COLLEGE of AMERICAN PATHOLOGISTS

June 3, 2019

Norman Sharpless, M.D.
Acting Commissioner
US Food and Drug Administration (FDA)
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) [Docket No. FDA-2019-N-1185-0001]

Submitted via Electronic Submission to www.regulations.gov

Dear Dr. Sharpless:

The College of American Pathologists (CAP) appreciates the opportunity to comment on the Food and Drug Administration draft guidance entitled, *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)*. As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. As physicians specializing in the diagnosis of disease through laboratory methods, pathologists have a long track record of delivering high quality diagnostic services to patients and other physicians.

Artificial intelligence (AI)- and machine learning (ML)-based technologies have the potential to transform healthcare. They are anticipated to become integral adjuncts to pathology and all of medicine. Given the impact AI/ML will have on pathology, the CAP supports a risk-based approach for the AI/ML SaMD regulatory framework. The robustness of the framework's requirements should depend on the risk classification of the AI/ML SaMD and include demonstration of analytical and clinical validity. Moreover, post-marketing (real world) quality control and performance monitoring requirements intended to prove efficacy of modifications should clearly define local verification and data capture responsibilities between the developers and end-users (eg, laboratories and pathologists). Lastly, transparency must be required in any regulatory framework, which should mandate that developers implement an open system that describes updates and modifications as they occur to patients and clinicians.

SPECIFIC COMMENTS

Helena Duncan
Assistant Director, Quality
t: 800-323-4040 ext. 7131

f: 847-832-8131
hduncan@cap.org

325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

Risk-Based Approach

The FDA proposed to adopt a risk-based approach that defines risk as directly related to the significance of information provided by a SaMD to a healthcare decision such as selection of a diagnosis or clinical management strategy. Risk associated with AI/ML SaMD should also explicitly incorporate user knowledge and expertise, including domain knowledge and familiarity with failure modes of the tool. The output of AI/ML SaMD may comprise detection, prioritization, prediction, or classification, tasks that include interpretive elements. Risk assessment for SaMD should include evaluation of the capability of the user to judge the validity of the tool's output in the context of routine use. Risk is higher in cases where the tool supplies expertise that the user does not have, or cannot otherwise validate, because in those cases the ability of the user to judge the quality of the tool's output is reduced. Assessment of user-related risk may appropriately lead to restriction of allowable users for a tool, or to a sliding risk scale with required safeguards that depend on the user and usage context.

Local Verification

The FDA proposed to regulate types of AI/ML-based SaMD modifications including (1) performance improvement (clinical and analytical performance), (2) changes in data inputs to an SaMD, and (3) intended use of the SaMD. The details of these kinds of modifications and the requirements for local verification and re-verification are critical and need to be better specified. Furthermore, data inputs to SaMD may be subject to variation in the real world, for example, laboratory test results that may be derived from kits with somewhat different characteristics that are produced by various vendors, or microscope slides that may be produced by different histology laboratories and scanned with different devices. Will an SaMD require explicit validation for use with test kits or scanning devices? If a laboratory test that is used as one of several inputs for an AI/ML predictive algorithm is changed for cost reasons to a similar test from a different vendor, would that change or invalidate an SaMD or require local re-verification? If the latter, what form of re-verification would be acceptable? In a setting where multiple algorithms are deployed, to what extent do the requirements for validation of those algorithms "lock in" methodologies and workflows for the clinical data elements upon which they depend? This kind of lock-in has the potential to reduce the organizational agility that the FDA is hoping to promote with these regulatory changes. Can general purpose validation and performance monitoring practices be defined that identify and mitigate these kinds of problems? Additionally, should data input devices (signal detectors such as whole slide imaging systems and chemistry and hematology analyzers) be held to reproducibility standards (color reproduction, resolution, adsorption, etc) that keep them within some performance envelope that all SaMD manufacturers can target?

In addition, these systems must ensure excellent performance monitoring and maintenance. Given the inherent black box nature of the advanced mathematical approaches that underpin the SaMD applications in question and the potential for drift

Helena Duncan
Assistant Director, Quality
t: 800-323-4040 ext. 7131
f: 847-832-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

over time in input data, there must be robust quality control, quality assurance and quality improvement processes, including strict delta checks and a high frequency of mandatory "result" review prior to verification. Any modification of inputs and/or intended uses (including the SaMD Pre-Specifications [SPS] concept with respect to the latter), however, should be viewed as an entirely new product in need of FDA approval.

Transparency and Real-World Performance

The FDA proposed the adoption of a total product life cycle (TPLC) approach in the regulation of AI/ML-based SaMD where manufacturers can work to assure the safety and effectiveness of their software products by implementing appropriate mechanisms that support transparency and real-world performance monitoring. The FDA would also expect the manufacturer to provide periodic reporting to FDA on updates. There is a significant issue related to real-world performance monitoring (RWPM) but the AI/ML proposal fails to specify the process for RWPM. Since RWPM is intended to replace at least a portion of clinical safety and efficacy studies, prescriptive requirements are needed. There are also implications that this data will be obtained by developers from their customers and reported to the FDA. This suggests a regulatory burden, contractual burden, or both, that will fall on laboratories as a requirement for using these technologies. The kind of data needed to gauge safety, efficacy, and performance stability over time may require duplicate analysis or downstream patient monitoring and chart abstraction to determine utility, adverse events, and outcomes. If done in an optimal way, this could be additional work, but could also put laboratories in a central role in the application and validation of exciting new technologies. If not done optimally, this could add a substantial burden to laboratories without a clear pathway to new resources and limit the ability to deploy these new technologies.

The FDA should consider separating the regulatory submission requirements for the onsite validation and performance monitoring plan for each product from the developer's approval process and require a separate approval of post-marketing surveillance processes. Since the post-marketing data occurs in the laboratory, the data accrual responsibilities are within the pathologist's purview. A separate process would ensure the post-market regulatory surveillance responsibilities are not transferred to the pathologists or physicians.

* * * * *

Thank you for the opportunity to submit these comments. The CAP looks forward to working with the FDA. Please direct questions on these comments to Helena Duncan at (202) 354-7131 or hduncan@cap.org.

Helena Duncan
Assistant Director, Quality
t: 800-323-4040 ext. 7131

f: 847-832-8131
hduncan@cap.org

325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org