Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)

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General Comments

General Comments /Rationale
The FDA's final Total Product Lifecycle Regulatory framework must be comprehensive enough to cover all of the different types of devices which may incorporate Artificial Intelligence/Machine Learning (AI/ML)-based Software as a Medical Device (SaMD), yet it must be specific enough to assist industry on defining exactly how to incorporate the provisions of any new FDA Guidance Document that is an output of the FDA's solicitation of feedback from industry on this Discussion Paper.
The FDA's referenced definitions must be objective and fairly applied in a consistent manner. For example, what is the FDA's definition of "improving performance" in the context of modifications made to AI/ML-based SaMD when that definition may be very different based on the specific type of device? This definition cannot solely be a general standard that applies across all devices. The definitions must be specific to the type(s) or category of device and how it is intended to be used, in addition to the risk level of the device.
The FDA's Discussion Paper makes numerous references to the *FDA Guidance on Deciding When to Submit a 510(k) for a Software Change to an Existing Device* and suggests that this guidance document continue to serve as the foundational framework for assessing certain types of modifications, and specifically those which affect safety or effectiveness, which may warrant submitting a new 510(k). This FDA guidance document is specific to 510(k)s, not PMAs. Although the same general methodology, reasoning, and analysis involved in assessing device software modifications may be applied to PMA devices, the actual impact of such modifications/changes on a PMA device are much greater than those of a 510(k)-device due to the higher risk level of PMA devices (life sustaining and/or life supporting). Arguably, most changes/modifications made to the AI/ML-based software of a PMA device would likely fall into a category which may affect safety or effectiveness, thus requiring new PMA filings to be submitted at a more frequent rate. This creates a valid concern for the financial impact and hardship to industry to be able to afford the Medical Device User Fees and other costs associated with filing an original PMA or PMA Supplement which may be necessary to occur at a more frequent interval for PMA devices incorporating AI/ML-based SaMD technology. Such costs would not likely be sustainable for a medical device manufacturer, and therefore, has the potential impact to limit a company's competitive advantage and position in the marketplace. To address this concern, the FDA must consider either eliminating the excessive Medical Device User Fees or establishing significantly reduced rates charged for filing submissions for these types of AI/ML-based software modifications.

General Comments /Rationale
This Discussion Paper states the proposed Total Life Cycle Framework is based on the International Medical Device Regulators Forum (IMDRF) risk categorization standards, but it does not specifically address the specific information and software documentation required to be submitted. The seasoned 2005 *FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* was very specific on the required software documentation based on the established Level of Concern (low, moderate, major). However, the new IMDRF risk categories do not specify exactly what software documentation and other information would be required to be submitted to the FDA in a regulatory submission. This must be specifically outlined in any future FDA guidance established as a result of soliciting industry feedback on the proposed framework for these types of devices. Although the *FDA's Guidance on Changes to Existing Medical Software Policies Resulting from the Section 3060 of the 21st Century Cures Act* was released, it is still in draft form and must now be revised to include provisions and guidance for these new AI/ML-based SaMD technologies.
The criterion for the FDA's Pre-Cert TPLC approach must be completely transparent and it must be applied consistently and fairly across industry taking into consideration the type, size, and status of the organization and the products they manufacture (i.e. mature company versus a new start-up company). The FDA must specifically lay out its process and parameters for exactly how it *"will assess the culture of quality and organizational excellence of a particular company and have reasonable assurance of the high quality of their software development, testing, and performance monitoring of their products"* across all different types of organizations. Depending on what the specific criterion are for meeting this standard, it's quite possible that the competitive advantage for a new, start-up company with a quality system in its infancy stage, would be limited when compared to a more mature organization which may be in a better position to meet this proposed standard of quality and organizational excellence.

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On page 10 of the Discussion Paper under *Section 2. Initial Premarket Assurance of Safety and Effectiveness*, it states that "this framework gives manufacturers the option to submit a plan for modifications during the initial premarket review of an AI/ML-based SaMD." However, if this suggestion is only a voluntary option to manufacturers instead of establishing it as a mandatory requirement for all manufacturers, it's reasonable to conclude that there would not be transparent and objective criterion established to be applied consistently and fairly across all manufacturers of AI/ML-based SaMD. Manufacturers whom elect such option to submit a plan would automatically have an advantage over a manufacturer who does not elect the option. Therefore, the FDA must make this a mandatory requirement instead of a voluntary option. Further, the FDA must clearly define the specific elements of the Predetermined Change Control Plan and the Algorithm Change Protocol, the format of the required information, and the methods/processes for how the FDA will consistently review and approve them.
The FDA must establish clearly defined criterion for transparency and real-world performance monitoring of AI/ML-based SaMD. The Discussion Paper states that *"many of the modifications to AI/ML-based SaMD may be supported by collection and monitoring of real-world data in support of the benefit-risk profile"* and that *"gathering performance data on the real-world use of the SaMD may allow manufacturers to understand how their products are being used, identify opportunities for improvements, and respond proactively to safety or usability concerns."* However, there is no discussion regarding exactly what the FDA's expectations are for how this is to be performed by manufacturers, nor does it mention the likely inconsistency for how this may be performed by different companies across different types of devices. Furthermore, the FDA does not discuss how they will review, assess, and approve the real-world performance monitoring proposed by a manufacturer. Therefore, the FDA must establish very clear criterion for the real-world performance monitoring. The FDA must also be completely transparent about their review and approval process for assessing real-world performance monitoring and to apply their final process both fairly and consistently across industry.

Specific Questions / Feedback Requested

FDA's Specific Questions / Feedback Requested	Response to FDA's Specific Questions / Feedback Requested
Questions / Feedback on the Types of AI/ML-SaMD Modifications:	Although the most common and obvious categories of software modifications that may require a premarket submission are mentioned, there is no reference to minor changes which may reasonably be

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• *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?* • *What additional categories, if any, of AI/ML-SaMD modifications should be considered in this proposed approach?* • *Would the proposed framework for addressing modifications and modification types assist the development AI/ML software?*	handled individually with internal documentation (i.e. Regulatory Letter to File), but which may collectively over time become a moderate or major change. A process must be defined for assessing "one-off type" changes and/or changes which may have originally been "one-off type" changes which later morphed into a more moderate or major change over time.
Questions / Feedback on GMLP: • *What additional considerations exist for GMLP?* • *How can FDA support development of GMLP?* • *How do manufacturers and software developers incorporate GMLP in their organization?*	The FDA must specifically outline their expectations and requirements of Good Machine Learning Practices (GMLP). The FDA states that it expects that "SaMD developers embrace the excellence principles of culture of quality and organizational excellence" yet this standard is essentially theoretical and may be different based on the size of an organization and the type(s) of devices it manufacturers. These known inconsistencies must be addressed by the FDA in the GMLP requirements it establishes. The FDA must apply the GMLP requirements and/or standards fairly and consistently across industry. How will the FDA inspect organizations to the GMLP? How will those inspections be performed? The FDA must provide transparent rules and guidance on exactly what the new GMLP requirements will be and how companies will be inspected against those requirements.
Questions / Feedback on SPS and ACP:	The FDA must clarify their general and specific expectations for what they deem are the appropriate elements for the SPS and the ACP as a minimum baseline for all manufactures to follow taking into account

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• *What are the appropriate elements for the SPS?* • *What are the appropriate elements for the ACP to support the SPS?* • *What potential formats do you suggest for appropriately describing a SPS and an ACP in the premarket review submission or application?*	the variability in the predetermined change control plans, anticipated modifications (SaMD Pre-Specifications-SPS), and Algorithm Change Protocols (ACPs) across companies.
Questions / Feedback on Premarket Review: • *How should FDA handle changes outside of the "agreed upon SPS and ACP"?* • *What additional mechanisms could achieve a "focused review" of an SPS and ACP?* • *What content should be included in a "focused review"?*	The FDA must define a mechanism for handling changes outside the agreed upon SPS and ACP because it is likely that over time, a company's SPS and ACP may change due to a number of different factors. The FDA must clearly define their expectations for the information that must be submitted for a focused review of an SPS and ACP and what their criterion are for how they review, assess, and conduct the focused review. A consistent and fair process must be established. The FDA must issue specific guidance on the required elements of the Premarket Review Submission and the process for the FDA's review for the submission must be completely transparent to industry.
Questions / Feedback on the Transparency and Real-World Performance Monitoring: • *In what ways can a manufacturer demonstrate transparency about AI/ML-SaMD algorithm updates, performance improvements, or labeling changes, to name a few?* • *What role can real-world evidence play in supporting transparency for AI/ML-SaMD?*	The FDA must first define an initial baseline structure for their expectations for demonstrating transparency about AI/ML-SaMD algorithm updates, performance improvements or labeling changes. The FDA should consider establishing a new searchable database for these types of products which provides more specific information about the device that is completely transparent and readily available and accessible to the public.

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• *What additional mechanisms exist for real-world performance monitoring of AI/ML-SaMD?* • *What additional mechanisms might be needed for real-world performance monitoring of AI/ML-SaMD?*	
Questions / Feedback on the ACP: • *Are there additional components for inclusion in the ACP that should be specified?* • *What additional level of detail would you add for the described components of an ACP?*	The high-level information provided in *Section VI. Appendix B: Proposed Content for an Algorithm Change Protocol (ACP)* is helpful as to suggesting the "what" may include, but it does not provide more insight on the "how" or method to accomplish it. Additional details about what the specific requirements for the Data Management Plan, the Re-Training Strategy, the Performance Evaluation Protocols, and the Update Procedures must be outlined by the FDA.
VII. Questions / Feedback ***Responses*** ***1. 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?*** ***Response:*** *At a high-level, possibly. However, there is so much variability in these types of devices that it is difficult at this early juncture to predict other types of changes that may occur because of the unique nature of these devices.* ***2. What additional categories, if any, of AI/ML-SaMD modifications should be considered in this proposed approach?*** ***Response:*** *Minor changes which may reasonably be handled individually with internal documentation (i.e. Regulatory Letter to File), but which may collectively over time become a moderate or major change should also be considered in this*	

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proposed approach. A process must be defined for assessing "one-off type" changes and/or changes which may have originally been "one-off type" changes which later morphed into a more moderate or major change over time.

3. Would the proposed framework for addressing modifications and modification types assist the development AI/ML software?
Response: *Yes, but the FDA must clearly define expectations and processes for the development of AI/ML software. In fact, the FDA should develop new software development guidance that is specific to this unique type of software.*

4. What additional considerations exist for GMLP?
Response: *The FDA must first define exactly what the GMLP requirements are and how manufacturers will be assessed by the FDA to ensure compliance to GMLP.*

5. How can FDA support development of GMLP?
Response: *The FDA must clearly define their expectations for how manufactures comply with the GMLP requirements and how they will be assessed by the FDA during inspection. There must be a consistent and fair approach that is applied the same way to every manufacture regardless of the size of an organization and/or the maturity or infancy of its quality management system.*

6. How do manufacturers and software developers incorporate GMLP in their organization?
Response: *Refer to the response to #5 above.*

7. What are the appropriate elements for the SPS?
Response: *Due to the expected variability across companies based on device types and technology, the FDA must establish the minimum set of requirements or elements they expect to be included in the SPS.*

8. What are the appropriate elements for the ACP to support the SPS?
Response: *The elements may be different per each manufacturer, so the FDA must establish a minimum baseline of the required elements for the ACP to support the SPS.*

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9. What potential formats do you suggest for appropriately describing a SPS and an ACP in the premarket review submission or application?
Response: *A standardized template or checklist would be useful to describe the required elements of a SPS and an ACP and the process or methodology for how the FDA assesses the elements.*

10. How should FDA handle changes outside of the "agreed upon SPS and ACP"?
Response: *The FDA must establish a general baseline process for all manufacturers as to how such changes outside of the agreed upon SPS and ACP are handled. Otherwise, there would not be a consistent process applied equally to the entire industry.*

11. What additional mechanisms could achieve a "focused review" of an SPS and ACP?
Response: *The FDA must define the minimum threshold for when a focused review of an SPS and ACP is required. This standard must be applied consistently and fairly across industry.*

12. What content should be included in a "focused review"?
Response: *The FDA must outline the content for a focused review, perhaps using a standardized template or checklist, and the FDA's process on how the focused review will be conducted must be transparent and applied consistently across industry.*

13. In what ways can a manufacturer demonstrate transparency about AI/ML-SaMD algorithm updates, performance improvements, or labeling changes, to name a few?
Response: *The FDA should consider establishing a new searchable database for these types of products which provides more specific information about the device that is completely transparent and readily available and accessible to the public.*

14. What role can real-world evidence play in supporting transparency for AI/ML-SaMD?
Response: *This is yet to be determined. The FDA must first establish and define their expectations for transparency and how real-world evidence may actually support it. The FDA's process must also be transparent.*

15. What additional mechanisms exist for real-world performance monitoring of AI/ML-SaMD?

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Response: *The FDA should consider establishing a new searchable database for these types of products which provides more specific information about the device that is completely transparent and readily available and accessible to the public.*

16. What additional mechanisms might be needed for real-world performance monitoring of AI/ML-SaMD?
Response: *The FDA should consider establishing a new searchable database for these types of products which provides more specific information about the device that is completely transparent and readily available and accessible to the public.*

17. Are there additional components for inclusion in the ACP that should be specified?
Response: *The specific elements of the Data Management, Re-Training, Performance Evaluation, and Update Procedures must be defined. These are only high-level suggestions of what may be included, but the specific details of those components also need to be clearly defined by the FDA since there will likely be variability across industry.*

18. What additional level of detail would you add for the described components of an ACP?
Response: *The FDA must specify exactly what they expect to see for the Data Management, Re-Training, Performance Evaluation, and Update Procedures components of the ACP. Standardized templates and/or checklists may be useful to describe the required sub-elements of these high-level components.*