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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-1185: Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback

To Whom It May Concern:

The Advanced Medical Technology Association ("AdvaMed") appreciates the opportunity to provide input on the Food and Drug Administration's ("FDA" or "Agency") Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Discussion Paper ("Discussion Paper").[1] AdvaMed represents manufacturers of digital health technologies, medical devices, and diagnostic products that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators and companies.

We applaud FDA for the development of this Discussion Paper and appreciate the Agency's commitment to address regulatory considerations for these emerging technologies. We have provided our comments to the questions posed in the Discussion Paper in the attached document. In addition, after responding to the questions, in the attached document we also provide general feedback to various provisions of the Discussion Paper.

Thank you for your consideration of these comments. Please do not hesitate to contact me at 202-434-7224 or zrothstein@advamed.org if you have any questions.

Respectfully submitted,

/s/

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Attachment

[1] *Available at* https://www.fda.gov/media/122535/download.

AdvaMed Comments

Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning Based Software as a Medical Device

Location	Question/Existing Text	Comment/Proposed Change/Rationale
FDA QUESTIONS		
Page 7, Section III	Do these categories of AI/ML-SaMD modifications align with the modifications that would typically be encountered in software development that could require premarket submission?	• Yes, these categories align with the modifications that would typically be encountered during software development. However, we recommend FDA clarify that traditional types of software changes should follow the Agency's modifications guidance (*i.e.*, that this AI discussion paper is a supplement to the software modifications guidance). • The category, "Modifications related to performance, with no change to the intended use or new input type," requires a more precise definition of "input type." • We note that FDA has not in the past provided clarity on what changes to AI/ML algorithms would require a new premarket submission. Such clarity is necessary to understand the full scope of this proposed framework. We believe that performance updates for general IT functions should not require a pre-market submission. • Relevant definitions now exist in multiple guidance documents (*e.g.*, SaMD, CDS, AI/ML). This patchwork of policy documents could lead to confusion. In addition, data has generally been exempt from medical device software design controls and changes (IEC62304), *e.g.*, dynamic training data; therefore, new guidance for "data controls" in addition to "design controls" should be considered.
	What additional categories, if any, of AI/ML-SaMD modifications should be considered in this proposed approach?	FDA should consider: • A new category about modifications that do not impact performance, intended use, or inputs: o Minor changes in pre-processing techniques, such as segmentation and normalization, with no change in performance (*e.g.*, only acceleration of runtime and fixing a "defect"). o Modifications to data pipelines and/or backend systems. o • FDA should consider the following for clarifications of the existing modification categories: o Dealing with modifications that provide new explanatory/causal information to the user, in addition to the predictive inferences obtained through the trained machine learning algorithm. For example, while the original clearance may have been granted to a SaMD that outputs a medical diagnosis/outcome prediction with a certain confidence score, future research might

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		allow elaboration as to why such a prediction has been made. This newly available insight could be presented to the user in support of the predicted outcome.
	Would the proposed framework for addressing modifications and modification types assist the development of AI/ML software?	Yes, and we believe it would be helpful to have a flowchart to show how these changes impact AI/ML software, and other non-AI/ML software, development.
Page 10, Section IV.1	What additional considerations exist for GMLP?	• GMLPs should consider the following aspects of development, deployment and post-market controls of ML algorithms: o Curation of data, definition of Ground Truth, and minimization of bias in data acquisition. SaMD Manufacturers should detail the mechanisms in place to infuse risk and severity adjustment methodologies into data stewardship and any resulting design or development processes. o Adequate data management (*e.g.*, separation of training, testing, validation and release dataset). Manufacturers should defend Data Relevance as well as Data Adequacy, including when clinical and statistical analyses are applied. o Measures to minimize overfitting and that ensure the robustness of the algorithm. o Performance assessments on representative data with adequate oversight from domain expert. (Adequate oversight extends beyond internal, finite data sets. Manufacturers should understand how input data evolves over time when the manufacturer is relying on external/uncontrolled data). o Feedback mechanisms to monitor and improve AI performance. o Transparency of algorithm performance, including expected global or local variations. o Explainability. • GMLPs should address practices unique to AI/ML and not just those practices within IEC 62304. • GMLPs should include an assessment to ensure that the algorithm is not "over trained." • GMLPs should include a methodology for knowledge transfer (*e.g.*, how to combine old and new training data to improve overall performance without introducing biases). • GMLPs should consider "data dropping" while AI/ML algorithms train (*e.g.*, when there is an accumulation of significant data, an organization may be tempted to drop the unnecessary files. However, dropping these files, while training the ML algorithm, can cause various issues and problems.). • Controls to ensure patient safety (*e.g.*, replacing an algorithm's output with a default safe value when sufficient training data is not available). • If opportunistic re-training of AI/ML-based SaMD is contemplated with the goal of performance improvement, GMLPs should consider a prospective assessment to determine whether more training data in the future may be needed to improve performance.

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		• An additional consideration should focus on how manufacturers can ensure confidence in datasets, such as how outliers may have been removed, which features were engineered, how feature selection/input dimensionality reduction may have been performed, various dataset sizes, etc. Discussion of dataset biases should also be encouraged (*e.g.*, manufacturers should analyze and ensure the diversity of the data taking into consideration age, gender, sources, geography, population distribution, source and quality of the data). • FDA should consider that different GMLP standards may be relevant to different software languages or implementations.
	How can FDA support development of GMLP?	• There are several multi-stakeholder groups that are developing GMLPs, such as the Xavier Health AI Initiative, which developed and published a white paper titled: Good Practices for AI and CLS in Healthcare," *available at* https://www.xavierhealth.org/cls-working-team. We believe FDA should continue to participate in these ongoing efforts. • FDA should provide clarification on how a manufacturer should apply existing design controls and lifecycle management principles (which are general and intended to apply to all devices) to AI/ML SaMD. In addition, FDA should communicate through guidance any expectations for premarket review. • FDA should share examples of best practices received across numerous AI/ML types without disclosing any submitters' confidential information.
	How do manufacturers and software developers incorporate GMLP in their organization?	Manufacturers and software developers continue to implement good software practices, including many practices that are beyond the scope of this document. For AI/ML software development, good software practices should include, for example, implementing data and quality metrics for AI/ML that are used in validation. These practices should be incorporated into the firm's quality system (*see, e.g.*, 21 C.F.R. § 820, ISO 13485, IEC 62304).
Page 12, Section IV.2	What are the appropriate elements for the SPS?	Elements of the SPS should be flexible to accommodate different models. Each manufacturer could then add model-specific details. The SPS should include whether a different model might be used, whether additional new types of inputs might be used, new performance goals, supported data types, and performance metrics. The SPS could include a justification for these anticipated modifications. Additional SPS elements could include: • Initial risk classification and expected new or modified risks as the algorithm learns. • Initial intended use claim and anticipated changes to intended use. • Algorithmic boundaries for which the SaMD remains the same device because it maintains the same safety and efficacy. To address the safety element, the boundaries of the device should be those for which risk management indicates that the SaMD maintains the same safety profile (and

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		same indication for use) as the original device. For efficacy, the boundaries are those for which the SaMD continues to have the same function: the output continues to provide the same type of information.
	What are the appropriate elements for the ACP to support the SPS?	The ACP should focus on assessing risk. With respect to algorithm retraining, generally the risk is associated with the use of the new data and any resulting changes made to the model. Therefore, appropriate elements for the ACP include: • Retraining objectives that address the potential extent of the retraining (*e.g.*, gradual with each new data item or total with a new dataset). • Performance assessment metrics, which may specify a fallback option if retraining results in worse performance. • Monitoring frequency and phase milestones, which may specify metrics for achieving proficiency at each stage of the learning process. • Software version change tracking records, which may record changes that are traced to the device history record or the service record. • Risk management processes specifying risk-benefit conclusions and risk controls by design, which may be defined at each learning change stage. • Documented plans for situations when algorithm changes result in unexpected outcomes not aligned with the SPS. • How much new data is added to training and testing data sets. • What the main differences are, if any, from existing data used in the prior algorithm version. • The nature and degree of data augmentation used, if any. • Increases in model capacity that might affect probability and degree of overfitting. • Establishment quality criteria to determine the data set from which the model is allowed to learn (*e.g.*, to mitigate the risk of bias).
	What potential formats do you suggest for appropriately describing a SPS and an ACP in the premarket review submission or application?	The SPS and ACP should be submitted as part of the premarket review submission or application. FDA should place an emphasis on interactive review of such elements, enabling a SaMD developer to walk FDA through its proposals and iterating on changes to them prior to clearance or approval, which could include a "review by demo," that is documented by "what" was demonstrated and "what" was approved and/or agreed to. We believe it is unnecessary to conduct a paper review of AI/ML when an interactive demonstration can more readily address questions reviewers may have and allow for real-time responses and demonstration of logic from developers.
Page 14, Section IV.3	How should FDA handle changes outside of the "agreed upon SPS and ACP"?	For minor changes to performance or input, FDA should implement a real-time review or focused review. For major changes (*e.g.*, changes to intended use or changes that result in a higher risk

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		classification), a traditional review is appropriate. FDA should consider how the Special 510(k) process can be used in this later scenario.
	What additional mechanisms could achieve a "focused review" of an SPS and ACP?	FDA could leverage its presubmission process or hold an interactive review that includes a "review by demo," where at the conclusion of the process a Confirmation Document is issued and can be submitted to FDA as the "file" for review. This would allow much shorter timelines for review and clearance/approval.
	What content should be included in a "focused review"?	• The changes (*e.g.,* modifications outside of the agreed SPS and ACP). • Data to support the change. • Risk documentation. • Known anomalies. • Labeling updates, if any.
Page 15, Section IV.4	In what ways can a manufacturer demonstrate transparency about AI/ML-SaMD algorithm updates, performance improvements, or labeling changes, to name a few?	The manufacturer can push electronic notifications to its customers through the SaMD. Additionally, the product "labeling," most usually the SaMD's "About Box," can be updated to notify the user of new claims or changes to intended use. Such information could also be included as part of the public database FDA is considering for the Software Precertification program, related to the SaMD Definition Statement. FDA should ensure that confidential and/or proprietary information, including trade secrets, are not publicly released (unless required under applicable FOIA processes).
	What role can real-world evidence play in supporting transparency for AI/ML-SaMD?	AI/ML SaMD can benefit from real world evidence. For example, real world evidence may be able to obtain critical health information in a timely manner. It can also allow for faster review of data and development of more informed clinical trials (when necessary), and be used to track clinical outcomes, quality of life, product usability and utility, perceived patient value, and technical metric tracking of product performance, unlike the limitations and controlled environment of a clinical trial. However, even though the device can collect such data on a continuous basis, that does not mean that such data will always be useable or appropriate for the given use. FDA should gather information from industry concerning how manufacturers control and clean RWE data.
	What additional mechanisms exist for real-world performance monitoring of AI/ML-SaMD?	• User feedback/ratings and usage patterns associated with AI/ML-SaMD. • Data representing the inputs to a SaMD can be used to assess the similarity of the distribution of the real-world population characteristics to the distribution of data used in the SaMD design and validation.

Location	Question/Existing Text	Comment/Proposed Change/Rationale
	What additional mechanisms might be needed for real-world performance monitoring of AI/ML-SaMD?	While we do not identify additional mechanisms, we note that use of RWE must occur within frameworks that consider the user's privacy and consent for specific data use. Any alternatives for monitoring real world performance should not be duplicative to corrections or removals, medical device reporting, and/or annual reports for class III devices.
Page 19, Section VI.6	Are there additional components for inclusion in the ACP that should be specified?	No.
	What additional level of detail would you add for the described components of an ACP?	FDA should clarify whether the ACP covers the type/process of promotional communications that may be presented to users regarding the modifications or improvements to the algorithm.
GENERAL COMMENTS		
General	This proposed framework, particularly Figure 5, appears to focus on 510(k)s. We believe the framework should consider PMA products as well.	Class III AI/ML SaMD can and should be developed using the same Quality System and therefore should be able to take advantage of this proposed regulatory framework.
General	We believe this proposed framework should not be limited to SaMD; software in a medical device ("SiMD") should also be within scope.	Device manufacturers that develop both hardware and software should not be at a disadvantage to manufacturers who develop only software.
General	The TPLC approach described by FDA shares the concepts of Culture of Quality, Organizational Excellence and Real-World Monitoring developed in the FDA Pre-Cert program. Pre-Cert participants will likely benefit from these common elements making access to such a framework easier for Pre-Cert participants. However, the proposed framework should not be restricted to Pre-Cert participants.	This proposed framework should be available to all manufacturers.
General	FDA should provide additional information about the full premarket review process for AI/ML-SaMD.	This proposed framework focuses on AI/ML-SaMD modifications; it does not address, and FDA has not addressed, initial clearance or approval requirements for these devices. While we believe a

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		discussion about modifications during the initial review is helpful, industry still has significant questions about how these products are able to gain initial clearance or approval from the Agency.
General	We recommend that the framework address least-burdensome approaches for SaMD regulation.	The approach to modifications should continue to follow the FDA's Least Burdensome Approach, yet no specific discussion of this topic is mentioned in the Framework. We suggest FDA include least burdensome principles, similar to language used throughout its Software Precertification Working Model v1.0, given that the need for modifications may considerably increase with such devices and analytical approaches.
General	This proposed framework focuses on the distinction between "locked" and "continuously learning" or patient-tailored algorithms, rather than the distinction between AI/ML and "traditional" algorithms. It is unclear, however, when the Agency considers an algorithm to become sufficiently complex that it starts learning continuously and is therefore no longer "locked." It would be helpful for FDA to define "adaptive algorithm" over the spectrum of different levels of adaptiveness, or various types of adaption enumerated in the document.	The group of "adaptive" machine learning algorithms is heterogeneous, and they should be broken down into smaller sub-groups and types. These different types will have inherently different risks.
Page 2, Section I, References	It is important to ensure that the references in the document do not provide conflicting direction, or if they do, that it is clear what the hierarchy is.	We agree with FDA's use of the IMDRF Risk-Categorization Framework for classification of SaMD. However, we strongly believe that the IMDRF language must be adapted to fit the U.S. regulatory paradigm. To that end, we have previously recommended to FDA language intended to clarify and appropriately categorize SaMD based on the significance of the information to the health decision and the state of the healthcare disease or condition, as applied within the U.S. framework. We developed this language based upon input from software developers, traditional device manufacturers, and health professionals. See the Appendix to this document for more information.
Page 4, Section II	This comment is in response to the following text: "AI, and specifically ML, are techniques used to design and train software algorithms to learn from and act on data."	To promote global harmonization of definitions and terms, FDA should define AI and ML in accordance with international standards. For example, both terms are defined in ISO/IEC 2382:2015.

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Page 5, Section II	This section of the proposed framework discusses the spectrum of "locked" and "continuously learning" AI/ML SaMD. FDA should distinguish two settings in which the learning may take place for further clarity.	The two settings are: (1) re-training of a population-level model; and (2) re-training/tuning of an individual-level model. FDA should address these different types of re-training because they could have an important impact on the pre-specifications and post-market review, documentation, and reporting framework.
Page 6, Section III	Section III, in general.	Regarding input modifications, it is unclear whether this provision refers to a change in the actual training data or a change to the type of data used as an input. Additionally, this section should distinguish between nested and interdependent models. The text seems to suggest each of these models is an aggregate solution. However, the models can also be modular and inter-related.
Page 7, Section III, iii	This comment is in response to the following text: "These types of modifications include those that result in a change in the significance of information provided by the SaMD (e.g., from a confidence score that is 'an aid in diagnosis' (drive clinical management) to a 'definitive diagnosis' (diagnose))."	FDA should elaborate on the factors used in the confidence score to determine whether software "aid[s] in diagnosis" or provides a "definitive diagnosis."
Page 8, Figure 2	Real-World Performance Monitoring, in general.	We recommend FDA provide additional information about the different types of RWE that may be used. We also recommend FDA add a model for edge computing (or a hybrid of the two scenarios that accounts for distributed computing).
Page 9, Figure 3	Clinical evaluation section, in general.	We recommend FDA consider providing additional clarity on determination of valid scientific evidence and generation of such evidence as it relates to AI/ML. We appreciate FDA's reference to IMDRF's Clinical Evaluation guidance, which FDA adopted, as a foundation for demonstrating the scientific validation needed for a particular technology, such as AI/ML, and its intended use. While we appreciate the flexibility provided by the guidance, we remain somewhat unclear as to what information constitutes valid scientific evidence and how a sponsor should generate such evidence to ensure safety and effectiveness. Additionally, FDA should consider including clinical endpoints and criteria in the ACP and SPS. Changes to performance often require clinical validation.
Pages 9-10	We recommend the following revisions:	We believe these changes better clarify the intent of this language.

Location	Question/Existing Text	Comment/Proposed Change/Rationale
	"Examples of GMLP considerations as applied for SaMD include: ● Relevance and reliability of data to the clinical problem and current or recent clinical practice; ● Data acquired is consistent, clinically relevant and ~~generalizable~~ broadly applicable ~~manner that aligns~~ with the SaMD's intended use and modification plans; ● Appropriate and documented separation between training, ~~tuning~~validation, and test datasets; and ● Appropriate ~~level of transparency (clarity)~~ documentation of the output and the algorithm aimed at users."	
Page 11, Figure 4	Figure 4, in general.	FDA should clarify that unsupervised learning is allowed under "Retraining: ML methods, including architecture and parameters." As drafted, the ACP does not specifically allow for unsupervised learning. We also recommend FDA clarify whether this Figure 4 is a proposed model or general example.
Page 13, Figure 5	We suggest modifying the box that states: "Modifications lead to a new intended use," to: "Modifications lead to a new intended use that cannot be addressed through newly approved SPS and ACP."	Figure 5 currently states that any modification that leads to a new intended use will require an FDA premarket review; however, as noted in the document, agreed upon SPS's and ACP's can include changes to intended use. Therefore, it is overly restrictive and inconsistent to require every change to an intended use to lead to a premarket review. Rather, it should be possible for a developer to modify its SPS and ACP and have an FDA focused review on those to address the possibility of modifications leading to a new intended use. Premarket review should be required only in situations in which a change to the intended use cannot be addressed through an updated SPS and ACP.
Page 14, Section IV, 4	This comment is in response to the following text: "FDA would also expect the manufacturer to provide periodic reporting to FDA on updates that were implemented as part of the approved	The frequency of periodic reporting should be based on the device's risk and agreed upon at the time of premarket review. Such an approach would prevent unnecessary reporting for lower risk or less often used functionalities. FDA should consider that periodic reporting may not be necessary for some low risk functions and/or that periodic reporting may not be needed past a certain point as the AI/ML matures.

Location	Question/Existing Text	Comment/Proposed Change/Rationale
	SPS and ACP, as well as performance metrics for those SaMD."	
Page 14, Section IV, 4	This comment is in response to the following text: "Transparency may include updates to FDA, device companies and collaborators of the manufacturer and the public such as clinicians, patients and general users."	Because these devices will evolve over time, the reporting or communication of changes should not be overly burdensome to the manufacturer or user, and commensurate with the level of risk associated with the AI/ML function. Automated mechanisms for reporting changes should be preferred. At the time of initial clearance or approval, FDA should identify the nature of changes considered to be within the scope of the approved SPS and ACP. This would provide the necessary transparency to users as to changes that are within scope of the approved SPS and ACP.
Page 16, Modification Scenario 1A	We recommend the following revision to Modification Scenario 1A: Increase in performance (type i modification), consistent with SPS and ACP: "In accordance with the ACP, data was collected and used to modify the algorithm in a way that the manufacturer believes will lower the false-alarm rate while maintaining the sensitivity. A separate independent test set ~~validation data set~~ was collected . . . ."	A validation set is only used to tune a model's hyper-parameters, such as its architecture and learning rate. "Test set," we believe, is a more appropriate term.

Interpretations of IMDRF Risk-Categorization Framework

IMDRF language = black text
Recommended interpretations = red text

A. Significance of Information
• To treat or to diagnose - To provide therapy to a human body; - To diagnose/screen/detect a disease or condition Output of the SaMD is intended to be used to: - Definitively diagnose a disease or condition; - Provide direct treatment or definitive treatment information for a disease or condition; Output of the SaMD is the sole determinant for clinical action and requires no further steps or confirmatory testing. Output of the SaMD is intended for immediate or near-term clinical action.
• To drive clinical management - To aid in treatment by providing enhanced support to safe and effective use of medicinal products or a medical device. - To aid in making a definitive diagnosis. - To triage or identify early signs of a disease or conditions. Output of the SaMD is intended to be: - One of several inputs used for clinical action and/or decision-making; and - Necessary for clinical action or decision-making by the health care professional or patient, i.e. determinative. Output of the SaMD is intended for immediate or near-term clinical action.
• To inform clinical management - To inform of options - To provide clinical information by aggregating relevant information Output of the SaMD is intended to be: - One of several inputs used for clinical action and/or decision-making; and - Not necessary for clinical action or decision-making by the health care professional or patient and may or may not lead to direct clinical action, i.e. informative or adjunctive.

B. State of the Healthcare Condition		
Critical	**Serious**	**Non-serious**
Situations or conditions where accurate and/or timely diagnosis or treatment action is vital to avoid death, long-term disability or other serious deterioration of health of an individual patient or to mitigating impact to public health. SaMD is considered to be used in a critical situation or condition where: The type of disease or condition is: • Life-threatening state of health, including incurable states, • Could result in permanent impairment of body function or in the structure of the body, • Requires major therapeutic interventions, • Sometimes time critical, depending on the progression of the disease or condition that • could affect the user's ability to reflect on the output information. • ~~Intended target population is fragile with respect to the disease or condition (e.g., pediatrics, high risk population, etc.)~~ • ~~Intended for specialized trained users.~~	Situations or conditions where accurate diagnosis or treatment is of vital importance to avoid unnecessary interventions (e.g., biopsy) or timely interventions are important to mitigate long-term irreversible consequences on an individual patient's health condition or public health. The type of disease or condition is: • Moderate in progression, often curable, • Could result in temporary impairment of body function or in the structure of the body, • Does not require major therapeutic interventions, • Intervention is normally not expected to be time critical in order to avoid death, long-term disability or other serious deterioration of health, whereby providing the user an ability to detect erroneous recommendations. • ~~Intended target population is NOT fragile with respect to the disease or condition.~~ • ~~Intended for either specialized trained users or lay users.~~ • ~~Note: SaMD intended to be used by lay users in a "serious situation or condition" as~~ • ~~described here, without the support from specialized professionals, should be considered~~	Situations or conditions where an accurate diagnosis and treatment is important but not critical for interventions to mitigate long term irreversible consequences on an individual patient's health condition or public health. SaMD is considered to be used in a non-serious situation or condition when: The type of disease or condition is: ▪ Slow with predictable progression of disease state (may include minor chronic illnesses or states), ▪ Is not likely to result in temporary impairment of body function or in the structure of the body, ▪ May not be curable; can be managed effectively, ▪ Requires only minor therapeutic interventions, and ▪ Interventions are normally noninvasive in nature, providing the user the ability to detect erroneous recommendations. ▪ ~~Intended target population is individuals who may not always be patients.~~ ▪ ~~Intended for use by either specialized trained users or lay users.~~

	• ~~as SaMD used in a "critical situation or condition".~~	

- **Justification for added text:**
  - The added text simply aligns the definition with current US definitions by taking into account risk of impairment of body function or structure.

- **Justifications for deleted text:**
  - *Patient population.* The fragile nature of the patient population would impact the type of controls (or risk mitigations) that are necessary, but it would not impact the risk classification. This is consistent with prior GHTF guidance.

  - As explained in the GHTF Classification guidance:

    The Risk Assessment (RA) takes account of the probability that harm will occur by modifying the evidence requirements at the conformity assessment stage rather than modifying the classification rules. Probability of harm is influenced by factors such as whether:
    - the technology is regarded as mature;
    - the device type is the source of many adverse event reports;
    - the device's manufacturer has a long experience of the device and the technologies it embodies;
    - the device user is a lay person

  - Therefore, the nature of the user could impact the *type or amount of evidence/information required, but not the classification itself.* In addition, we believe that simply because the software is intended to be used only by a specialized user should not increase the risk to patients. Conversely, use by a specialized user should reduce the risk of the software.

- In reviewing the applicable GHTF documents and IMDRF SaMD documents, these descriptions seem appropriate with the changes noted above. Consideration was also given to how health hazard evaluations (HHEs) are currently conducted (including the FDA HHE). Additions based on this review are underlined in the recommended modifications above.

- Note, if FDA determines it is necessary to keep the concepts in the deleted text, we recommend that FDA refer to these areas as factors that a developer should consider or guidance, rather than determinative.

- FDA should consider that SaMD may have general indications for use rather than for a specific disease or condition (*e.g.*, minimally invasive surgery compared to minimally invasive neurosurgery). This is also true for target populations, which may be general rather than a specific sub-population.

- FDA should also clearly define terms, such as "major therapeutic interventions" and provide examples. FDA should consider language that references SaMD that may monitor or predict a condition, which may not necessarily be considered an intervention.