May 31, 2018

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

Re: (Docket: FDA-2017-N-4301) U.S. Food and Drug Administration Software Precertification Program (v0.1); Comments of the American College of Radiology

The American College of Radiology (ACR)—a professional organization representing more than 35,000 radiologists, radiation oncologists, interventional radiologists, nuclear medicine physicians, and medical physicists—appreciates the opportunity to comment on the Food and Drug Administration's (FDA) Software Precertification Program (v0.1 - April 2018). The ACR supports the FDA's goal of reimagining a Software As a Medical Device (SaMD) regulatory paradigm that facilitates innovation, promotes efficiency and the least burdensome approach, ensures the clinical safety and effectiveness of products, and enables ongoing post-market assessments of real world performance.

ACR Data Science Institute

The ACR established a Data Science Institute (DSI) program in 2017 to collaborate with physicians, patients, industry leaders, and federal agencies to develop a framework for implementing machine learning/augmented intelligence in medical imaging, interventional radiology, and radiation oncology. The ACR DSI is working to define use cases and associated data elements to analyze AI algorithm performance across multiple sites and to provide clinical validation/certification prior to FDA review. ACR DSI is also engaging with developers on workflow integration/deployment considerations and to enable registry-based post-market data collection to assist developers with compiling and reporting real world performance data to FDA.

To that end, the ACR is working with FDA on a proposal to leverage the ACR DSI's third-party validation process as a future Medical Device Development Tool (MDDT) to inform FDA's review of software that uses AI/machine learning methods. ACR is also collaborating with FDA and the National Evaluation System for Health Technology Coordinating Center (NESTcc) on a demonstration to determine the end-

to-end workflow from deployment of an AI algorithm in a radiology reporting system through capture of performance metrics within a national registry. NESTcc selected the "Lung-RADS Assist: Advanced Radiology Guidance, Reporting and Monitoring" use case among its first projects. We believe that these and other promising FDA programs/initiatives can be leveraged in SaMD streamlined reviews and real-world performance assessments.

General Recommendations

Third Party Participation In the Software PreCert Paradigm

The ACR recommends that FDA incorporate qualified, clinician-led, third-party validation/certification services as a component of the streamlined review process for SaMD from precertified companies. Additionally, the ACR recommends that FDA and precertified companies leverage national clinical data registries, such as those administered by specialty societies, as a component of the real world performance data (RWPD) assessment and reporting loop. We believe the availability of these options could reduce FDA's and precertified developers' burden during the pre-market review and post-market surveillance activities for SaMD. Moreover, third-party validation and performance monitoring would increase healthcare providers' trust, market adoption, and successful clinical workflow integration of new and innovative SaMD—particularly for algorithms that leverage machine/deep learning methods to provide augmented intelligence functionalities to clinicians.

Need for Adequate SaMD-Specific Review/Assessment for Higher Risk SaMD

While company-based appraisals could be useful for helping determine whether their SaMD submissions are able to take advantage of the reimagined regulatory pathways in the Software Precertification Program, the overall success of this initiative will hinge on the ability of FDA to adequately ensure the safety and effectiveness of specific SaMD submissions via a combination of streamlined review and real world performance assessment—not on the appraisal component of the program. Because of this, FDA should require some level of review for all initial products and all major updates of higher risk SaMD that involve diagnosis/treatment or drive care management, regardless of the developer's level of precertification. The coverage and requirements of premarket review can be commensurate with the company's precertification level, type and intended use of the SaMD, extensiveness of post-market assessment commitments, participation in third-party validation and/or assessment programs, and other considerations. Additionally, FDA must ensure a proactive and robust post-market surveillance/RWPD-reporting paradigm to facilitate ongoing assessment and SaMD improvement, as well as to alert regulators, developers, and stakeholders to concerning trends.

Consider Impact of Using Precertification Level as a Driver of the Review Pathway Determination

A potential unintended consequence of focusing on a company's precertification status (i.e., level 1 or level 2) as a primary driver of the SaMD "review pathway determination" rather than focusing exclusively on SaMD-specific considerations is that small developers new to FDA's medical device regulatory process may be disadvantaged as compared to larger firms with extensive resources and those that have a long history of FDA medical device submissions. Decreased time to market for new SaMD solutions could provide a competitive advantage for level 2 precertified companies over SaMD

developed by level 1 precertified companies. Any such bias would be inequitable and could possibly hamper innovation without offsetting benefits in terms of ensuring the safety and effectiveness of the SaMD in question.

Instead, the FDA should take steps to make sure all appropriately precertified companies will be on equal footing from the outset of the program—perhaps by eliminating the two-level proposal for Pre-Cert status or by eliminating the proposed differences in the plan regarding when precertified companies can take advantage of "no review" versus "streamlined review." Most importantly, we recommend that premarket and post-market regulatory requirements for SaMD from precertified companies be driven by SaMD-dependent variables.

Responses to Select Challenge Questions

Section 1: Excellence Appraisal

1.7. How might an excellence or maturity assessment balance the FDA's "least burdensome" approach with the obligation to assure stakeholders that SaMD are safe and effective?

Precertification status by itself will be unlikely to assure healthcare providers and members of the public that specific SaMD products developed by precertified organizations are safe and effective, particularly for SaMD above Type I intended to diagnose/treat or drive care management. We urge FDA to consider precertified status the determinant of whether or not companies are able to leverage the benefit of streamlined review pathways for higher risk SaMD—not as a substitute for any degree of SaMD-specific premarket review. This is particularly true for any SaMD viewed as new/emerging technology lacking clinical validation by a trusted entity.

1.10. Are there specific approaches to developing SaMD, such as machine learning and artificial intelligence, that raise different considerations with respect to the excellence principles, e.g., such that the appraisal would be different and/or precertification for the company based on processes/culture using one technology should not apply to other SaMD development methods? Why or why not?

The ACR believes that streamlined reviews and real world performance assessments of SaMD are more critical components for ensuring the safety and effectiveness of machine learning/artificial intelligence solutions than the precertification status, level, or adherence to excellence principles of the precertified organization submitting the SaMD for FDA review.

For higher risk SaMD leveraging machine learning/deep learning methods, FDA must require an adequately extensive premarket review process, which could include third-party clinical validation where feasible in order to augment FDA's review efforts and reduce the burden for all involved. Key components of algorithm validation processes/certification services provided by third parties can be reviewed and qualified through other FDA initiatives, such as the MDDT program.

Additionally, FDA must ensure that higher risk functionality—such as SaMD types intended to diagnose/treat—are subject to extensive, multi-layered post-market surveillance, including leveraging qualified data registries such as those administered by national physician associations. The overall real

world performance assessment portfolio employed by developers should include the key ability to identify and promptly relay information on sentinel events and other safety concerns to regulators and customers. There is likewise a need for transparency and explicability of the outputs, particularly in terms of healthcare AI/machine learning/deep learning functionality.

Section 2: Review Pathway Determination

2.5. How should FDA think about a major change versus a minor change for SaMD, and about how these changes should be handled?

For certain SaMD, identification of the circumstances of real world software failures identified through post-market evaluation could be used by developers to retrain, test and revalidate their products so that the algorithm would be more generalizable to broad practice settings. These updates would not need additional review. If the developer adds a new specific feature to the algorithm, then premarket review of the new feature should be obtained.

2.7. Should FDA be informed about new products, major changes, and minor changes from precertified organizations that do not undergo premarket review, and if so, how?

If a given solution meets the "medical device" definition, per the clarifications in the recent 21st Century Cures Act, it is reasonable for FDA to collect information on the product in question even when the initial launch is not subject to premarket review—however, this may not be practical for all lower risk SaMD.

If a given SaMD launch product is subject to premarket review, subsequent updates should be catalogued/tracked in some fashion by FDA. SaMD submitted by precertified companies/units will be subject to continuous real world performance assessment, thus FDA will need to understand the current status of those products to know when there may be cause to examine the real world performance more closely (and to request updated RWPD reports).

Section 3: Streamlined Review

3.1. Given that one goal of this program is to significantly reduce the average premarket review timeline, what would be the best way for precertified companies to share product review information with us? Specifically:

> ***3.1.1. What specific elements of review could be shifted to the company-specific excellence appraisal (as opposed to the product-specific review)?***
>
> For SaMD subject to premarket/streamlined review, the FDA's requirements to make a safety and effectiveness determination should be commensurate with the SaMD type/subtype, risk level, intended use, post-market surveillance commitments of the developer, and other considerations. The company's precertification status could inform the availability and extensiveness of streamlined review, but should not categorically substitute for entire elements of review. Physicians, patients, and other stakeholders would typically expect FDA-reviewed SaMD to be determined, on a product-specific basis, safe and effective.

3.1.3. What product-specific content would be expected to be reviewed premarket?

SaMD should be reviewed for clinical need and validated in accordance with FDA's *SaMD: Clinical Evaluation* guidance. SaMD leveraging AI/machine learning/deep learning methods should be validated using datasets that differ from training datasets (as opposed to a subset of the training dataset), preferably using validation services provided by independent and qualified third parties where feasible. SaMD should also be reviewed for cybersecurity and other considerations.

3.1.4. What specific postmarket real world data could be collected to support the assurance of safety and effectiveness for each product if an element is not reviewed premarket?

The requisite post-market data requirements would vary depending on the specific SaMD and potentially include safety data, results from performance studies, other clinical evidence generated on an ongoing basis, new research publications/results that support or strengthen the clinical association of the SaMD output to a clinical condition, and direct end-user feedback. For certain SaMD types it would be generally reasonable for non-reviewed launch products and updates to require a higher level of post-market RWPD reporting.

3.1.5. What updates should FDA require, and at what interval, to provide continuous assurance of safety and effectiveness?

The extensiveness and time interval between RWPD reports/SaMD updates should generally be decided by the FDA on a product-specific basis. It is critical for algorithms that leverage machine learning to improve post-market release to be closely assessed on a continuous basis with regular RWPD reports to FDA. This feedback loop can be made less burdensome for developers and FDA by leveraging clinical data registries and services provided by qualified third parties, such as national specialty societies, as part of the overall post-market surveillance strategy for the SaMD in question.

3.2. Beyond number of days, what are additional key factors important for a successful streamlined review?

The streamlined review component of the Software Precertification Program will be successful if it is able to consistently ensure the clinical need, validity, safety and effectiveness of the SaMD while simultaneously reducing the burden of premarket review experienced by precertified developers and FDA reviewers. We believe the key to the least burdensome approach in this regard is to leverage qualified third party validation/certification services where feasible.

3.3. Once a review decision is made:

3.3.2. Should the public know that a product comes from a precertified company and if so, what is the best way to share that information?

The precertification status of the company is only relevant to FDA's regulatory processes and would not typically be viewed as a pertinent piece of information for end-users or members of the public. If FDA chooses to announce the precertification of companies/units or to allow developers to feature their company's precertified status in product marketing/labelling, it

would be critical that the agency educates stakeholders about what precertification does and does not mean. In particular, it is critical to avoid any public perception that a given SaMD solution is safe and effective based solely on a precertified company's appraisal/status. It is also critical that liability associated with SaMD from precertified companies not be shifted to end-users as a result of regulatory pathway modifications.

3.8. Is premarket clinical performance necessary to assess SaMD safety and effectiveness? Please explain your answer and provide your rationale.

For SaMD above Type I, we believe it is necessary to review premarket clinical performance to assess safety and effectiveness, particularly if the SaMD in question provides new functionality of a variety not yet adopted and trusted in clinical practice. The SaMD products potentially subject to FDA premarket review and their associated levels of risk will vary, and it will be necessary for FDA in dealing with higher risk algorithms to have confidence in how those solutions perform in various clinical settings using input data from diverse patient populations.

Section 4: Real World Performance

4.1. As FDA conducts a landscape assessment of existing RWPD frameworks and use cases, what are important sources of information and stakeholders to include?

FDA should include national physician associations/specialty societies, research agencies/clinical investigators, and third-party validation/certification organizations in future landscape assessments of existing RWPD frameworks and use cases. Sources of data should include not only information about efficacy of the SaMD in clinical practice as determined by the end users, but also metadata about the examinations so that the specific circumstances around SaMD failure can be analyzed to determine if there are any trends or opportunities for more specific algorithm training. The American College of Radiology's Data Science Institute would be pleased to provide input into the development of FDA's approach to RWPD assessment/reporting.

4.3. What are critical RWPD elements to be monitored by SaMD manufacturers?

Per the *SaMD: Clinical Evaluation* guidance, SaMD manufacturers should monitor any RWPD that verifies the safety and effectiveness of the SaMD when used as intended; the validity of the clinical association between the output and the targeted clinical condition; and the ability of the SaMD to correctly process input data into accurate, consistent output data that achieves the intended purposes in the targeted populations and contexts of care. SaMD manufacturers should ideally partner with third-parties, such as national specialty societies with robust data registry capabilities, to aid in the continuous assessment and reporting of various RWPD.

4.7. RWPD can come in different shapes and sizes. Should RWPD requirements depend on the risk level of the intended product claim or modification in claims?

RWPD requirements, including the interval between reports of RWPD to FDA, should depend on the risk level of the SaMD type, including the intended product claim and other determinations—such as the manner by which the algorithm is updated over time (e.g., manually coded improvements or automated/machine learning, etc.). The data elements that should be collected in RWPD assessments

will be specific to each algorithm use case. The output of the algorithm should have data elements that specify what specific parameters should be collected in addition to end user assessment of SaMD performance. These parameters, including end user assessment, should be collected in the background and not interrupt the clinical workflow of the physician.

4.9. How can FDA and SaMD manufacturers ensure that least burdensome principles are applied in collecting real world data? That is, what is the minimum amount of RWPD necessary to adequately determine precertification through the most efficient manner at the right time?

In order to best adhere to the agency's least burdensome principles, FDA and SaMD manufacturers should leverage trusted/qualified third parties, such as national specialty societies with robust clinical data registries, to assist with RWPD collections, assessments, and reporting. The minimum amount of RWPD necessary to inform SaMD pathways should be primarily dependent on SaMD-specific variables.

Developing standards for real world data collection should be championed by the FDA. Requiring algorithm outputs be interoperable with existing electronic resources and specification of common data elements will ensure that data collection can occur in the background without being burdensome to physicians or their health systems.

4.11. Should an organization that meets a higher level of precertification have the same requirements for RWPD monitoring as an organization at a lower level of precertification and why?

The level of requirements for RWPD monitoring/reporting should be SaMD-specific because safety and effectiveness should ultimately be determined on a product-specific basis. I.e., the real world performance of one SaMD from a level 2 precertified organization may have little bearing on the real world performance of another SaMD from the same organization. Moreover, SaMD from a level 1 precertified company involves the same concerns and RWPD monitoring needs as similar SaMD functionality provided by a level 2 precertified company.

Thank you for your consideration of these comments. The American College of Radiology and its Data Science Institute welcome the opportunity for continued dialog with FDA and SaMD manufacturers regarding the development of FDA's Software Precertification Program. Please contact Gloria Romanelli, JD, ACR Senior Director of State and Regulatory Affairs, and Michael Peters, ACR Director of Legislative and Regulatory Affairs, at (202) 223-1670 | mpeters@acr.org.

Sincerely,

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