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VIA ELECTRONIC SUBMISSION

May 31, 2019

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

Re: Docket No. FDA–2019-N-1185: Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning ("AI/ML")-Based Software as a Medical Device ("SaMD") - Discussion Paper and Request for Feedback" dated April 2, 2019 (the "Discussion Paper"). The CPC applauds FDA's efforts to solicit feedback from stakeholders before formalizing the AI/ML regulatory framework in a draft guidance. Overall, the CPC believes that the Discussion Paper represents a positive step forward in clarifying FDA's expectations for application of AI/ML for SaMD, which are not currently described in other guidance documents.

The CPC has carefully evaluated FDA's proposed approach on AI/ML and although we believe the proposed approach is well-constructed, we ask that the Agency consider the following general comments, as well as our specific responses to the questions posed by FDA, which are provided below.

- The scope of applicability of AI/ML to healthcare is not yet known; however, based on industry's early understanding, we can predict that this technology will have a fundamental impact on how we execute clinical trials, interpret clinical data, and help inform healthcare practitioners of ideal therapies for patients. The CPC notes that the scope of the Discussion Paper is quite narrow and is essentially limited to how the medical device industry should plan for post-market changes to AI/ML SaMD after clearance through a single premarket pathway (510(k) premarket notification). Class III AI/ML SaMD can and should be able to

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

take advantage of this proposed regulatory framework. The CPC requests that FDA compose any future discussion papers on AI/ML to consider broader and more pressing issues around AI/ML, including use of AI/ML in interpreting real-world and well-controlled clinical data as well as human understanding and interpretation of AI/ML algorithms, and the extent to which those algorithms must be understood for the manufacturer and regulator to make an appraisal of safety and efficacy.

- The CPC requests that FDA address the critical question of when a continuously adaptive AI/ML may require a premarket submission, as the proposed framework currently addresses only incremental learning algorithms with gating mechanisms for updates. Given the rapid advances in AI/ML in recent years, and its great potential applications to medicine, the CPC believes a framework for such software will be necessary in the near future.

- The CPC further requests that any future discussion papers on AI/ML, as well as any other topic papers or communications related to digital health, involve the Center for Drugs Evaluation and Research ("CDER") and the Center for Biologics Evaluation and Research ("CBER") and include considerations around systems that achieve or influence use of drug and biological products. The CPC urges FDA to develop coordinated and consistent digital health policies across FDA centers to reduce regulatory burdens and support digital health innovation that ultimately helps patients.

- As AI/ML has been developed and deployed by other industries where safety critical aspects must be considered (e.g., the automotive industry), the CPC strongly recommends that FDA learn from these industries to adopt best practices and apply the appropriate aspects of these practices to AI/ML systems for medical purposes.

- The CPC recommends that FDA address the least-burdensome approaches for AI/ML SaMD in the future guidance, similar to language used throughout the FDA Software Precertification Working Model. Specifically, FDA should provide clarity in what least burdensome AI/ML submissions from industry look like throughout the product lifecycle. Clarity is needed to ensure that the submissions include "the minimum amount of information necessary to adequately address a regulatory questions or issue." This approach will ensure good use of FDA's resources and timely access of life-saving AI/ML SaMD to patients who need them.

Responses to FDA's Specific Questions

Questions / Feedback on the types of AI/ML-SaMD modifications

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?**

   Generally yes, the high-level categories of AI/ML-SaMD modifications align with the modifications that would typically be encountered in software development. However, additional specificity is needed when discussing the intended use of software. Intended use is a broad regulatory concept. We would suggest adoption of a term such as 'software functionality' to describe changes to functions and features of software. Often, a SaMD manufacturer might add a new function, but might not translate that function to a high level claim or intended use of the device. Additional detail around how industry should or must consider new software functions as new 'intended uses' should be provided.

2. **What additional categories, if any, of AI/ML-SaMD modifications should be considered in this proposed approach?**

   The categories of changes described in the Discussion Paper are central to the AI/ML aspects of software functionality; however, it is possible that future SaMD will have AI/ML and non-AI/ML functions as well. The Discussion Paper does not explicitly discuss how changes to more traditional medical device functions and claims should be evaluated when a portion of the system is not related to AI/ML.

3. **Would the proposed framework for addressing modifications and modification types assist the development AI/ML software?**

   While the proposed framework is useful in understanding FDA's current thinking for AI/ML changes, the Discussion Paper does not directly account for past categorizations of software changes as outlined in FDA's guidance, "Deciding When to Submit a 510(k) for a Software Change to an Existing Device." This document contains several change categories and flowcharts that do not appear to have been considered within the Discussion Paper. Therefore, it is not clear how industry should plan for regulatory evaluation of post-market changes using both of these resources.

   To ensure the utility of the upcoming guidance, we ask that FDA include within the document a flow diagram that clearly depicts examples of AI/ML-based software modifications which do not require a new submission and those that will require a new submission.

Questions / Feedback on GMLP:

4. **What additional considerations exist for GMLP?**

   AI/ML-based SaMD can be associated with drugs, whether as a drug-device combination product or when AI/ML-based SaMD otherwise references a drug. The Discussion Paper's

proposed framework does not discuss how FDA would regulate AI/ML-based SaMD associated with drugs.

It is presently unclear whether CDRH believes the considerations in the Discussion Paper apply in full to device-led, drug-device combination products with an AI/ML-based software component, where the software associated with a drug is not a device or where the software references drugs marketed by third-party drug manufacturers. The Discussion Paper also leaves open the question of whether FDA will regulate clinical and patient decision support tools that utilize AI/ML-based software that evolve over time and include recommendations about pharmaceuticals.

In summary, the CPC recommends that FDA clarify how the proposed Discussion Paper interacts with CDER and CBER's proposed approach to digital health issues, including Prescription Drug-Use-Related Software ("PDURS"). The CPC also recommends coordination between center-specific frameworks for regulating AI/ML-based software to ensure consistent treatment of AI/ML-based software products, including software disseminated by or on behalf of a drug sponsor.

5. How can FDA support development of GMLP?

Development of a GMLP should involve key stakeholders from industry, academia, and FDA. As such, FDA should consider holding public workshops and webinars to examine real-world case studies and encourage dialogue between the key stakeholders. This will ensure robustness and utility of the GMLP.

Furthermore, we ask that FDA also consider the following CPC recommendations:

- Endorse and further support proliferation of Office of the National Coordination for Health Information Technology ("ONC") driven interoperability standardization efforts, and provide incentives for device manufacturers to participate and benefit from such activities (Fast Healthcare Interoperability Resource ("FHIR") proliferation etc.)
- Support training for hospitals around good practices for data integrity, and perhaps start to regulate those practices so that all stakeholders can benefit from "clean" data.
- Establish guidance for manufacturers on how to handle "user errors" and poor data integrity practices.
- As AI/ML has been developed and deployed by other industries where safety critical aspects must be considered (e.g., the automotive industry), the CPC strongly recommends that FDA learn from these industries to adopt best practices and apply the appropriate aspects of these practices to AI/ML systems for medical purposes.
- Provide clarification on how a manufacturer should apply existing design controls and lifecycle management principles (which are general and intended to apply to all devices) to AI/ML SaMD.

6. How do manufacturers and software developers incorporate GMLP in their organization?

The FDA model for the Total Product Lifecycle ("TPLC") Approach to the Regulation of AI/ML-Based SaMD involves the following four elements: (1) culture of quality and organizational excellence through the proposed SaMD manufacturer pre-certification program, (2) premarket assurance and safety and effectiveness, (3) review of SaMD pre-specifications and change protocol, and (4) real-world performance monitoring. Relative to the current 510(k) regulatory paradigm, one should note that item (2) remains the same while items (1), (3), and (4) are new requirements placed on SaMD manufacturers. On the surface, the TPLC approach proposed by FDA for AI/ML-based SaMD appears reasonable, though we are concerned that the actual implementation of this TPLC approach could be unduly burdensome for both FDA and SaMD manufacturers.

For example, details of the pre-certification program to ensure a "Culture of Quality and Organizational Excellence" are at an early pilot stage based on a limited dataset of manufacturers. It appears that the purview of SaMD pre-specifications and change protocol will be a critical element during FDA review of AI/ML-based SaMD. However, SaMD sponsors and FDA have little experience submitting and reviewing this type of information. As FDA develops specific guidance related to AI/ML, the CPC strongly encourages FDA to post "real-world" examples and case studies to provide additional clarity for developers.

Finally, 510(k) SaMD products currently do not have an annual reporting requirement and it appears that item (4) – Real World Data Monitoring – is a step towards 510(k) product up-regulation. The CPC recommends piloting of a Real World Data Collection Program to demonstrate its benefits relative to the increased regulatory burden to both FDA and the SaMD sponsor for mandatory post-market surveillance reporting for all SaMD products. In summary, FDA's TPLC approach toward SaMD seems reasonable at first glance, but it appears that the approach is a significant "up-regulation" compared to the current 510(k) regulatory paradigm.

Questions / Feedback on SPS and ACP:

7. What are the appropriate elements for the SPS?

FDA's suggested principle of a "predetermined change control plan" is appropriate for AI/ML SaMD systems. In defining the types of anticipated modifications to the system, the SaMD Pre-Specifications ("SPS"), the CPC's recommendations below align with FDA's statements in Section II of the Discussion Paper, which note that "the rigor of performance evaluation for both locked and continuously adaptive algorithms depend on the test methods, quality and applicability of dataset used for testing, and the algorithm's training methods," and that "[r]obust algorithms typically require the availability of large, high-quality, and well-labeled training data sets."

Recommended elements for the SPS include:

- Detailed description of the initial training sets used;
- Detailed description of any additional training sets used after deployment;

- Documentation of the detailed data requirements;
- Documentation of the defined "safe behaviors" within which the ML component must operate (i.e., what "boundaries" has the manufacturer placed on the system, based on their risk management plan, to ensure that the ML component(s) cannot operate in a way that would create a patient safety hazard);
- Documentation of identified hazards and post-deployment hazards that have been identified;
- Description of identified faults and failure modes and any that have been identified post deployment;
- Description of the baselines used for comparison of any classifiers in any ML component(s);
- Description of the methods and results of statistical significance testing of all ML components and the system; and
- Description of anticipated change to the SaMD risk categorization, core functionality, or performance.

8. What are the appropriate elements for the ACP to support the SPS?

In addition to the Algorithm Change Protocol ("ACP") overview provided in Figure 4 of the Discussion Paper, the CPC recommends that the Agency consider the following requirements for methods that a manufacturer should employ to appropriately control the risks of the changes made in the SPS:

- Methodology to describe the error rate associated with an ML model, including statistical methods and results;
- Method to establish how representative a training set is and risk management to address training sets that underrepresent safety-critical cases;
- As training sets are not "specifications," due to being incomplete by their nature, and training is not "verification," traceability should flow from high level requirements to detailed data requirements that ensure that appropriate training, validation, and testing sets are obtained;
- Use of fault detection tools and techniques that take into account the unique features of ML (e.g., complex interactions between linked ML components);
    - An example of a method would be to have redundant features use different ML models and training sets to detect potential failures when there is disagreement between the features;
    - Another example is to define a "safety envelope" of possible known safe behaviors and limit the ML component to choose only from among those;
- Establish safety requirements for ML functionality that is inherently unspecifiable (i.e., with the knowledge that they have an error rate and will periodically fail);
- Express requirements in terms of the intent and maturity of the technique being employed (i.e., because not all models are implemented using an imperative programming language);
- Ensure that preprocessing is consistent and uniform in its approach to the removal of outliers, incomplete data, or noise;

- Ensure that representative data are free of sampling bias (techniques to mitigate bias should be used); and
- Describe the methods and results of statistical significance testing.

9. What potential formats do you suggest for appropriately describing a SPS and an ACP in the premarket review submission or application?

The SPS and ACP should be submitted as part of the premarket review submission or application. FDA should place an emphasis on dedicated interactive review of such elements, enabling a SaMD developer to walk FDA through its proposals and iterating on changes to them prior to clearance or approval. The CPC recommends FDA apply a novel regulatory pathway for SPS and ACP to ensure a timely review process. For example, FDA's "real-time-review" ("RTR") regulatory mechanism, which routinely applies on PMA-approved devices, may be applied, with the exception that the RTR should be done in a much shorter timeframe.

Questions / Feedback on premarket review

10. How should FDA handle changes outside of the "agreed upon SPS and ACP"?

In Section IV, Subsection 4 (transparency and real-world performance of AI/ML-based SaMD), the Discussion Paper states that "FDA would also expect the manufacturer to provide periodic reporting to FDA on updates that were implemented as part of the approved SPS and ACP, as well as performance metrics for those SaMD." The CPC believes that if a SPS and ACP have been approved, the requirement for updating FDA seems redundant if the proposed approach in Figure 5 is to document this modification. The net effort of this requirement is notification instead of documentation.

The CPC recommends that all SaMD manufacturers establish a robust quality system that is inclusive of good machine learning practices and software risk management principles. For changes outside of the "agreed upon SPS and ACP," the CPC encourages FDA to apply a pragmatic, risk-based framework on lifecycle management for SaMD software. An effective regulatory framework that allows timely and efficient introduction of software changes is important to the quality, safety, and availability of innovative software products. It is acknowledged that software changes vary from low to high potential risk with respect to their impacts on product safety and/or efficacy. The regulatory reporting mechanisms associated with the changes should be commensurate with the potential risk.

11. What additional mechanisms could achieve a "focused review" of an SPS and ACP?

SaMD undergoes frequent refinements and, importantly, changes of Al/ML may occur in real-time. As such, the "traditional" regulatory pathway such as pre-submission is inherently not compatible with the rapid lifecycle management of SaMD. The CPC recommends that FDA utilize a novel regulatory pathway for SPS and ACP to ensure a timely review process. For example, as noted above, an RTR regulatory mechanism, which routinely applies on PMA-approved devices may be applied, with the exception that the RTR should be done in a much shorter timeframe.

12. What content should be included in a "focused review"?

The CPC recommends focusing on substantive changes of the approved SPS and ACP only. As such, the "focused review" should focus on (a) description of the proposed changes, and (b) rationales and the outcome of the risk assessments.

Questions / Feedback on the transparency and real-world performance monitoring:

13. In what ways can a manufacturer demonstrate transparency about AI/ML-SaMD algorithm updates, performance improvements, or labeling changes, to name a few?

The CPC recommends a risk-based approach to transparency requirements for AI/ML-SaMD modifications. Use of AI/ML-SaMD will generate vast amounts of data, and the adaptive, iterative nature of AI/ML-SaMD could result in continuous, incremental, minor modifications. The CPC recommends that transparency requirements consider when a significant "change" within FDA's benefit-risk framework would trigger a notice or a premarket submission to ensure unnecessary, voluminous information is not provided to FDA. FDA suggests periodic reporting on updates implemented as part of an approved SPS and ACP as well as performance metrics for AI/ML-based SaMD. FDA also suggests that updates may need to be shared with collaborators of the manufacturer and the public on changes that were implemented in accordance with the approved SPS or ACP. It will be important for manufacturers to understand when a change implemented within the scope of an approved SPS or ACP is sufficiently significant to trigger a reporting requirement, and when these will trigger a notice requirement to the user. The CPC recommends that FDA define how AI/ML-based SaMD modifications align with FDA's benefit-risk framework and International Medical Device Regulators Forum ("IMDRF") risk categorizations, which should inform the appropriate reporting requirements. For example, whether a modification is within the parameters of the approved SPS or ACP should also factor into the benefit-risk analysis.

The CPC agrees that transparency is important in ensuring the public is informed on how the SaMD functions, when substantive changes or improvements occur, and any limitations to the software in order to ensure patient safety and trust in using AI/ML-based SaMD. For those changes that do not trigger a label change or safety analysis, FDA and the manufacturer should agree on which modifications require notification to users, the method of communication, and frequency of the notice. The complexity of the software algorithm, the risk categorization of the SaMD, and target patient population should be considered in determining what information should be provided to users, clinicians and the public, and how that information should be delivered.

In addition to the reporting requirements, FDA expects manufacturers to commit to real-world performance monitoring of the AI/ML-based SaMD to further transparency. The CPC recommends that FDA clarify its expectations on real-world performance monitoring of AI/ML-based SaMD versus the real-world performance monitoring under the Pre-Cert Program. It is unclear whether manufacturers of AI/ML-based SaMD will need to *pre-certify*.

14. What role can real-world evidence play in supporting transparency for AI/ML-SaMD?

Real-world evidence can play a role in helping to validate and test AI/ML-SaMD and modifications to AI/ML-SaMD. As use of AI/ML-SaMD generates data, that data can in turn be used to test the algorithm's function to ensure continued reliability and trust in the SaMD. Additionally, the ability to communicate real-world evidence generated from use of the AI/ML-SaMD can be another important way to communicate its function and reliability to users, clinicians, and the public.

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

Post-market safety surveillance and reporting requirements are additional mechanisms to monitor the use and safety of AI/ML-SaMD. In addition, FDA states that manufacturers will be expected to commit to a TPLC approach to real-world performance monitoring for AI/ML-SaMD; however, it is unclear how this may differ from the real-world performance monitoring under the Pre-Cert Program. The Pre-Cert Program approach is still unclear with respect to how this information will be made available to FDA. The CPC recommends that FDA continue its engagement with stakeholders to clarify how real-world performance monitoring for AI/ML-SaMD may have similar or different data elements from the Pre-Cert Program.

16. What additional mechanisms might be needed for real-world performance monitoring of AI/ML-SaMD?

The CPC recommends piloting a Real-World Data Collection Program to demonstrate its benefits relative to the increased regulatory burden borne by both FDA and the SaMD sponsor for mandatory post-market surveillance reporting for all SaMD products.

Questions / Feedback on the ACP:

17. Are there additional components for inclusion in the ACP that should be specified?

- Consider using leave-one-out cross-validation as a mitigation strategy to latent information that is highly correlated to labels, annotations, or other supervised information; and
- Limit channel effects (e.g., spurious correlations due to the manner data were collected: limited clinical settings, geographies, patient populations, etc.) using statistical techniques like factor analysis.

18. What additional level of detail would you add for the described components of an ACP?

N/A

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We appreciate the opportunity to provide input on the proposed framework and are happy to meet with the Agency to clarify or discuss any of our suggested revisions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition