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Will the Final Chapter Come? FDA's Action Plan for Oversight of Artificial Intelligence/Machine Learning-Based Medical Software

The U.S. Food and Drug Administration (FDA) continues eyeballing evolving medical technology fields such as artificial intelligence/machine learning (AI/ML)-based software as a medical device (SaMD). In January 2021, FDA issued its Action Plan for how the agency intends to further address its regulation of this area. Although not formal guidance, the document does indicate FDA's current thinking on the subject and helps clarify what FDA's next steps will be in the ongoing development of its regulatory framework. While the Action Plan focuses on SaMD, the agency expects some of this work will also be applicable to other medical device areas, including software in a medical device (SiMD). FDA continues to emphasize its collaborative approach to establishing a final regulatory framework and invites stakeholders to proactively provide feedback.

Overall, the Action Plan builds on the foundation FDA previously laid down in its April 2019 Proposed Regulatory Framework for Modifications to AI/ML-Based SaMD (Proposed Framework). Because AI/ML-based SaMD continuously learns, and modifies its algorithms, it would be impractical to solely regulate the technology under FDA's regulatory framework for SaMD. The general approach FDA has settled on is that pre-market submissions for AI/ML-based SaMD should allow FDA to review and assess the range of modifications to the device that can be expected to result from the AI/ML, and the pre-market submission should also allow FDA to review and assess how such modifications would both stay within that range and occur in a controlled manner.

The Proposed Framework elaborated on this general approach by outlining the following ways FDA intends to approach its regulation of AI/ML-based SaMD:

- Leverage practices from its current premarket programs, including the 510(k), De Novo, and PMA pathways.
- Utilize FDA's current benefit-risk framework, the risk-categorization principles established by the International Medical Device Regulators Forum, and the risk-management principles described in FDA's software modifications guidance.
- Adopt the organization-based total product lifecycle approach envisioned in FDA's Digital Health Software Precertification Program.
- Expect pre-market submissions for AI/ML-based SaHD to include a "Predetermined Change Control Plan," which would include the types of anticipated modifications that the AI/ML would effectuate (which FDA refers to as "SaMD Pre-Specifications" (SPS)), and to also include the associated methodology being used to implement those changes in a controlled manner that manages risks to patients (which FDA refers to as the "Algorithm Change Protocol"(ACP)).
- Expect the SaMD manufacturers to be transparent with FDA and monitor the real-world performance of their SaMD device, to enable FDA and manufacturers to evaluate and monitor a SaMD from its premarket development through post-market performance – a total product lifecycle approach.

FDA's 2021 Action Plan builds on this approach by explaining:

- FDA will continue developing its framework for regulating AI/ML-based SaMD, including issuing a draft guidance about the Predetermined Change Control Plan in 2021. This effort will lead to a more customized framework to help manufacturers determine information they should include in the SPS and ACP to support the safety and effectiveness of AI/ML SaMD algorithms. After initial FDA clearance, future modifications within the scope of the cleared SPS and ACP could be made without a pre-market submission.
- FDA will resume its efforts to promote international harmonization of "Good Machine Learning Practice" (GMLP), which describes a set of AI/ML best practices for issues such as data management, feature extraction, training, interpretability, evaluation, and documentation. FDA has been working with several international standards organizations, including International Medical Device Regulators Forum. Regulatory harmonization in this space may still be premature given that the majority of the countries have not embarked on development of the relevant framework for AI/ML-based devices. If FDA's thinking becomes the backbone of the international standard, developers that invest in compliance with the U.S. standard will be able to roll out their devices onto the global market more easily.
- FDA will hold a public workshop to help the agency develop recommendations on the types of information that should be included on AI/ML-based device labels, to support transparency and enhance user trust. Transparency is key to the patient-centered approach.
- FDA supports regulatory science efforts to develop methodology to evaluate and improve machine-learning algorithms, including for the identification and elimination of bias (e.g., with respect to race, ethnicity, and socio-economic status), and for the evaluation and promotion of algorithm robustness.
- FDA has received a lot of questions regarding how the manufacturer can collect and monitor real-world data, which are an important mechanism to assess usage of the AI/ML-based SaMD, potential improvement opportunities, and safety or usability concern mitigation. FDA will advance pilot

programs for monitoring and utilizing real-world performance data, in coordination with stakeholders on a voluntary basis and with other FDA programs, to provide additional clarity on what a real-world evidence generation program could look like for AI/ML-based SaMD.

Although FDA's Action Plan is primarily intended to be deliberative, FDA may incorporate some of the Action Plan concepts into its ongoing reviews of AI/ML-based devices. Beside the agency's current focus on the commercial AI/ML-based SaMD, FDA may move to address the usage of AI/ML-based SaMD in research, such as its application in drug discovery and development.

The Proposed Framework has a continued interest from Capitol Hill. Most recently, Sen. Bill Cassidy (R-La), who serves on the Senate Health, Education, Labor and Pensions Committee, has asked for the agency's response before mid-March about its plans for regulating AI/ML-based SaMD, the associated timeline, and the approach to publish guidance. While the agency has said it will rely on the authority already granted to it to move forward, it has also admitted it may need additional mandates from Congress to effectively regulate AI/ML-based SaMD, especially in the context of the 510(k) pathway. Congress and FDA may be able to finalize a fairly comprehensive framework by taking advantage of the ongoing Medical Device User Fee Amendments V negotiations, which will need to be concluded no later than 2022. In other words, 2021 can be an exciting moment for the relevant stakeholders to play an important role to shape the final paradigm.

Because many AI/ML-based SaMD developers are from small academic studios and venture companies; in addition to big technology companies, investors in or the incubators of such technology developers should proactively engage themselves in the applicable rulemaking or legislative process.

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