Industry 4.0 & Medical Devices

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1. Introduction

As we progress through the 4th Industrial Revolution, technology is advancing quicker and quicker. More and more medical devices are being developed using AI/ML, Cloud Computing, and Internet of Things (IOT). This technology in the life sciences domain is uncharted, leaving a regulatory gap that the FDA is diligently working to close. The purpose of this white paper is to discuss the quality and regulatory approach for medical devices and software tools that contain AI/ML-based software. Along with the regulatory approach, our secondary motive is to explore a case study for developing a Next Generation (NGen) eQMS. The case study focuses on how an eQMS could be integrated with modern technologies to deliver a full-fledged software product. We also discuss the standard software validation principles that describe what activities manufacturers should implement to ensure their software is compliant with the required regulations, regardless of if it is a medical device or a tool used to develop a device like an eQMS.

2. The Regulatory Approach for Generic and AI/ML-based Medical Devices.

In the medical device industry, software verification and validation are important, especially if patient outcomes and care depend on the software data outputs. In this section, we discuss the basic elements required for software validations and what regulatory guidelines are present for AI-based medical devices.

2.1. Testing Software in an FDA Regulated Space

Software verification is the process of verifying if the objectives or targets collectively fulfill the intended use at a unit level, which may be an individual file output or a module-based integrated output. Software validation is the checkpoint to verify that the entire software package implements every software requirement and achieves the dedicated intended use for what it was designed for. The initial step for validation includes documenting the Software Requirement Specifications, Software Architecture, Detailed Design, and the Interfaces.\(^1\)

Software Requirements are the building blocks of the software system and they specify the software design at an atomic level. They collectively contribute towards the overall intended use of the medical device. If all requirements are integrated and visualized, the resultant product is the Software Architecture which represents a blueprint of the entire software system. Breaking down the architecture to a modular design pattern yields the Software Detailed Design where each module is constituted by its respective software requirements. Another key component of the architecture is the Software Interfaces. These interfaces specify the mechanisms through which modules or files communicate with each other and with external systems. In the case of an eQMS, the interface would be a TCP/IP protocol or the IoT MQTT through which the software components would communicate and exchange messages. The major purpose of documenting these entities is to always track that from the unit level to a system level, the design of the system always accounts for the intended use of the medical device.

Additionally, the key activities in the validation process are the Risk Assessment documentation, Integration Testing, System Testing, and the Requirements Traceability Matrix. All the identified software and hardware hazards should be logged in the Risk Assessment documents such as the Software Hazard Analysis report. Examples of software or hardware risk
include unexpected hardware failure, potential data leaks or data breach access points, or power failure. Manufacturers should identify all such risks and list them in the risk assessment documents. Also, they should provide objective evidence reflecting all risks from the system are mitigated and resolved ensuring the system is safe and effective. Validation implies testing of the overall system functionality and this step is performed using Integration Testing. In this case, the overall system functionality is verified against the system requirements and the defined intended use.

One of the most powerful tools to verify if each requirement is precisely implemented is the Software Requirements Traceability Matrix. This document maps between every software requirement, program files that fulfill these requirements, the associated risks or hazards, and the test cases that verify these requirements. Also, this document signifies the completeness of the drafted software design. With upcoming changes, quality engineers can refer to this document and prepare a plan to reflect which specific requirements will undergo changes, which corresponding test cases will get affected, and what test cases should be retested to maintain system performance, quality, and safety.

Verification involves implementing in-depth code inspections and unit-level code testing. Unit testing is the process where every file of the application is checked against its standard programming conventions. Also, unit testing identifies bugs, redundant loops, or any elements which might add drag on the system performance. These steps are of utmost importance as they unravel the hidden risks or unidentified hazards in the application. While the software is in the development stages, manufacturers or software engineers should encourage incorporating Good Programming Practices. Especially for web applications, from a quality perspective, examples include starting the code with a file header block which comprises of author details and when the program file was created, adding the appropriate number of self-explainable comments, adding a detailed file revision history, and encouraging maximum reusability of code to avoid redundancy of similar functional components. Such good programming practices promote better code readability and are efficient for future codebase maintenance.2

2.2 The Basic Workflow and Significance of an AI/ML, Cloud, IoT-based Software System

Before we move on to the discussion on regulatory approaches for AI/ML-based medical devices, we need to understand the workflow of a typical AI algorithm. Nowadays, if a standard application is built to deliver AI-based results, it would also use a ‘Tech-stack’. Tech-stack implies that the software itself is not only powered by a single technological platform but instead it would use a set of technologies to deliver the expected results with high performance. In the case of an AI/ML-based tool, a Cloud Computing service would be an essential platform as it would fulfill the necessity of data storage and AI module training. In cases of hardware integration, software engineers would employ “Internet of Things (IoT)” along with current security protocols and integrate it with the AI/ML layer. This section introduces such technologies and provides their dedicated functionalities as seen in a standard digital application.

Applications are primarily hosted as Web, Mobile, and Desktop (Local) applications. All these application types must be highly scalable and fault tolerant.3 ‘Scalability’ implies that even though the number of users in a system may rise from 100 to 100,000, the application should function without any glitches. Fault tolerance means when a service goes down for some unexpected reason, the entire system should not be affected by it.
These features can be achieved with the help of the Cloud. With Cloud Computing, data is automatically backed up, making the system resilient and fault tolerant. Multiple virtual servers offer almost infinite storage plus high computing performance. Enabling these components adds up to scalability. This is profoundly important for a SaMD or eQMS. In an eQMS, even if basic user data rises exponentially, it can be handled through multiple local or basic servers, but if eQMS modules are hosting thousands of documents every day, Cloud Computing’s availability, scalability, and performance play a key role in efficient data and file handling.

Truly, Cloud helps in improving performance, but IoT and AI assist in integrating a SaMD or eQMS with exceptional features. IoT can be shortly defined as an ability of an application to connect with hardware devices using internet connectivity. Examples of IoT in the healthcare industry are glucose monitoring devices, remote robotic surgery, and smartwatches. These devices are interconnected with each other through lightweight internet protocols and use Cloud for storing data. If an eQMS is IoT enabled, it can facilitate continuous monitoring of certain elements. Also, a single update can notify all connected devices as well as all users associated with devices, enabling instant messaging.

AI is defined as the process of providing the ability for computing systems to solve human problems. In the current 4th Industrial Revolution, AI is getting employed in almost every domain. The significant ability given by an AI algorithm is the elimination of a massive number of computation steps. Its major subsets are Machine and Deep Learning (ML/DL) algorithms, which are utilized not only as decision-making tools but also for forecasting or prediction.

The magic which drives these AI algorithms is the mathematics behind them. Initially, an AI/ML model is selected based on a problem statement and mathematically trained using a huge amount of task-related data. This dataset may be present in the local file system or retrieved from Cloud data servers. Additionally, this data generally consists of inputs as well as the computed outputs. After training, it is tested with new input data. The newly computed AI-algorithmic outputs are compared against existing outputs (which were used in training). If the difference between the existing outputs and AI-computed outputs is found to be minimal, the AI-tool is selected for optimizing computations, decision-making, and even prediction.
2.3. FDA’s Proposed Regulatory Framework and The Medical Device Action Plan for AI/ML-based Software as a Medical Device

One of the major issues with Artificial Intelligence algorithms is that even in a finalized product design, the system may completely change the AI model to get more accurate and precise results. From a regulatory point of view, this becomes a challenge as for commencing the software validation, since all software requirements should be compiled and finalized. AI-based medical devices are required to comply with all regulatory requirements but documenting these frequent changes can be difficult as AI models, or the data used for training and testing, is not always constant or fixed.

To capture such frequent AI/ML changes, the FDA released a discussion paper that reflects the proposed regulatory approach for AI/ML-based medical devices. The discussion paper introduced key components such as the Risk Categorization Matrix and the Pre-determined Change Control Plan.

In collaboration with IMDRF (International Medical Device Regulators Forum), the FDA’s discussion paper initially stated a 2-dimensional Risk Categorization matrix to determine the class of device based on the associated risk. The class is selected based on two major parameters, the State of Healthcare Condition, and the SaMD’s Significance of Information. The State of Healthcare Condition identifies if the SaMD is serving its intended use in either a non-serious, serious, or a critical patient healthcare environment and the Significance of Information offers the actual intended use of the SaMD. There are three categories in the SaMD’s Significance of Information which are treating patients or use in the diagnosis, driving clinical management, and informing clinical management. The highest risk-based class, class ‘IV’, is selected when the Significance of Information is to treat a patient and the State of Healthcare Condition is critical. Alternatively, the lowest risk-based class ‘I’ is selected when the intended use of SaMD is to only inform the clinical management and the State of Healthcare Condition is non-serious.

One of the most significant elements from the discussion paper is the Predetermined Change Control Plan which is classified into Software Pre-specifications (SPS) and the ACP or Algorithmic Change Protocol. SPS specifies all the potential software requirement changes that may be issued during the development process or even after the AI/ML SaMD is hosted. In some cases, manufacturers or software engineers might list out what components in the system might change as the software keeps evolving based on continuous learning. Such a list of requirements constitutes SPS. Simply, SPS specify “what” software modules might change even after the application is hosted as the ML tool continues to learn and deliver consistent results.

ACP’s define the specific methodologies that manufacturers would implement to maintain system consistency from quality, efficacy, and safety perspectives while performing algorithmic changes in the system. In ACPs, manufacturers specify what documentation changes or risk-assessment activities might be implemented if a potential change such as updating specific classes, or a part of the algorithm comes up. Simply, ACP’s specify “how” the SaMD will be consistently safe and effective irrespective of the module or program file updates. For example, if there is a need to re-evaluate the AI model performance, the ACP might include updating or reverifying certain elements from the Risk Assessment matrix.
Indeed, manufacturers will have to initially submit their packet to the FDA to get the AI-based medical device reviewed. The proposed framework states that this submission should include the SPS and ACP, specifying what components might change and what components of the system including documentation might be updated to ensure system safety, quality, and efficiency. While updating the system, if the changes are present within the scope of the submitted SPS and ACP along with the intended use, manufacturers do not need to provide additional submissions to the FDA. If these changes exceed the defined scope of SPS and ACP, and if the updates to the system are not within the limits of previously defined intended use, manufacturers or AI developers should perform a new submission to the FDA.

Following the discussion paper, FDA released an update in January 2021 which is referred to as the Medical Device Action Plan for AI-based software. Initially, the FDA intends to issue a detailed guidance document that would provide a sophisticated approach for regulating the AI-based medical devices. Considering the component mentioned in the discussion paper, the Predetermined Change Control Plan (SPS and ACP), the FDA intends to provide “what” components manufacturers should specify that will experience changes along with the methodologies they would implement to maintain the system safety. A major update is that the guidance document that will provide the step-by-step process of product submission and review.9

The action plan also encourages manufacturers to increase the harmonization of Good Machine Learning Practices (GMPL) such as data management, extraction, and detailed documentation. The GMPL activities also apply to all SaMDs as such quality programming practices facilitate better code readability and future maintenance. Harmonization across various platforms also includes involving the AI developer and testing communities for discussing consensus standards, which include efficient risk management processes along with improved AI training/testing methods.

Additionally, the FDA plans to conduct a public workshop for discussing how AI-based medical device labeling will promote transparency, ensuring that the AI models are safe and efficient, even if the modules experience minor to major changes. Transparency implies trustworthiness. According to the action plan, transparency could be promoted with factors such as validating data and the originating sources used for module training, logging the module inputs, outputs with the main functionality or business logic, and tracking the overall performance.

In the end, the action plan points out the elimination of bias that is observed during AI model training and collecting data from manufacturers for real-world AI performance monitoring. Most likely, in the healthcare sector, the AI/ML models would be trained using healthcare or patient-related data. If this input training data is itself biased based on factors such as race or ethnicity, this bias will be reflected in the recommended or predicted output of the software. Hence, the action plan focuses on such bias elimination by utilizing regulatory science to develop and improve AI/ML-based algorithms. Moreover, tracking the real-world performance for AI/ML-based medical devices would supply information to manufacturers on how existing live AI models are functioning in real-time, what specific components are improved based on learning, and what needs more improvement. Additionally, real-world performance monitoring provides risks other manufacturers have identified and the methodologies they have implemented to mitigate the identified hazards.9
3. Developing a Next-Generation (NGen) eQMS

AI/ML-based SaMD’s are not the only product that falls under the scope of regulatory requirements. If a company in the life sciences industry deploys an eQMS, and especially an eQMS with any sort of AI/ML algorithm, that platform must be compliant as well. The following section describes how AI/ML could be integrated to develop an NGen eQMS.

3.3. Core Artificial Intelligence Algorithms and Predictions

From “timeline” computation to pathway detection, AI algorithms could be employed to optimize and simplify the complexity of tasks, ultimately saving several resources. An example of AI NGen is the prediction of timelines. Consider a case where a complaint is received from a client, and the complaint triggers a CAPA. While drafting a CAPA, many parameters are recorded such as the start of CAPA, the problem severity, the Five Whys, and the number of people working on CAPA. At such times, product owners or clients may demand a rough estimate of when the complaint would be resolved. It can be tricky to compute a timeline as this type of problem includes inconsistent data. In such cases, where the data is not normally distributed, and the team is looking for an answer, Machine Learning algorithms such as Support Vector Machines (SVMs) or Logistic Regression could be utilized. Irrespective of ML model selection, the AI model will be trained using the CAPA data. The trained module will be then tested with new CAPA inputs. The outcome of this core AI tool would be the prediction of an approximate timeline of CAPA closure. Several AI measures could be utilized to check the validity of predicted results. If the model performs with more than 80% accuracy, it is good enough to be installed as a “CAPA timeline predictor”.

4. Conclusion

This paper discussed software validation and verification activities along with the upcoming regulatory approach for AI/ML-based medical devices. As technology advances, AI/ML is becoming increasingly popular in the life-sciences space. Whether the technology is directly integrated with your medical device or is being used to facilitate your Quality Systems activities through an eQMS, all regulatory requirements must be followed. It is to be expected that the FDA will continue to develop and refine the regulatory approach as we advance through the 4th Industrial Revolution. The agency has made it clear that it intends to work with the industry to ensure that the regulatory approach is in alignment with AI/ML technology development.

EMMA International specializes in quality, regulatory, and compliance services which also include providing regulatory guidance for SaMDs/ SiMDs (Software As/In a Medical Device). If you have a medical device or an application that is a web, desktop, or mobile application and is coupled with modern technologies such as Cloud Computing, AI/ML, and Internet of Things, our regulatory and software experts can help ensure you are FDA compliant. Call us today at 248-987-4497 or email us at info@emmainternational.com for more information.
Bibliography


