

May 31, 2018

Scott Gottlieb, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb:

On behalf of the physician and medical students members of the American Medical Association (AMA), I appreciate the opportunity to provide comments on the Food and Drug Administration's (FDA) *Developing a Software Precertification Program: A Working Model (v0.1-April 2018)* (Precertification Program), and to offer additional recommendations related to stakeholder engagement. The AMA strongly agrees that patients, physicians, and other clinicians increasingly rely on information provided by the output of software as a medical device (SaMD) in order to make decisions that impact clinical outcomes and patient care. The AMA supports the goal of the FDA to construct an alternative, optional oversight model that incentivizes SaMD quality and excellence while prioritizing regulatory oversight based on risk. Overall, however, the AMA continues to have questions concerning each of the components of the proposed Precertification Program.

OVERARCHING PRIORITIES

In contrast to other medical devices where many physicians and national medical specialty societies often have either training or experience or both in the development, design, validation, and/or use of the product and related services, most physicians (and other clinical end users) are not trained or experienced in design, development, and validation of SaMD. Yet, physicians and physician organizations have clinical expertise, experience with clinical integration strategies and barriers involving technology, and access to data sources needed for clinical validation and/or monitoring (through, for example, clinical registries). Therefore, we strongly urge more focused and intensive engagement with the AMA and national medical specialty societies to ensure that all elements of SaMD are well-understood by physician stakeholders, and they are, in turn, able to make informed recommendations and suggestions as the FDA continues to develop the Precertification Program.

In the past, integration of health information technology into medical practice too often has been more burdensome than it should have been due to lack of user-centered design principles, interoperability, transparency, and adequate and affordable ongoing technical and vendor support. A precertification model promoting excellence should leverage physician clinical and practice workflow expertise while addressing the foregoing.

In addition, a precertification program must also ensure product-specific clinical association as well as analytical and clinical validation as articulated in the FDA December 2017 Guidance on SaMD Clinical

Evaluation. **Fundamentally, such a program must not shift the risks of any design or update defects of SaMD to patients and health care providers.**

Finally, the AMA strongly supports incentivizing transparency and urges the FDA to explicitly identify transparency requirements for each component of the Precertification Program. In particular, the Precertification Program should not permit developers that utilize gag clauses or other measures that undermine transparency.

EDUCATION AND REGULAR ENGAGEMENT FOR MEANINGFUL PARTICIPATION

The AMA understands the confluence of factors that are driving the need to develop alternative options for regulatory oversight of SaMD, including the rapid iterations in SaMD, the capability of SaMD-supporting technologies to track post-market impact, and the proliferation of SaMD which is outpacing regulatory agency capacity to review and surveil. Further complicating the landscape is SaMD, that is powered by continuously learning algorithms. Such software offers significant promise for advancing medical knowledge and increasing accessibility, but due to rapid cycle iterations will easily overwhelm the FDA's current resources.

It is understandable that the FDA and industry have been intensively engaged for over a year in the development of the Precertification Program. However, many stakeholders, including most physician organizations, were either not aware of these ongoing efforts or, alternatively, did not understand the significant changes to current health care delivery that SaMD will enable, the potential risks and benefits, and the implications of the unfolding FDA initiative. At this critical juncture, given the potential of SaMD to drive transformation and its widespread and rapid adoption, the FDA should allocate time for an intensive effort to onboard the full continuum of stakeholders to this process, including physicians and the organizations that represent them. Furthermore, given the very short timeframes in which FDA is requiring feedback on these increasingly detailed proposals, physician organizations may have difficulties in gathering input from their members and submitting adequate feedback to FDA. **The AMA frequently serves as a convener of state medical associations and national medical specialty societies in close collaboration with other federal agencies to ensure meaningful engagement and feedback on mission critical priorities.** For example, at the request of other federal agencies the AMA frequently convenes meetings in our Washington, DC office for federal officials with the national medical societies. **The AMA would welcome working with the FDA to ensure increased physician and national medical specialty society involvement.**

Physician organizations have the capacity to provide helpful substantive feedback on all of the components of the proposed Precertification Program and will need to play a key role if the Precertification Program is to engender trust and successfully scale. The foregoing is best demonstrated by the American College of Radiology's (ACR) Data Science Institute (DSI). ACR has been a pacesetter in recognizing the impact SaMD and software in a medical device (SiMD) have on medical practice in radiology. DSI will be well-positioned to provide independent third-party validation with the requisite expertise and capabilities to augment the Agency's capacity as part of a final Precertification Program. There will be a similar need for other physician organizations individually or in concert with other stakeholders to provide capacity and expertise in other clinical areas.

The AMA urges the FDA to schedule, prior to launching the Precertification Program, an intensive stakeholder education and engagement with physician organizations, including national medical

specialty societies, to place them on an even field of engagement with developers. The foregoing will ensure that the Precertification Program is well-vetted and stress-tested by a large cohort of end-users. It will also enhance the likelihood that the FDA will garner support of stakeholders with substantial clinical expertise, knowledge of workflow constraints in clinical practice, and access to and understanding of available data sources and potential bias. Furthermore, physician stakeholders' support will be essential when the FDA seeks regulatory and/or legislative changes as well as for the overall acceptance and success of the program.

PRECERTIFICATION PROGRAM COMMENTS

The AMA appreciates the materials that the FDA has issued related to the Precertification Program. Below are preliminary responses and feedback. However, these responses are necessarily conditional as a number of components remain under development and the interlocking nature of the Precertification Program components means that an alteration of elements within one component could change the AMA's response.

Excellence appraisal and precertification

The FDA proposes to evaluate applicants for precertification based on a culture of quality and organizational excellence (CQOE) as demonstrated by five excellence principles—patient safety, product quality, clinical responsibility, cybersecurity responsibility, and proactive culture. These principles are relevant and appropriate. The FDA also provides that a requirement for precertified organizations will include the capacity and commitment to collect real world performance data of marketed SaMD products related to safety, effectiveness, and performance. The AMA strongly supports this requirement and considers it to be an essential and necessary prerequisite to any other requirement in the precertification program.

To assess whether an applicant meets the CQOE, the AMA agrees that the FDA should utilize relevant existing standards where possible and should account for varied size of applicants. An example of the foregoing would be the National Institute of Standards and Technology's (NIST) Framework for Improving Critical Infrastructure Cybersecurity (Cybersecurity Framework) as briefly described below:

This voluntary Framework consists of standards, guidelines, and best practices to manage cybersecurity-related risk. The Framework is comprised of multiple modules and utilizes a common organizing structure while still allowing for flexibility—enabling organizations to implement differing aspects of the Framework to account for their unique needs. Framework effectiveness depends upon each organization's goal and approach in its use. For instance, an organization can leverage it to create an overall assessment of cybersecurity-related risks, policies, and processes. Additionally, an organization can use it to measure and track specific outcomes, such as better management of cybersecurity with its suppliers or greater customer confidence. Effectiveness measures vary per use case and circumstance. Accordingly, the Framework leaves specific measurements to the user's discretion. Individual entities may develop quantitative metrics for use within that organization, but there is no specific model recommended for measuring effectiveness of use.

We use this Cybersecurity Framework as an example for two reasons. First, the Framework illustrates that there are widely recognized “gold standard” frameworks, processes, and programs available to support the proposed excellence principle on cybersecurity responsibility. Second, it is instructive as the FDA develops the Precertification Program overall. Conformance to these Framework standards means different things to different stakeholders. NIST’s Framework is an analog for the overarching FDA goal to balance flexible excellence principle demonstration with the need to ensure an appropriate level of consistency and structure across organizations seeking precertification.

The AMA supports consideration of “conformity assessments” that leverage trusted independent third-party organizations to validate that a product, service, or system meets specified requirements. Each organization would retain flexibility in meeting requirements, with the output of the assessment activity being used to demonstrate an organizations’ commitment to a framework, process, or program’s standards. Properly structured conformity assessments could provide a needed level of confidence, are efficient, sustainable and scalable. Furthermore, implementation of recognized frameworks, processes, or programs should drive the conformity assessment activities that will address the confidence and information needs of stakeholders. This will require specific attention on process transparency. While testing, certification, and inspection are typical assessment methods, we also recognize the FDA’s desire to streamline organizational precertification. The AMA recommends that the FDA work with expert groups, such as, but not limited to, the Healthcare Sector Coordinating Council Cybersecurity Working Group’s Regulation and Policy Task Group in refining this approach.

A number of the proposed metrics discussed during the *Fostering Digital Innovation: Developing the Software Precertification Program Public Workshop* could be appropriate for assessing whether an applicant should qualify for the Precertification Program. However, from the end users’ perspective, the key metrics for the Precertification Program that should carry significant weight will measure whether an applicant has a proven track record of deploying quality SaMD. Appropriate metrics (discussed at the Public Workshop) to assess the foregoing include (but are not limited to):

usability testing results; outputs from human factors studies; responsiveness to end-user reported issues; end-user satisfaction metrics; timeliness of product and service delivery; rate and severity of reported serious or critical adverse events; responsiveness to safety concerns of end-users; end-user engagement and retention rates; integration into healthcare delivery systems; percentage clinical findings that undergo independent review; product defect rates; rate of product returns; products and services are promoted and marketed to optimize end-user experience and end-user understanding of intended use; data are collected to assess end-user understanding of intended use of the product; organization proactively anticipates accurate staffing needs; end-user experience is optimized, and safety issues are monitored, managed and mitigated; and, the availability of multiple channels of communication for end-user to provide feedback on products and services.

Because an established track record of quality SaMD is important, the AMA has reservations with the creation of two certification levels. The AMA supports precertification for an applicant with documented robust quality systems and demonstrated experience in health. However, there has not been a sufficient discussion of and/or examples of applicants that should receive precertification where the applicant has a robust quality system, but has no or little demonstrated experience in health care. As this will be a new program, a two-tiered system could create another layer of differentiation that end-users are unlikely to

understand or appreciate, particularly when applied to the already complex proposed risk categorization framework and review pathways. This also seems to undercut the goal of establishing an imprimatur of excellence on the Precertification Program designation. By the same token, the AMA does not support establishing “pending” precertification designations.

In light of the foregoing, the AMA asks the FDA to share how the Agency expects the above safeguards would impact entry for differently sized developers. Although the AMA strongly urges the FDA to provide flexibilities that will ensure that smaller developers are able to participate in this alternative program, this is conditioned on an assurance that safety risk is not shifted to end-users, such as physicians and patients. We also urge the FDA to consider how third-party validators structured similarly to the ACR’s DSI could prove an essential resource to smaller developers. Similarly-structured initiatives offered by other physician organizations could advance the goal of fostering a diverse and robust ecosystem of innovators through transparent standards, SaMD use case ideation and stress testing, software validation, and, in some instances, post-market surveillance including data access and facilitation. This is another reason to onboard physician organizations at this stage before the FDA’s launch of the Precertification Program as scaling up such initiatives will also take significant planning, resources, and time.

In addition, the FDA has not elaborated on the specific risks associated with SaMD using artificial intelligence (AI) methods and systems (which the AMA refers to as augmented intelligence) where the algorithms can be altered through continuous learning. To the extent that developers utilize AI systems, such as deep learning and neural networks, the FDA may need to establish different risk designations, post-market capabilities requirements, and labeling. The FDA should also consider the need for differentiation in other precertification excellence principles in addition to the post-market capability requirement. Efforts are underway and are supported by the physician community to ensure that current “black box” AI can be engineered to provide transparency so that, at a minimum, developers know how the algorithm produced the intended output and end-users (clinicians and patients) will understand the relevance, validity and reliability of the algorithm output. As part of its principles of excellence, the FDA should prioritize such transparency for SaMD leveraging AI systems.

Product Specific - level risk categorization & review pathway determination

The AMA has reviewed the FDA’s SaMD guidance documents that incorporate the International Medical Device Regulators Forum guiding principles for regulation of SaMD. The AMA understands the need to advance international harmonization and supports such efforts. However, we are concerned that the proposed risk-stratification for determining the review pathway may not be appropriate, particularly to the extent that the FDA establishes two levels of precertification. The complexity is challenging to assess without specific examples for each level of review, risk subtype, and whether what is under review is an initial product or a major or minor change to an already approved product. **To the extent that the FDA is able to share specific examples, the AMA would welcome an opportunity to provide a more detailed response that includes feedback from the perspective of varied medical specialties and medical practices.**

The AMA supports the requirement that prior to product launch (pre-market) the developer must generate and provide evidence of the product’s accuracy, specificity, sensitivity, reliability, limitations, and scope of use in the intended use environment with the intended user, and generates a SaMD definition statement. The AMA also generally supports a risk-based approach where an independent review of

clinical evidence of certain low-risk SaMD may be less important and the developer may “self-declare” the appropriateness of the evidence, subject to post-market assessment. The AMA also agrees that independent review of clinical evidence of more high-risk SaMD is more important in providing end-users the confidence in the SaMD performance metrics, including but not limited to, identification of design errors or limitation, broadening technical competence, testing the appropriateness of assumptions, and management of bias.

The AMA strongly urges the FDA to consider that it may be necessary to more fully evaluate not just risks associated with the developer’s intended use, but also include an assessment of potential expected uses. Unlike other devices such as implantable devices used by surgeons, SaMD could more easily be used in ways that the developer did not intend, including by end-users not specified, but which are reasonably foreseeable. For example, we are concerned by suggestions in social media that individuals could be diagnosed without physician input using an AI-based device to detect certain diabetes-related eye problems. While labeling ostensibly is designed to address this problem, it is magnified in the context of SaMD due to the difficulties associated with labeling the “product” in order to ensure appropriate notice to end-users. This underscores the pressing challenge of unwarranted hype around health care AI in particular and the potential for misuse beyond the intended use.

It is clear that an in-depth discussion is needed to better understanding labeling requirements and the necessary elements that should be disclosed, particularly for SaMD systems that utilize AI systems that allow continuous learning. For all precertification SaMD, labeling must include clear designation that it is from a precertified developer and went through the precertification pathway. It is important, therefore, for widespread buy-in from national medical specialty societies and other physician organizations that the Precertification Program represents quality SaMD.

Real World Performance (post market surveillance)

From the AMA’s perspective, qualification to participate in the Precertification Program hinges on the capacity and commitment to collect and share with the FDA or independent third-party validators real world performance data of marketed SaMD products related to safety, effectiveness, and performance. The AMA agrees that SaMD presents unique challenges, including:

- SaMD might behave differently when deployed to different hardware platforms.
- Updates made available by the developer could be left to the user to install.
- Due to its non-physical nature (key differentiation), SaMD may be duplicated in numerous copies and widely spread, often outside the control of the developer.

The foregoing underscores the need for well-crafted, strategically developed and scaled, reusable post market capabilities to assess real world performance and to quickly address adverse events or other SaMD related errors or bugs that negatively impact use of SaMD as intended. **While the AMA understands that this will be more fully vetted in the next Precertification Program draft that the FDA will issue, we would welcome a joint briefing by the FDA and the National Evaluation System for health Technology (NEST) leadership.** Specifically, we would like to more fully understand the shared expectations for NEST’s role and timeline for scaling in building post-market active sentinel capabilities for the Precertification Program. We also urge the FDA to plan to meet other stakeholders that are essential sources of real world data. The AMA is able to assist with this dialogue.

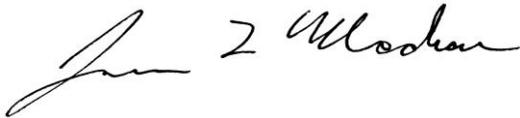
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The AMA applauds the vision and effort that the FDA has put forth to advance an alternative pathway for SaMD oversight. **We welcome the opportunity to work closely with you in the next year to increase the engagement of the physician community in this critically important FDA initiative.** The health care landscape will change rapidly and SaMD will drive a significant part of that change. Physicians and other clinicians along with patients and consumers will need to play a far more informed and active role in this oversight model. We look forward to further discussion. Please contact Shannon Curtis, Assistant Director, Division of Federal Affairs at 202-789-8510 or shannon.curtis@ama-assn.org, so we are able to arrange regular engagement with physician organizations as the Precertification Program is developed.

Sincerely,

A handwritten signature in black ink, appearing to read "Jim L Madara". The signature is written in a cursive style with a large, sweeping initial "J".

James L. Madara, MD