MDS – G010

Guidance on Artificial Intelligence (AI) and Machine Learning (ML) technologies based Medical Devices

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Introduction

Purpose

The purpose of this guidance is to clarify the requirements for obtaining Medical Devices Marketing Authorization (MDMA) for Artificial Intelligence (AI) and Machine Learning (ML) based medical devices, in order to place them on the market within KSA.

Scope

This guidance applies to Artificial Intelligence (AI) and Machine Learning (ML) technologies that diagnose, manage or predict diseases by analyzing medical data.

Background

SFDA has issued this guidance document in reference to the following:

- Article 8 stipulating that "medical devices cannot be marketed/used unless obtaining a registration and marketing Authorization, and The SFDA may exempt some medical devices from the requirement to obtain a marketing Authorization, after ensuring their safety, and not using them for commercial purposes".
- Requirements specified in "Requirements for Medical Device Marketing Authorization (MDS– REQ 1)".
- Guidance to Pre-Market Cybersecurity of Medical Devices MDS-G38
- Guidance to Post-Market Cybersecurity of Medical Devices MDS-G37

Medical Device Item Classification and Criteria

Medical Device Classification Criteria

A. Overview

Development of Artificial Intelligence (AI) and Machine Learning (ML) medical devices is continuously evolving and rapidly improving at a rapid pace. Diverse and more complex functions are coming in line with the purpose of improving patients care. This section aims to present the Medical device classification criteria and control methods for these emerging medical devices.

The intended use of Artificial Intelligence (AI) and Machine Learning (ML) technologies will determine whether they will be regulated as a medical device. The intended use is based on the product specifications and instructions of use along with any information provided by the product developer.

If the Artificial Intelligence (AI) and Machine Learning (ML) devices are intended by the Product developer to be used for investigation, detection diagnosis, monitoring, treatment, or management of any medical condition, disease, anatomy or physiological process, it will be classified as a medical device subject to SFDA's regulatory controls.

Examples of Artificial Intelligence (AI) and Machine Learning (ML) technologies that are classified as medical device:

- In-vitro diagnostic tools. Artificial Intelligence (AI) and Machine Learning (ML) technology that has the ability to recognize different types of cells, quantify, and analyze the results.
- AI-based biosensors that predict tendencies and probability of disease, the device may provide information of dangerous vital signals and give recommendations for health improvement.

B. Regulatory approach to Artificial Intelligence (AI) and Machine Learning (ML) medical devices

Premarket Review Considerations

The manufacturer (developer) of Artificial Intelligence (AI) and Machine Learning (ML) based medical devices or in vitro diagnostics is expected to meet the technical documentation required for Medical Devices Marketing Authorization that is specified within MDS-REQ 1, Annex (3) Medical Device Technical Documentation, or Annex (4) IVD Technical Documentation, which list them as follow:

1) Device Description and Specification, Including Variants and Accessories.

2) Information to be provided by the Manufacturer.

3) Design and Manufacturing Information.

4) Essential Principles of Safety and Performance.

5) Benefit-Risk Analysis and Risk Management.

6) Product Verification and Validation.

7) Post Market Surveillance Plan.

8) Periodic Safety Update Report and Post Market Surveillance Report

Special consideration:

When a manufacturer is conducting verification and validation testing, the nature and extent of the validation depends upon the risks associated with the device, the intended purpose, the anticipated use of the device in the digital health system, and the intended use of the device, Documentation which demonstrates the following performance testing should be included in the submission:

- Verification that the device meets its design specifications;
- Validation that the device performs as intended;

- Usability study that verify that the information provided to the user to connect to the device and to allow the user to ensure that the connection has been made correctly; and
- Validation that the device will perform safely and within specification when used under normal conditions and abnormal conditions that are reasonably likely to occur (e.g. receives data outside of specification, connected to an unintended device or system).

Intended use

Medical devices are classified based on their intended use and degree of potential risk to human body upon use in accordance with the Medical Devices Marketing Authorization requirements that are specified within MDS-REQ 1, Annex (5) Risk Classification Rules for Medical Devices".

In accordance with Article (1) of the Medical Devices Law, a medical device means Any instrument, apparatus, implant, in vitro reagent or calibrator, software, or material used for operating medical devices, or any other similar or related articles, intended to be used alone or in combination with other devices for diagnosis, prevention, monitoring, controlling, treatment, or alleviation of disease or injury, or for compensation for an injury; investigation, replacement, modification, or support of the anatomy or of a physiological process; supporting or sustaining life; controlling or assisting conception; sterilization of medical devices and supplies; providing information for medical or personal purposes by means of *in vitro* examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

Clinical Evaluation

There is no internationally aligned framework for the clinical evaluation of AI/ML-based medical devices. A manufacturer of AI/ML-based medical devices is expected to provide clinical evidence of the device's safety, effectiveness and performance before it can be placed on the market.

According to IMDRF description of the process of clinical evaluation explained in the SaMD: Clinical Evaluation guidance, the manufacturer needs to generate evidence to demonstrate a ***valid clinical association***, ***analytical/technical validation***, and ***clinical validation*** of AI/ML-based medical device. This clinical evaluation pathway emphasis that this process should be an iterative and continuous as part of the quality management system for AI/ML-based medical devices. The requirements for clinical evaluation apply to all risk categories of AI/ML-based medical devices.

To demonstrate ***a valid clinical association*** between the output of AI/ML-based medical device and the targeted clinical condition, the manufacturer need to provide evidence that the device output is clinically accepted based on existing evidence in published scientific literature, original clinical research, and/or clinical guidelines. The manufacturer should demonstrate the relevance of available data to the clinical problem and current clinical practice, and that it aligns with the AI/ML-based medical device's intended use. If the manufacturer cannot confirm the scientific validity of the device based on an established body of evidence, new evidence needs to be generated, for example, through conducting secondary data analysis or a clinical trial. Since the evidence underlying the clinical association validity of AI/ML-based medical devices are immature, and due to the low confidence in this evidence as applied to AI/ML-based medical devices, AI/ML-based medical devices often will be classified as having novel clinical association as these devices may involve new inputs or outputs, novel algorithms, new intended target population, or new intended use.

Next, the manufacturer of AI/ML-based medical devices should demonstrate the expected ***analytical/technical validation***. The analytical validation evaluates the correctness of input data processing by the AI/ML-based medical devices to create reliable output data. The manufacturer should provide objective evidence that the device specified requirements have been fulfilled, and demonstrate that the device meets its specifications for a specific intended use. This evidence is generally generated during the verification and validation activities as part of the quality management system; usually using labeled reference datasets.

Lastly, AI/ML-based medical devices' manufacturers are expected to demonstrate ***clinical validation***. Clinical validation is a necessary component of clinical evaluation for all AI/ML-based medical devices and it measures the ability of AI/ML-based medical device to yield a clinically meaningful outcome associated to the intended use of the device output in the target population in the context of clinical care. Clinical validation may only be conducted upon successful completion of analytical/technical validation. Clinical validity is evaluated during the development of the AI/ML-based medical device before it is placed on the market (pre-market) and after placement on the market (post-market). The manufacturer can demonstrate the clinical validity by referencing existing data from studies conducted for the same intended use, or if available data references studies conducted for a different intended use, extrapolation of such data can be justified, otherwise, the manufacturer will be required to generate new clinical data for the intended use.

The clinical validation should list the data sources that have been evaluated and that both support and contradict the manufacturer claim that the benefits have been achieved. The types of data necessary to assure safety and effectiveness during the clinical validation, including study design, will depend on the function of the AI/ML-based medical device, the intended use, and the risk it poses to users. Example of metrics of clinical validation in the intended use environment with the intended user include, but not limited to: specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio negative (LR-), likelihood ratio positive (LR+), and clinical usability. The likelihood ratio of a positive result should be as large as possible whereas the likelihood ratio of a negative result should be as small as possible. All metrics, except the likelihoods, are evaluated in the range of 0-1 or in percentage from 0 to 100%:

This is a device dependent example, not a rule.

Evaluation
<0.6 – unsuitable
0.61 - 0.8 – revision required
> 0.81 – admissible for clinical validation

Certain AI/ML-based medical devices may require ***independent review*** of the results of the clinical evaluation to ensure that the AI/ML-based medical device is clinically meaningful to users. In this case, the clinical evaluation of the AI/ML-based medical device should, where possible or as far as possible, be reviewed by someone who has not been significantly involved in the development of the AI/ML-based medical device, and who does not have anything to gain from the device, and who can objectively assess the device's intended purpose and the conformity with the overall clinical evaluation evidence. The level of evaluation and independent review should be proportionate with the risk posed by the AI/ML-based medical device.

If the clinical evaluation is based on a comparator device, the manufacturer must demonstrate sufficient clinical and technical equivalence of the other device, including explicit evaluation of the AI/ML algorithm/model. Manufacturers that cannot demonstrate equivalence must have sufficient evidence or conduct clinical trials to establish and verify clinical safety and effectiveness.

Since there are no international standards for the clinical evaluation of AI/ML-based medical devices, the minimum standards and good practice for clinically evaluating AI/ML-based medical devices as partially adapted from WHO:

- The manufacturer should assess whether the promised medical benefit is achieved is consistent with the state of the art.
- The manufacturer should list alternative methods, technologies and/or procedures and compares these alternatives with respect to clinical benefits, safety/risks, and performance.
- The manufacturer should assess whether the promised medical benefit is achieved with the quality parameters.
    - ✓ The outcomes assessed should be pre-defined by manufacturers and should be reported using standard performance metrics for the specific field to facilitate comparisons across studies.

- ✓ Manufacturers should provide assurance that metrics of effectiveness and safety include outcomes that are meaningful to patients and clinical outcome, i.e. measures of improvement in patient outcomes, clinical process or time efficiency, measures of acceptable unintended consequences, and absence of harm to patients.

- Manufacturers are advised to evaluate user and system elements, this may include assessments of:
  - ✓ Acceptability and changes in user's experience.
  - ✓ Human-computer interactions, including how the output is interpreted and actioned.
  - ✓ Human factors surrounding its use, i.e. account for user variability (such as the learning curve, understanding, trust, and behaviors) and the added biases occurring as a result.
  - ✓ Variance in practice settings.
  - ✓ Wider impact on care pathways.
- Analytical validation should be done using large independent reference dataset reflecting the intended purpose and the diversity of the intended population and setting. The reference dataset should meet the following requirements unless there is sufficient evidence to show that a requirement does not need to be met:
  1. The normal-to-abnormal ratio should reflect the prevalence of the target condition in the population;
  2. Several medical centers should source the reference dataset to introduce the data heterogeneity;
  3. Demographic, socio-economic characteristics and basic health indicators in the reference dataset should correspond to the population's average characteristics in the target region;

4. The proposed size of the reference dataset should be justified per statistical considerations, and the desired diagnostic accuracy by the standard metrics indicated above;

5. Reference datasets used in clinical tests for registering the device as a medical device should not be publicly available (to exclude the possibility of training AI algorithms on reference datasets).

- The manufacturer should generate evidence on device performance that can be generalized to the entire intended population, demonstrating that performance will not deteriorate across populations and sites:
  - ✓ Conduct multisite clinical investigation that account for variations on different sites and allow identification of unintended bias and reliability.
  - ✓ Analyze the performance of the model for appropriate subgroups, i.e. demographics, geographic location, disease subtype, etc. The statistical distribution of data must correspond to the real environment.
  - ✓ Demonstrate adequacy of the sample size and power calculation.
  - ✓ Consider the effects of confounding factors.
- The manufacturer of AI/ML-based medical devices should test performance by comparing it to gold standard, i.e. the reference standard that is being used to evaluate the model has to be evidence-based, demonstrating that the results are repeatable and reproducible in different settings.
- The effects of AI/ML-based medical devices should be evaluated in clinically relevant conditions, i.e. this requires integration into the existing clinical workflow with a platform to collect, store, and process data, and to deliver the outputs to users in a timely manner. This will provide assurance that AI/ML-based medical devices are safe, effective and performant – not just under test conditions but in the real world.
- Because AI/ML-based medical devices aim to enhance users' performance, not to replace them, evaluation of model performance in efficacy/effectiveness studies requires comparisons of clinicians' performance with and without the AI/ML-based

medical device; not the performance of clinicians versus AI/ML-based medical device alone, in order to demonstrate the impact of the device on clinical practice.

- Manufacturers in their study design should consider proactively the effects that their studies may have on healthcare organizations and potentially explore the possibility of prospective real-world studies in order to minimize selection bias, have more control over variables and data collection, and examine multiple outcomes. The majority of published evidence to date has consisted of early phase retrospective validation studies which are in fact in silico (i.e. performed by computer, as opposed to in vivo) assessments of datasets used to test performance accuracy of AI/ML-based medical devices' algorithms.
- Report the result of the clinical investigation using AI-specific reporting guidelines and standards.
- The manufacturer should locally validate the AI/ML-based medical devices that developed and approved in other jurisdictions.
- AI/ML-based medical device is unique in its ability for continuous learning, hence, manufacturers are required to use post-market continuous monitoring of safety, effectiveness, and performance to gather and validate relevant performance parameters and metrics for the AI/ML-based medical device in real-world setting in order to understand and modify software based on real-world performance.

Risk Management

The implementation of new technologies such as Artificial intelligence (AI) and Machine Learning (ML) may present risks that could jeopardize patient health and safety, increase inequalities and inefficiencies, undermine trust in healthcare, and adversely impact the management of healthcare. Thus, in line with SFDA "Requirements for Medical Devices Marketing Authorization (MDS-REQ 1)" manufacturers are required to demonstrate that their medical devices do not pose unacceptable risks, and that the benefits of their intended use outweigh the overall residual risk.

Since Artificial intelligence (AI) and Machine Learning (ML) are software-driven, the unique or elevated risks are those around data management, feature extraction, algorithm training, model evaluation, and cyber and information security. Safety risk may be introduced by Machine learning systems by learning incorrectly, making wrong inferences, and then recommending or initiating actions that, instead of better outcomes, can lead to harm. Occasionally, machine learning systems detect correlations in data sets instead of causations, which can lead to incorrect conclusions.

The fundamental requirements for safety should include results of the evaluations regarding the limitations and the performance of the ML algorithm that may not produce 100% accuracy and the necessary training of human personnel for an adequate management of the algorithm errors. Thus, data scientists should be included in the cross-functional team that perform risk management tasks.

There should be a risk management plan that includes:

- The scope of risk management activities
- Assignment of responsibilities
- Requirements for review of the activities
- Risk acceptability criteria
- Method to evaluate overall residual risk
- Activities of the implementation and effectiveness of the risk control measures
- Activities to collect and review post-production information

- The criteria used to trigger an update, risk management of the update process itself, and provisions for returning the product to a previous version if necessary
- For ML-based medical devices that communicate with other devices or IT systems, the scope of the plan should include risks related interoperability.
- Cyber security risks

Risk analysis should include the following questions about ML medical device and explore the risks associated with each:

- Does the software provide diagnostic or treatment recommendations?
- If so, how significant is the information in influencing the user?
- What is the target population of the device (e.g., is the patient condition non-serious, serious, or critical?
- Which is the urgency/emergency of the information provided?
- Does the algorithm provide options and likelihood of appropriateness?
- Are errors detectable?
- What autonomous functions, if any, does the system provide? Is the algorithm configurable
- Does the ML-enabled medical device have the ability to learn over time?
- Is the device capable of adjusting its performance characteristics over time?
- What are potential off-label uses of the device? What are the potential foreseeable misuse?
- Are there contra-indications due to restricted patient's conditions in data used to train, test, and validate the ML?
- Is the system intended to learn over time, and if so, is there any potential impact to the intended use?

Additional risks that should be taken into consideration include: failure to act (the user does not have confidence in the ML), data (or use) drift (locked ML that performed well a decade ago might not perform as well today), abundance of data but a lack of knowledge and Fragmented data throughout different formats

- Where the probability of occurrence cannot be estimated (which can often be the case for ML applications), the risk should be estimated based on the severity of possible harm alone
- Risk controls for data collected by MD-based medical devices should include process activities through the data lifecycle such as ensuring the data is complete, correct, and consistent (affecting data integrity), as well as ensuring data is the best representative data at that time.
- Operational risk controls are features in the software itself that directly interact with the user (e.g., human oversight.).
- Design of the human user interface should be reviewed to ensure this does not introduce bias or unduly influence the user.
- For autonomous systems, there might be a need for a hand-off strategy where control is passed from the system to the user.
- Risk management review according to Clause 9 of ISO 14971:2019 and essential principles 3,4,5 and 8 should be performed before commercial release of the ML-based medical device

Quality Management Systems

The AI/ML device shall be designed and manufactured, and monitored in accordance with Medical Devices Quality Management System (ISO 13485) to document and implement all processes, reduce mistakes, and guarantee continues quality and safety of the device. The Quality Management System in place shall ensures compliance with this Regulation.

QMS and Regulatory requirements: The organization, which designs and deploys the AI/ML, is responsible for implementing the QMS, which include developing a quality policy, quality objectives, procedures, and project-specific plans that are customer focused. It is also required to provide the appropriate level of resources (including people, tools, environment, etc.), needed for ensuring the effectiveness of the AI/ML lifecycle processes and activities in meeting SFDA regulation and customer requirements.

Human resources: It is important to ensure that personnel who are assigned to AI/ML projects should be competent in performing their jobs. For AI/ML, such a team should have competencies in technology and software engineering including an understanding of the clinical aspects of the use of the software.

Infrastructure: Such as equipment, information, communication networks, tools, and the physical facility, etc., should be made available throughout AI/ML lifecycle processes. Such infrastructure is used to support the development, production, and maintenance of AI/ML and consequently needs to be provided and maintained.

Traceability: The QMS shall assist the organization to produce a systematic documentation of the AI/ML and its supporting design and development, including a robust and documented configuration and change management process, and identifying its constituent parts, to provide a history of changes made to it, and to enable recovery/recreation of past versions of the software, i.e., traceability of the AI/ML.

Measurement and Monitoring: Post market surveillance including monitoring, measurement and analysis of quality data can include logging and tracking of complaints, clearing technical issues, determining problem causes and actions to address, identify, collect, analyze, and report on critical quality characteristics of products developed.

Aspects important for the measurement, analysis, and improvement of AI/ML processes and products can include:

- Evaluation of the AI/ML and its lifecycle processes should be based on defined responsibilities and predetermined activities including using leading and lagging safety indicators and collecting and analyzing appropriate quality data.
- Corrections and corrective actions may be required when a process is not correctly followed or the AI/ML does not meet its specified requirements.
- Nonconforming AI/ML should be contained to prevent unintended use or delivery. The detected nonconformity should be analyzed and actions taken to eliminate the detected nonconformity (i.e., correction); and to identify and eliminate the cause(s) of the detected nonconformity (i.e., corrective action) to prevent recurrence of the detected nonconformity in the future.
- Actions taken to address the cause of AI/ML nonconformities, as well as actions taken to eliminate potential AI/ML nonconformities, should be verified/validated before AI/ML release and should be evaluated for effectiveness.
- Lessons learned from the analysis of past projects, including the results from internal or external audits of the AI/ML lifecycle processes, can be used to improve the safety, effectiveness, and performance of AI/ML. The manufacturer should also have processes in place for reporting adverse events to the SFDA, the collection of active and passive post market surveillance information in order to make appropriate decisions relating to future releases.
- After the product is in the market, it is important to maintain vigilance for vulnerability to intentional and unintentional security threats as part of post market surveillance.

Change Notification

- According to SFDA "Requirements for Medical Devices Marketing Authorization (MDS-REQ 1)" , the SFDA shall be informed, via the electronic system "GHAD", within (10) days of the occurrence **any significant change** to the relevant information or (30) **non-significant change**".
- Major/Significant change: It could reasonably be expected to directly affect the safety or effectiveness of a device.
- Minor/Non-significant change: It could reasonably be expected to indirectly affect the safety or effectiveness of a device.
- Manufacturer shall have **procedures** within the manufacture's QMS for evaluating the changes and shall cover:
    - Change control
    - Categorizing the changes as significant or not.
    - Informing the SFDA of the changes.
- All changes shall be evaluated, verified and validated according to the accepted procedures in the manufacturer's QMS
- Changing that could not reasonably be expected to affect the safety or effectiveness of a device shall be updated at the time of renew the MDMA certificates.

- Manufacturer shall fill the below form and submit it to SFDA:

Table 1 Version Control Method

Medical Device Model:				
	Description of Change	Major or Minor	Date and Reason for changes	Relevant Document
1				
2				
3				

For more information, kindly see the SFDA Guidance on MDMA Significant and Non-Significant Changes.

Annexes

Annex (1): Definitions & Abbreviations

KSA	Kingdom of Saudi Arabia
SFDA	Saudi Food and Drug Authority
MDS	Medical Devices Sector
Manufacturer	Means any natural or legal person with responsibility for design and manufacture of a medical device with the intention of making it available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person.
Authorized Representative (AR)	Means any natural or legal person established within the KSA who has received a written mandate from the manufacturer to act on his behalf for specified tasks including the obligation to represent the manufacturer in its dealings with the SFDA.
Artificial Intelligence (AI)	Technology that realizes some or all of intellectual abilities (intelligence) of human such as recognition and learning based on methods including machine learning using a computer
AI-based Medical Devices	Medical devices that support the work for medical professionals by diagnosing, managing or predicting diseases based on analysis of medical big data with AI technology
Artificial intelligence system (AI system)	Engineered system that generates outputs such as content, forecasts, recommendations or decisions for a given set of human-defined objectives.
Machine Learning (ML)	is an artificial intelligence technique that can be used to design and train software algorithms to learn from and act on data. Software developers can use machine learning to create an algorithm that is 'locked' so that its function does not change, or 'adaptive' so its behaviour can change over time based on new data.
Genetic algorithm GA	Algorithm which simulates natural selection by creating and evolving a population of individuals (solutions) for optimization problems. (ISO)
Machine learning algorithm	Algorithm to determine parameters of a machine learning model from data according to given criteria.

Reference Standard	It is a result of checking whether a certain disease or condition wants to diagnose or predict exists or not
Prospective study	It is a method to trace changes for a certain period of time after pre-setting factors (risk factors) to be studied, observing the changes caused by risk factors.
Retrospective study	It is a method of conducting a study without direct contact with study subjects. It is a clinical trial conducted to verify the safety and effectiveness of medical devices using medical data of subjects obtained through previous medical care or clinical trials rather than recruiting subjects.