Paper SA07

Regulatory Challenges and Strategies for AI/ML (SaMD) Enabled Medical Device Data Submission

Shashikant Kumar, Ephicacy Lifescience Analytics, Bengaluru, India
Mrityunjay Kumar, Ephicacy Lifescience Analytics, Bengaluru, India

Abstract

With the latest advancement in medical device industry and its regulatory requirement, it has become evident that the industry needs to adapt new approaches of data collection and submission. Recent trends show that new approaches of data collection and submission necessitates the increased use of real-world evidence (RWE), digital health technologies, and artificial intelligence (AI)-driven devices. These innovations often lead to data in non-traditional formats, complicating the submission process across Regulatory Authorities (RA).

Key challenges include the lack of regulatory frameworks for AI/ML enabled devices (e.g SaMD Software as Medical Device) and harmonization among regulatory authorities for submission. This presentation will discuss effective strategies to handle software version control, including the adoption of standardized data formats (ISO 13485), analytics tools, and employing new AI/ML methods. With latest guidance on SaMD from regulatory, we aim to provide actionable insights and best practices to optimize data submission processes for cutting-edge medical devices.

Introduction

The term “Software as a Medical Device” (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device [source: IMDRF]. It performs functions such as diagnosis, monitoring, treatment, and disease prevention by analysing data from medical imaging, biosensors, wearables, and other health-related sources. SaMD is transforming healthcare by improving diagnostics, patient management, and treatment outcomes.

AI/ML enabled devices (e.g. SaMD Software as Medical Device) are new and there are no new frameworks for data management and analysis which poses a challenge for regulatory bodies to establish guidelines on how AI-processed data should be handled. Also, these AI/ML softwares may get updated on frequent intervals so guidance on version control becomes necessary.
AI technologies enable real-time analysis of data, which can be beneficial for early detection of safety and efficacy signals. Regulatory bodies need to adapt to this shift towards real-time data submission and analysis.

"AI/ML-Based Software as a Medical Device Action Plan has been drafted by FDA in 2021. The European Medicines Agency (EMA) has also started to adapt its regulatory framework to address AI and data-driven technologies however there is no guidelines, yet which poses a risk of harmonization among regulatory authorities.

Examples of SaMD

Any software associated with a medical device regardless of the specific technology or terminology, SiMD, SaMD, MDSW, firmware, or embedded software. The platform doesn’t alter its classification. Whether the software runs on mobile, cloud, desktop, or inside physical medical device hardware, it retains its designation as medical device software.

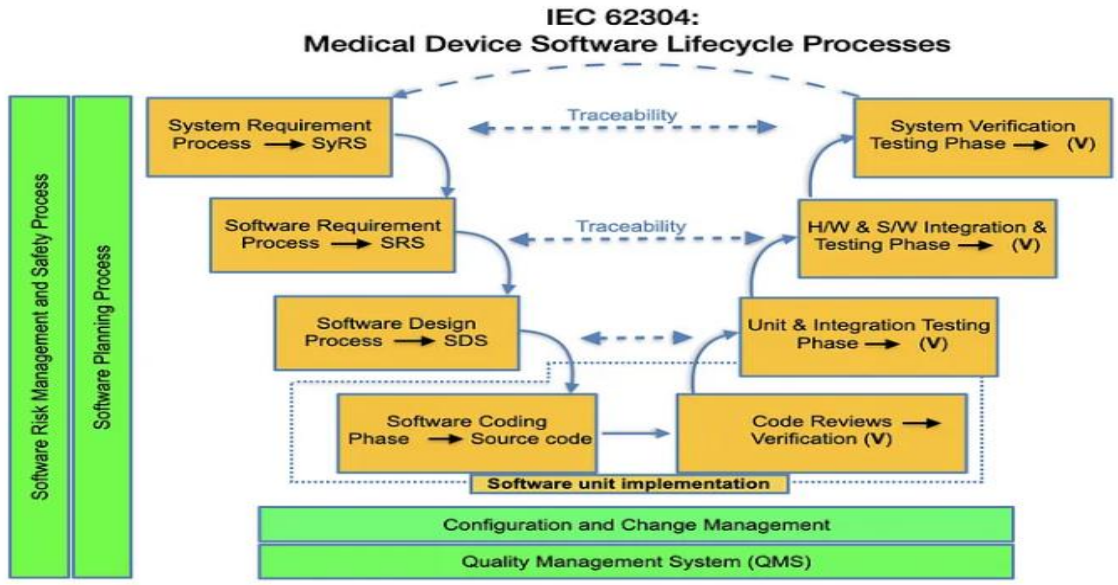
- Pacemaker programming software (likely an accessory to pacemaker software, can be SiMD or SaMD)
- Insulin pump control software (typically SiMD or embedded software)
- Diagnostic imaging software (likely SaMD software using images from other medical devices)
- Electronic health record systems (SaMD software, depending on regulations, it might not be a medical device)
- Telemedicine software platforms (probably SaMD running on generic hardware platforms)

Standards can be helpful to meet otherwise challenging regulatory requirements. Choosing the right standards is vital to navigating regulatory approval processes.

The **IEC 62304 standard**, a globally recognised standard for medical device software which applies to:

- Medical devices with embedded software, and
- Standalone software - known as Software as a Medical Device (SaMD).

IEC 62304, titled “Medical device software - Software lifecycle processes,” is an international standard that provides a framework for the development of quality medical device software. It establishes standards for managing software development, verification, validation, and maintenance within the context of medical device development.

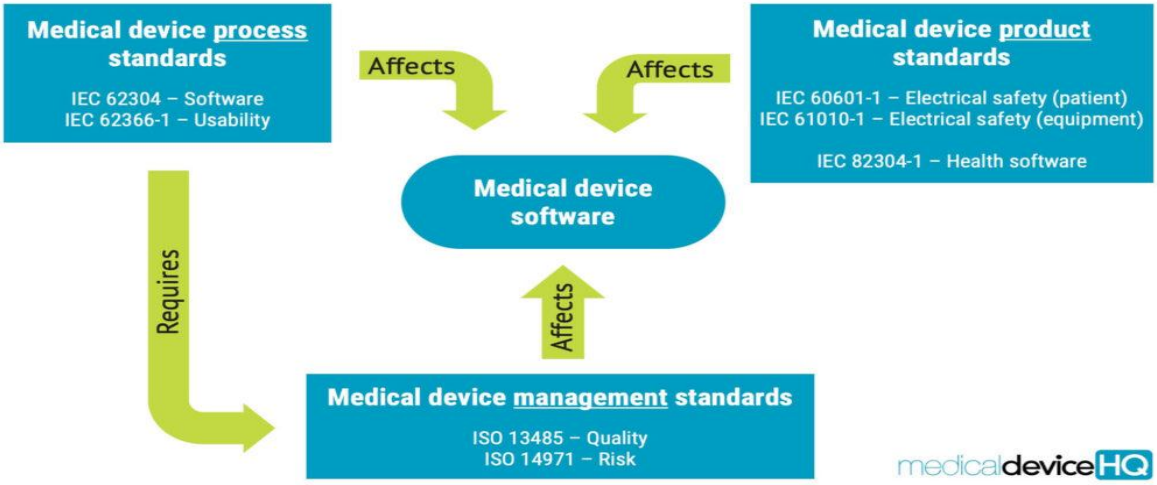


Summary illustration of IEC 62304

- When manufacturers build software that either functions as a medical device (SaMD) or that is to be incorporated into a medical device (SiMD), the stakes are high and therefore clear and high standards are needed.

- IEC 62304 is the international standard for medical device software development and other medical device software life cycle processes.

Flow diagram for Medical Device Software



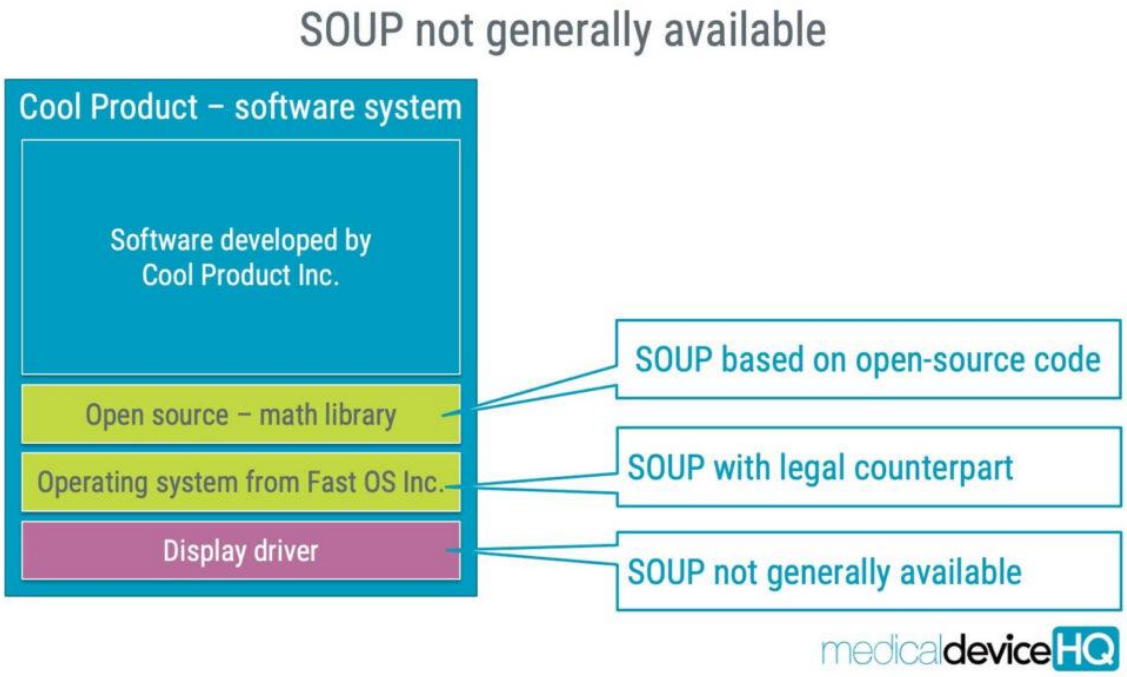
Software of unknown provenance (SOUP)

Software of unknown provenance, (SOUP) is software component that is not developed for use in medical devices but that you want to include in a medical device software system.

This could include software such as:

- Operating systems
- Databases
- Libraries

SOUP can originate from different sources, such as open-source projects, a company delivering generic software components or, eventually, a source code snippet from another project in your organisation.



Using SOUP in medical devices requires risk analysis and a robust software design. The purpose is to ensure that the reliability of the SOUP components won't compromise the medical devices' overall safety, performance, and efficacy.

IEC 62304 Software Safety Classification

The main aim of the standard is to lower risk. The more potential risk the software can cause, the stricter are the requirements of the standard.

The software safety classification is based on the potential injury the software can contribute to and can be summarized as follows:

- Class A: No injury
- Class B: Non-serious injury
- Class C: Serious injury or death

Unit verification is required for class B and C while there are no such requirements for class A software.
Detailed design documentation is required for class C but not for class A and B.

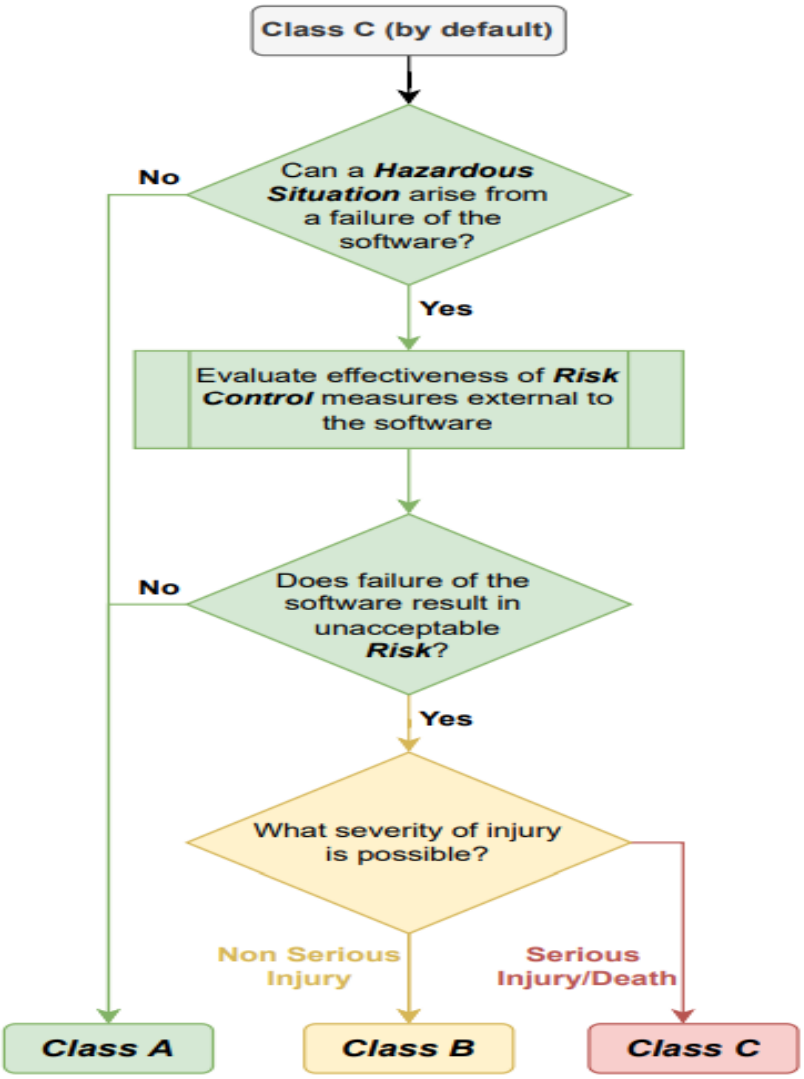


Figure 2. Software safety classification according to IEC62304

Medical Device Classification

Some examples for medical device based on FDA and MDR (Medical Device Regulation, EU)

Table 1. Medical device classification according to FDA and MDR.

Risk	FDA Class	MDR Class	Example
Low	Class I	Class I	Bandages
Moderate	Class II	Class IIa	X-ray-Machines
Moderate to High	Class II/III	Class IIb	Defibrillators
High	Class III	Class III	Pacemakers

Regulatory Challenges in AI/ML-Enabled SaMD

Based on unique features of Software, regulators across the globe recognized the need to converge on a common framework and principles for Software as a Medical Device that enables all stakeholders, including regulators, to promote safe innovation and protect patient safety.

The International Medical Device Regulators Forum (IMDRF) is a voluntary group of medical device regulators from around the world who have come together to reach harmonization on medical device regulation. IMDRF develops internationally agreed upon documents related to a wide variety of topics affecting medical devices. In

2013, IMDRF formed the Software as a Medical Device Working Group (WG) to develop guidance supporting innovation and timely access to safe and effective Software as a Medical Device globally.

On January 6, 2025, the FDA published the *Draft Guidance: Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations*. This draft guidance proposes both lifecycle considerations and specific recommendations to support marketing submissions for AI-enabled medical devices. The draft guidance highlights recommendations from other guidances to assist manufacturers with applying those recommendations to AI-enabled devices, as well as providing additional recommendations on topics of specific relevance for AI. Notably, this draft guidance is specific to AI-enabled medical devices continues to demonstrate the agency's efforts to provide transparency and to help ensure product safety and effectiveness while supporting innovation in this rapidly growing field.

1.1 Lack of Standardized Regulatory Frameworks

Various regulatory bodies requirements for AI-Driven SaMD

Regulatory Body	Key Frameworks & Guidelines	AI-Specific Considerations	Approval Pathways
FDA (USA)	Digital Health Center of Excellence	Algorithm Change Protocol (ACP): AI updates need pre-specified protocols	510(k) clearance for moderate-risk devices
	FDA's Proposed AI/ML-Based SaMD Framework (2021)	Focus on real-world performance monitoring	De Novo pathway for novel devices
	Good Machine Learning Practice (GMLP) Principles (2023)		PMA (Pre-Market Approval) for high-risk AI/ML-based SaMD
EMA (Europe - EU MDR)	EU Medical Device Regulation (MDR 2017/745)	Risk-based classification (Class I, IIa, IIb, III)	Conformity Assessment via Notified Bodies
	Artificial Intelligence Act (Pending)	Emphasis on human oversight and transparency	Clinical Evaluation Report (CER) mandatory for AI SaMD
	Guidance on Qualification of Digital Health Applications	CE Marking is required for EU market access	
IMDRF (Global Framework)	Software as a Medical Device (SaMD) Guidelines (2014, 2019)	Focus on harmonization of regulations	Not a regulatory agency but provides recommendations adopted by FDA, EMA, and others
	Risk Categorization Framework (based on Intended Use)	Encourages post-market monitoring and iterative improvements	
Health Canada	Software as a Medical Device (SaMD) Guidance	AI-based SaMD follows risk-based classification	Requires Medical Device License (MDL)
	Digital Health and Cybersecurity Framework	Regulatory sandboxing approach to allow safe AI adaptation	AI algorithms subject to continuous performance monitoring
MHRA (UK)	UKCA Marking for Medical Devices	Emphasizes Explainability and Transparency in AI models	Uses risk-based classification
	AI & Digital Regulation Service (Pilot)	Aligns with EU MDR but follows UKCA pathway post-Brexit	Requires Clinical Evidence Submission for AI model

Challenges in Harmonizing Global Regulations for AI-driven Medical Devices

1. Varying Risk Classification Systems
   - The FDA, EMA, and IMDRF classify SaMD differently (e.g., FDA uses low, moderate, high risk; EMA follows Class I, IIa, IIb, III).
   - AI-based continuous learning models do not fit neatly into traditional regulatory frameworks.

2. AI-Specific Challenges (Black Box Models)
   - Regulators require explainability and transparency in AI decision-making, but Deep Learning models are inherently opaque.
   - The EMA, FDA, and MHRA are actively researching Explainable AI (XAI) methods.

3. Algorithm Change Protocols (ACP) and Continuous Learning AI
   - AI models evolve post-market, but current regulations focus on static, pre-approved models.
   - FDA's ACP (Algorithm Change Protocol) attempts to address this, but the EMA lacks a clear counterpart.

4. Cybersecurity and Data Privacy Concerns
   - AI SaMD interacts with sensitive patient health data, leading to cross-border compliance issues (e.g., HIPAA in the US, GDPR in Europe).
   - No unified global AI-specific cybersecurity standards exist yet.

5. Lack of Unified Global Regulatory Framework
   - Different jurisdictions have different review timelines, leading to delayed market access for AI-driven SaMD.
   - The IMDRF is pushing for harmonization, but practical implementation is slow.

1.2 Data Integrity and Transparency Issues

Ensuring data reliability, completeness, and traceability for AI models

1. Data Reliability
   - Data Quality Management: Ensuring accurate, consistent, and complete data collection from validated sources (e.g., Electronic Health Records, Wearables).
   - Data Versioning: Keeping track of data changes, including updates and corrections, to ensure reproducibility.
   - Validation & Testing: Conducting rigorous validation of input data, including cross-validation and external validation sets.

2. Data Completeness
   - Comprehensive Data Capture: Including diverse data types (e.g., demographics, clinical outcomes, imaging) to improve AI model performance.
   - Handling Missing Data: Implementing strategies like multiple imputation, data augmentation, or sensitivity analysis to address gaps.
   - Regulatory Compliance: Aligning with standards such as FDA's Good Machine Learning Practice (GMLP) and EU MDR for comprehensive data reporting.

3. Data Traceability
   - Audit Trails: Maintaining detailed records of data sources, transformations, and usage throughout the AI lifecycle.
   - Data Lineage Tools: Utilizing software solutions like Apache Atlas or Talend for tracking data origin and movement.
   - Regulatory Documentation: Preparing clear documentation (e.g., Data Management Plans (DMP)) for regulatory submissions.

Addressing concerns of data bias, fairness, and explainability in AI decision-making

1. Data Bias and Fairness
   - Bias Detection & Mitigation:
     Perform bias audits (e.g., demographic parity, equalized odds) to identify disparities in model outcomes.
     Use re-sampling, re-weighting, or fair representation learning techniques to minimize bias.

- Inclusive Data Collection:
  Ensure representation of diverse age groups, genders, ethnicities, and socio-economic backgrounds.
  Collaborate with stakeholders to define fairness criteria relevant to clinical contexts.
- Regulatory Guidelines on Bias:
  Follow FDA's guidance on addressing demographic factors in AI models.
  Adhere to EU's AI Act provisions on fairness and non-discrimination.

2. Explainability in AI Decision-Making

- Model Interpretability Tools:
  Use techniques like SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-agnostic Explanations) to elucidate AI decisions.
  Implement decision trees or rule-based models for scenarios requiring high transparency.

- Transparent Reporting:
  Provide model cards detailing intended use, limitations, and performance metrics.
  Develop explainability reports for clinical stakeholders and regulatory bodies.

- Patient & Clinician Communication:
  Simplify AI outputs into user-friendly formats for clinical decision support.
  Include human-in-the-loop mechanisms, allowing clinician oversight of AI recommendations.

1.3 Cybersecurity & Data Privacy Concerns

Cybersecurity Threat	Description	Potential Impact
Data Breaches	Unauthorized access to sensitive patient data.	Compromised patient confidentiality, legal liabilities.
Adversarial Attacks	AI models manipulated with deceptive inputs.	Misdiagnoses, incorrect treatment recommendations.
Ransomware Attacks	Malicious software encrypts patient records.	Loss of critical healthcare data, system downtime.
Data Poisoning	Training data tampered with to corrupt AI predictions.	Model biases, unreliable medical outcomes.
Model Inversion Attacks	Hackers reconstruct patient data from AI model outputs.	Exposure of personal health records (PHRs).
Regulatory Non-Compliance	Failure to meet data security regulations.	Heavy fines, legal action, product recalls.

2. Strategies for AI/ML-Enabled SaMD Data Submission

2.1 Regulatory Framework Alignment

Overview of FDA's Predetermined Change Control Plan (PCCP) for AI-based SaMD
The Predetermined Change Control Plan (PCCP) is an FDA regulatory mechanism that allows manufacturers of AI-based Software as a Medical Device (SaMD) to proactively define planned modifications to their AI models without requiring additional regulatory submissions for each change.

Key Components of PCCP

Component	Description
Scope of Modifications	Defines the types of AI model changes expected over time (e.g., performance improvements, retraining with new data).
Rationale for Changes	Justifies why planned modifications are necessary and how they align with clinical safety and effectiveness.

Data and Re-training Approach	Details the data sources, quality controls, and re-training methodology to maintain model performance.
Performance Evaluation Plan	Specifies validation strategies (e.g., real-world evidence, statistical tests) to ensure AI model updates remain safe and effective.
Risk Management Strategy	Identifies potential risks associated with model changes and defines mitigation plans.
Change Management Process	Establishes governance for implementing updates while ensuring compliance with regulatory standards.

Benefits of PCCP for AI-Based SaMD

Regulatory Flexibility: Allows AI models to evolve without frequent resubmissions.
Faster Innovation: Enables manufacturers to implement AI model improvements efficiently.
Improved Patient Safety: Ensures continuous validation and risk management for AI-based SaMD updates.

Good Machine Learning Practices (GMLP) for compliance

GMLP is a set of best practices that guide the development, validation, and deployment of AI/ML in medical devices, ensuring reliability, transparency, and generalizability.

GMLP Principle	Description
Data Quality and Curation	Use high-quality, unbiased datasets that are representative of the intended patient population.
Robust Model Training & Validation	Ensure AI models undergo rigorous validation with independent test datasets.
Algorithm Explainability & Transparency	Provide clear documentation on AI decision-making to support regulatory review.
Performance Monitoring & Adaptability	Implement continuous monitoring of AI model performance and drift detection mechanisms.
Human Oversight & Risk Mitigation	Design AI models to support clinical decision-making rather than operate autonomously.

2.2 Risk Assessment Framework for AI/ML-Based SaMD

A structured Failure Mode and Effects Analysis (FMEA) or ISO 14971-based Risk Assessment helps in systematically identifying risks in AI/ML models.

Risk Type	Potential Issues	Mitigation Strategies
Data-Related Risks	Bias, missing data, low-quality inputs	Use diverse, high-quality, representative datasets
Algorithmic Risks	Overfitting, lack of generalization	Validate with independent datasets, real-world data
Model Transparency	Black-box AI decision-making	Implement explainable AI (XAI) methods
Human-AI Interaction Risks	Over-reliance, automation bias	Design for human oversight and intervention
Security & Privacy Risks	Data breaches, adversarial attacks	Use encryption, adversarial robustness techniques
Regulatory Risks	Non-compliance with global standards	Align with ISO 13485, FDA, EU MDR, IMDRF

Regulatory Guidelines for a Risk-Based AI/ML Approach

Regulatory Body	Guidance
US FDA	AI/ML-Based SaMD Risk Management (PCCP, Total Product Lifecycle)

IMDRF	SaMD Risk Categorization Framework
ISO 14971	Medical Device Risk Management
EU MDR	AI Risk Classification under Medical Device Regulation
Health Canada, MHRA	AI Transparency and Explainability

2.3 Best Practices for AI Model Explainability & Transparency

Model interpretability techniques (e.g., SHAP, LIME) for regulatory approval

To gain regulatory approval, AI/ML-based Software as a Medical Device (SaMD) must provide transparent and interpretable decision-making that clinicians, regulators, and patients can understand. Model interpretability techniques such as SHAP, LIME, Integrated Gradients, and Rule-Based Approaches help explain how AI models reach their conclusions.

Techniques	Description	Use Case in SaMD	Regulatory Relevance
SHAP (Shapley Additive Explanations)	Quantifies the contribution of each feature to a model's prediction. Uses cooperative game theory principles.	Identifying key biomarkers influencing AI-driven disease risk scores.	Aligns with FDA Good Machine Learning Practices (GMLP) for AI transparency.
LIME (Local Interpretable Model-agnostic Explanations)	Generates local surrogate models to approximate black-box model behaviour.	Explaining AI-assisted radiology or tumor detection predictions.	Supports SaMD Risk Categorization Framework (IMDRF) by providing case-specific justifications.
Integrated Gradients	Measures feature importance in deep learning models by computing gradients.	Deep learning models for medical imaging and ECG/EEG analysis.	Aligns with EU AI Act and FDA SaMD Regulatory Framework.
Decision Trees & Rule-Based Models	Uses hierarchical tree structures to make human-readable predictions.	Clinical decision support systems (CDSS) for AI-driven diagnostics.	Preferred for low-risk AI/ML models in medical decision-making.

Regulatory Checklist & Documentation Template for AI Explainability in SaMD Submissions
Below is a checklist and a documentation template that can be used when preparing regulatory submissions for AI/ML-based Software as a Medical Device (SaMD), ensuring compliance with FDA, EU MDR, and Health Canada requirements.

Regulatory Checklist for AI Explainability in SaMD

This checklist helps ensure that AI-based SaMD meets transparency, safety, and compliance standards.

General Explainability Requirements

✓ Clearly define how the AI model makes predictions.
✓ Identify which interpretability technique is used (e.g., SHAP, LIME, Integrated Gradients).
✓ Explain why this technique is suitable for your AI model.
✓ Provide visual evidence (e.g., heatmaps, feature importance charts).

Feature Importance & Transparency

✓ Justify why each input feature is relevant to model predictions.
✓ Show SHAP/LIME feature importance scores for key inputs.
✓ Compare AI model decisions with human expert assessments.

Bias & Risk Management

✓ Demonstrate how bias was identified and mitigated in model training.
✓ Provide counterfactual explanations for false positives/negatives.
✓ Include risk management steps related to AI decision-making.

Regulatory Documentation & Compliance

✓ Align explainability approach with FDA Good Machine Learning Practices (GMLP).
✓ Ensure compliance with IMDRF's SaMD Risk Categorization Framework.
✓ Follow EU AI Act requirements for high-risk AI systems in healthcare.
✓ Document explainability methods in Pre-Market Approval (PMA) or 510(k) submissions.

2.4 Real-World Data (RWD) & Post-Market Surveillance

Integration of real-world evidence (RWE) in AI/ML regulatory submission

Real-World Evidence (RWE) refers to clinical evidence derived from the analysis of Real-World Data (RWD), such as data from electronic health records (EHRs), insurance claims, patient registries, and wearable devices. RWE plays a crucial role in AI/ML regulatory submissions, especially for Software as a Medical Device (SaMD) that involves machine learning or AI models. Regulatory agencies like the FDA, EMA, and others are increasingly accepting RWE as part of the approval process for AI/ML-based medical devices.

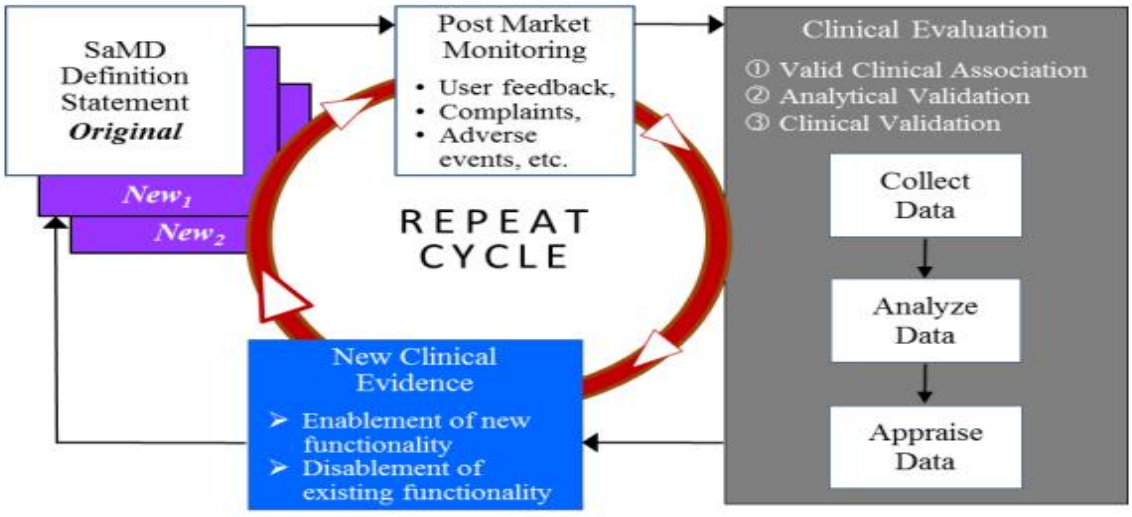


Figure 14 - Pathway for Continuous Learning - Use of Real World SaMD Performance Data in Ongoing SaMD Clinical Evaluation

Why is RWE Important for AI/ML Regulatory Submissions?

Demonstrates Effectiveness in Broader Populations: Traditional clinical trials may not fully capture the variability found in real-world patient populations. RWE allows AI/ML models to be validated in more diverse settings, which is crucial for AI-based SaMD.

Model Validation and Generalization: AI/ML models often perform well in controlled trials but may face challenges when deployed in diverse, real-world settings. RWE provides data to confirm the generalization of AI models across different populations and conditions.

Ongoing Post-Market Monitoring: RWE is also critical for post-market surveillance. After a product has been approved, RWE helps in the continuous evaluation of the model's safety and performance in clinical practice.

3. Challenges and Considerations for Using RWE in AI/ML Submissions

1. Data Privacy and Security

Regulatory bodies require that the use of RWE in AI submissions complies with data privacy regulations (e.g., GDPR, HIPAA). Manufacturers must ensure that patient data is anonymized and protected.

2. Validation of RWD Sources

Regulatory authorities often require evidence that the RWD sources (e.g., EHRs, registries) used for the submission is validated and reliable. Manufacturers should demonstrate that these sources accurately represent the clinical environment in which the AI device will be used.

3. Understanding of RWE Limitations

RWE is not as controlled as clinical trial data, so its use must be carefully considered, with an understanding of potential biases or confounders in the data. The submission must address how these limitations are mitigated.

Conclusion

The regulatory landscape for AI/ML-enabled Software as a Medical Device (SaMD) presents significant challenges due to the complexity and continuous learning nature of AI/ML models. Traditional regulatory pathways were primarily designed for more static medical devices, which makes adapting them to AI-powered SaMDs a challenging task. However, regulatory agencies such as the FDA, EMA, and ISO are increasingly recognizing the unique nature of these devices and are evolving their frameworks to accommodate AI/ML technologies.

The regulatory approval and oversight of AI/ML-enabled SaMDs remain complex and will continue to evolve. The strategies outlined for navigating regulatory challenges, including the integration of RWE, model explainability, and continuous monitoring, will ensure that AI technologies meet rigorous safety and performance standards. As the landscape matures, future trends in adaptive AI, personalized medicine, and dynamic regulatory frameworks will lead to more flexible and innovative approaches to AI/ML in healthcare, ultimately benefiting both patients and the broader healthcare ecosystem.

The continued focus on transparency, collaboration, and real-world validation will guide the responsible and effective use of AI in healthcare, ensuring that its potential to improve patient outcomes is fully realized.

Acknowledgments

Authors would like to extend their sincere thanks to Ephicacy Lifescience Analytics for giving them an opportunity to write and present this paper. Any brand and product names are trademarks of their respective companies.

Recommended Reading

Software as a Medical Device (SaMD): Key Definitions

https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf

https://kvalito.ch/what-is-and-what-is-not-a-software-as-medical-device-samd/

https://medium.com/retina-ai-health-inc/iec-62304-medical-device-software-lifecycle-processes-2b7967577c3f

https://galendata.com/a-quick-guide-to-categories-of-samd/

https://appinventiv.com/blog/software-as-a-medical-devices-samd/

Threat Assessment and Risk Analysis (TARA) for Interoperable Medical Devices in the Operating Room Inspired by the Automotive Industry

Latest FDA News on Draft AI/ML Action Plan

Draft Guidance: Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations

Draft Guidance on AI/ML by FDA

AI/ML Discussion Paper released by FDA

https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd

https://medicaldevicehq.com/articles/the-illustrated-guide-to-medical-device-software-development-and-iec-62304/

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence

https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles?utm_source=chatgpt.com

FDA AI/ML in SaMD: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

U.S. Food and Drug Administration (FDA). (2020). Real-World Evidence: Data and Evidence for Regulatory Decision Making

Contact Information

Your comments and questions are valued and encouraged. Contact the authors at:

Shashikant Kumar, Director - Statistical Programming
Ephicacy Lifescience Analytics
Bengaluru, India
E-mail: shashikant.kumar@ephicacy.com
www.ephicacy.com

Mrityunjay Kumar, Associate Director II - Statistical Programming
Ephicacy Lifescience Analytics
Bengaluru, India
E-mail: mrityunjay.kumar@ephicacy.com
www.ephicacy.com