is for the diagnosis, treatment, and to educate clinical management.⁽³⁾

- 2) **State of health care situation or condition**, which describes patient’s criticality.⁽³⁾

Considering the above two factors, depicting the expected use of these AI/ML based SaMD, the SaMD were categorized from the least(I) to the riskiest (IV) to mirror the danger related with the clinical situation for the device use.⁽¹⁶⁾

The TPLC approach evaluates and monitor the SaMD right from its premarket development to the post marketing excellence while providing a chance for the change.

Types of AI/ML Modifications in SaMD:

Not all modifications need a review, the modification that don’t need the review were described in the “Deciding when to submit a 510(k) for a software change to a existing device.” But the modifications that are compulsory for the review are related to:

- 1) Modifications in the Performance : clinical and analytical performance.⁽¹⁷⁾
- 2) Modifications in Inputs used by the AI/ML algorithm: changes related to the inputs used for the clinical assessment or the SaMD output.

Extending the device compatibility with the other devices or program or Adjoining different input data⁽³⁾.

- 3) Modifications related to the Intended use of SaMD’s: the intended to use must be according to the IMDRF guidelines.⁽³⁾

The algorithm change may have different impact on the users, patients and the caregivers.

A Total Product Life Cycle TPLC Regulatory approach for AI/ML based SaMD:

This is totally from the Software Pre-Cert Program, “The Pre cert program goal is to provide more streamlined and efficient regulatory oversight of software based medical devices from manufactures who have demonstrated a robust culture of quality and organizational excellence (CQOE) and are committed to monitoring real- world performance.”^(4,18)

The steps involved in the TPLC is: ⁽³⁾

1. Maintaining the culture of quality systems and Good machine learning practices.
2. Premarket assurance of safety and effective for continuous support to the patient.⁽¹⁹⁾
3. Review of SaMD pre specifications and algorithm change protocol specified in (“Deciding when to submit a 510(k) for a software change to an existing device”).⁽²⁰⁾
4. Real world performance monitoring and providing transparency to the users and FDA.⁽⁴⁾

Maintaining the culture of Quality systems and good machine learning practices (GMLP)

The FDA expects every medical device manufacture to have an establishes quality system that is geared toward the development, delivering and maintaining

high quality products throughout the lifecycle that conform to the appropriate standards and regulations as per 21 CFR part 820.⁽²⁾

All the SaMD's are demonstrated for the clinical evaluation.

Clinical evaluation components include:

1. Valid clinical association
2. Analytical validation
3. Clinical validation/ evaluation⁽²⁾

Clinical validation/Evaluation: it is defines as a set of ongoing activities conducted in the assessment and analysis of a SaMD's clinical safety, effectiveness and performance as intended by the manufacturer in the SaMD,s definition statement.⁽²²⁾

Valid clinical association: it is also known as scientific validity⁽⁵⁾. A valid clinical association is an indicator of the level of clinical acceptance and how much meaning and confidence can be assigned to the clinical significance of the SaMD's output in the intended healthcare situation and the clinical condition/physiological state.⁽²³⁾

Analytical/ technical validation: it is done to check the reliability, accuracy and pericision of the SaMD on the clinical condition and also demonstrates that

- a) The software meets its specifications
- b) The software specifications conform to user need and intended uses⁽²⁴⁾

Every GMLP i.e. Data management, feature extraction, training and evaluation are related to the good software engineering practices and quality system practices.

GMLP include:

- Relating the available data to the clinical issue and current trends,
- Differentiating the training, tuning and test databases,
- Significance level of transparency of the output
- Data procuring is a reliable manner with clinical importance and lining up with the SaMD use and modifications assessment.^(3,5)

Premarket assurance of safety and effective for continuous support to the patient.

These steps give an appropriate option for submitting a plan for the premarket review with "pre-determined change control plan."

The pre-determined plan may include the fore-shadowed change plans:

SaMD pre specifications (SPS) ^(2,3): SPS defines "what" modifications are intended to the SaMD, the modifications might be related to the device perfor-

mance and intended use of the SaMD. The manufacturer must have a detailed idea of the modifications that might be intended to the device and should develop the algorithm to learn in the drawn "region of potential change"

Algorithm change protocol (ACP): ACP is a portrayal of a flow chart that has to be followed by the manufacturer to make the SPS modifications.

Algorithm change protocol describes "how" the algorithm will learn and change.^(2,3)

Review of SaMd pre specifications and algorithm change protocol and establishing them:^(2,3)

Here the proposed SPS and ACP were reviewed to properly oversee dangers to the patient from these changes while give a chance to the manufacturers to improve the potential and performance in the patient care.

The changes must be with in Quality system regulation (QS), 21CFR Part820.

The manufacturer has to evaluate the risks based on "Deciding when to submit a (k) for a software change to an existing device" guidance. The guiding principles are:

- 1) Submission of a new 510(k) for pre-market review with full description of the changes that trigger the requirement for submission.
- 2) Documentation requirement of the modifications and the risk management.⁽³⁾

If the SPS and ACP as with the bounds then the manufacturer must document the change in the change history with records and a file of reference as per the Document approach in the guidelines⁽²⁾.

4)Real world performance monitoring and providing transparency to the users and FDA.

The company must bound to principles of the monitoring and transparency rules.it is very important to the SaMD that changes over time to be transparent about the changes that are made and the key aspects of safety and effectiveness of the device.

The Real-world monitoring is the mechanism with which the risk engaged with AI/ML based SaMD alterations, in support of the risk management profile in evaluation of as specific AI/ML based SaMD. The manufacturers can be transparent in updating the users with letters, emails, software notifications and can also decide what information to be provide in respect to the changes.⁽²⁾

Trend: After a clear crosscheck and validation has found that only 64 AI/ML based announcements were made from different regulatory authorities and of them only 29 devices were related in the FDA announcements and the rest 35devices were approved from various sources other than FDA. and of these 29 devices 23 devices were approved under 510(k)

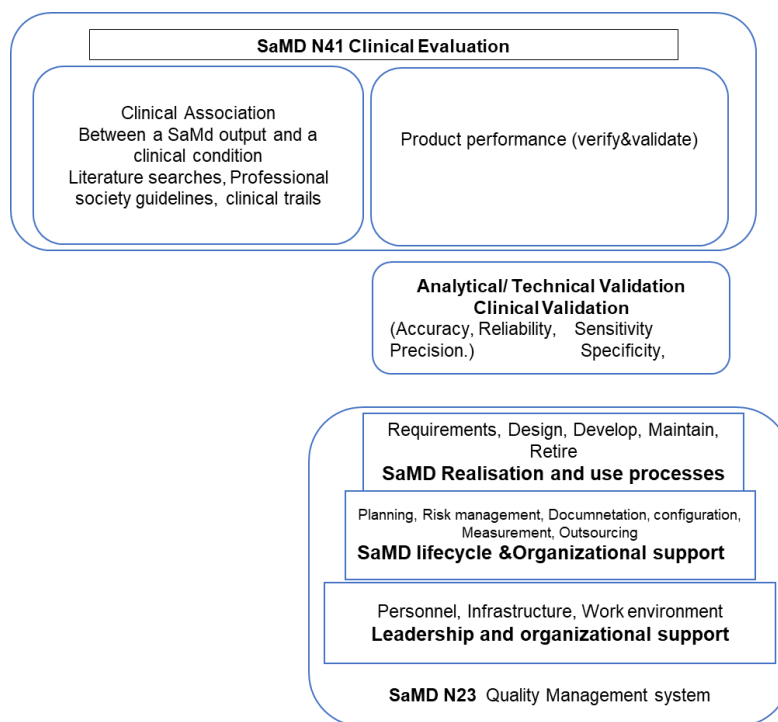


Figure 1: Clinical Evaluation Landscape

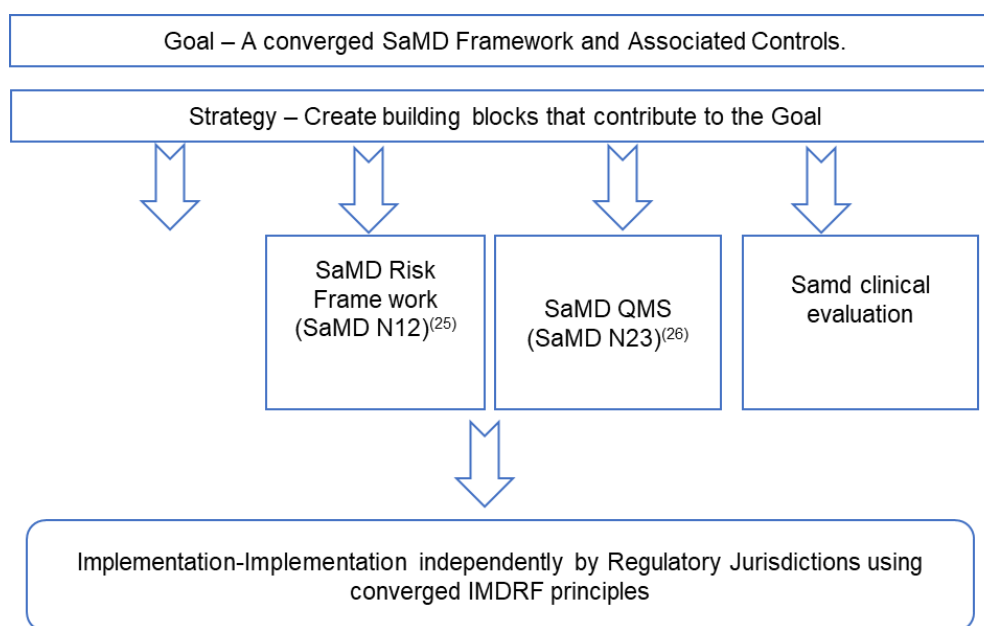


Figure 2: SaMD regulatory pathway

clearance, 5 devices have cleared de novo pathway and one devices has approved with PMA clearance.⁽¹⁾

First approval was made in 2016 by FDA ,3 in 2017 ,3 in 2018 and 10,2 devices in 2019 and 2020 respectively. all the FDA approved devices are under the Innovations of cardiology and radiology with 21 and 4 devices respectively.⁽¹⁾

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