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Client Alert

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FDA Publishes Draft AI/ML-Enabled Medical Device Guidance. Is it Everything We Hoped?

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First mentioned in a 2019 discussion paper entitled "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)," the idea of a defined set of FDA expectations for AI/ML-based SaMDs centering on the use of a "Predetermined Change Control Plan" (or PCCP) has been widely discussed by industry for years. In January 2021, FDA committed to publishing PCCP guidance in the Agency's "Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan." Further, Section 3308 of the Food and Drug Omnibus Reform Act of 2022 added Section 515C to the Federal Food, Drug, and Cosmetic Act, which granted FDA authority to approve a PCCP "submitted in an application . . . that describes planned changes that may be made to the device . . . if the device remains safe and effective without any change."

Earlier this week, on April 3, 2023, FDA released the much-anticipated "Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions" draft guidance (PCCP Draft Guidance). FDA is accepting comments on the PCCP Draft Guidance until July 3, 2023 (Docket No. FDA-2022-D-2628).

Although you will see some concerns and areas needing clarification below, the publication and future implementation of this draft guidance has the potential to significantly reduce the number of regulatory submissions required for modifications to AI/ML-enabled medical devices. The release of software updates driven by the learning capabilities of these systems may be significantly accelerated under the PCCP mechanism.

INSIDE THE PCCP

Varying from the expectations set in the 2019 discussion paper and the 2021 action plan, the PCCP Draft Guidance does not include either Software Pre-Specifications (SPSs) or Algorithm Change Protocols (ACPs) as elements of a PCCP. Instead, a PCCP is to be composed of three elements: (i) a Description of Modifications; (ii) a Modification Protocol; and (iii) an Impact Assessment.

DESCRIPTION OF MODIFICATIONS

The first PCCP element—the Description of Modifications—itself includes three elements:

1. An enumerated list of individual proposed device modifications;
2. A specific rationale for the change to each part of the Machine Learning Device Software Function (ML-DSF); and
3. Reference to the labeling changes associated with each modification.

MODIFICATION PROTOCOL

The second element of a PCCP—the Modification Protocol—describes "the methods that will be followed when developing, validating, and implementing modifications delineated in the Description of Modifications section of the PCCP." The Modification Protocol should have four primary content elements, each with its own content requirements:

1. Data Management Practices

First, the Modification Protocol should include an outline of how data supporting proposed modifications will be collected, annotated, curated, stored, retained, controlled, and used—including how the reference standard will be determined. In addition, the Modification Protocol should clarify the relationship between Modification Protocol data and data that is used to train and test both the initial and subsequent versions of the ML-DSF. FDA refers to this as the "data sequestration strategy" to ensure separation of training data sets from testing data sets. Finally, the Modification Protocol should include a description of the control methods used to ensure that data or performance information does not "leak" into the modification development process.

2. Re-training Practices

Second, the Modification Protocol should include information about re-training practices, including the objective of re-training, a description of the ML model, the device components that may be modified, re-training practices that will be followed, and triggers for re-training.

3. Performance Evaluation

Third, the Modification Protocol should address how and when the performance of the AI/ML-based SaMD will be evaluated. For example, the Modification Protocol should outline how evaluation of a device modification against its specifications will be triggered, how sequestered test data that is representative of the clinical population and intended use will be applied for testing, what specific performance metrics will be computed, and what statistical analysis plans will be employed to test hypotheses relevant to the performance objectives for each modification to the device.

4. Update Procedures

Finally, the Modification Protocol must include a description of how devices will be updated to implement modifications. This includes confirmation that the verification plans and validation plans have not changed or that any

changes are justified. It also includes transparency on how differences in performance and testing methods will be communicated to users, including legacy users. Any required user training on the modifications also should be included, as should information regarding how real-world monitoring and any subsequent notification to stakeholders will be addressed. Finally, labeling changes resulting implementation of the modification must be set forth.

FDA expects each of these four elements of the Modification Protocol to be traceable to each modification described in the Description of Modifications.

IMPACT ASSESSMENT

The third element of a PCCP is the Impact Assessment. The PCCP Draft Guidance refers to the Impact Assessment as an assessment of the benefits and risks of implementing a PCCP, but its relationship to a Benefit-Risk Analysis (also known as a Benefit-Risk Determination or Risk-Benefit Analysis), which is required under safety risk management, is unclear.

As set forth in the PCCP Draft Guidance, there are five elements of an Impact Assessment: (i) comparison of the version of the device with each modification implemented to the version of the device without any modifications implemented; (ii) discussion of the benefits and risks (including risks of social harm) of each individual modification; (iii) discussion of how the activities proposed within the Modification Protocol continue to reasonably ensure the safety and effectiveness of the device; (iv) how the implementation of one modification impacts the implementation of another; and (v) the collective impact of implementing all modifications.

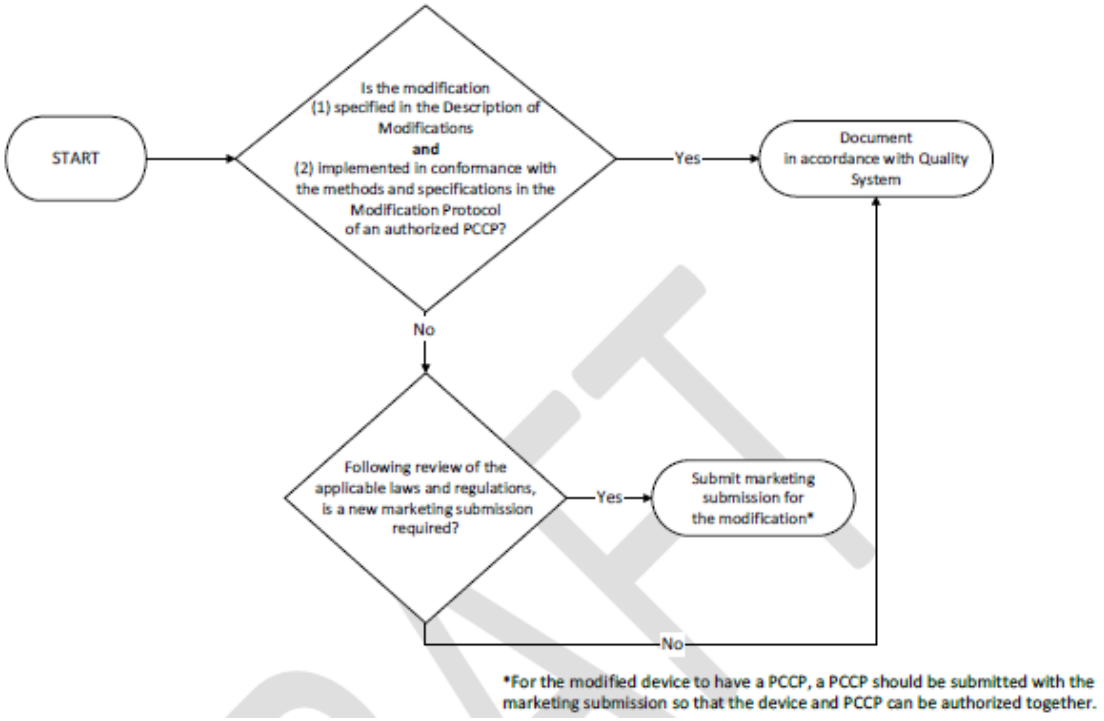
REFERENCING A PCCP IN A SUBMISSION

The PCCP Draft Guidance calls for the PCCP to be included in a standalone section of the submission, mentioned in the cover letter to the submission, and identified in the submission table of contents as “Predetermined Change Control Plan.” When the device is approved or cleared by FDA, the PCCP becomes and “Authorized PCCP.”

If a manufacturer wants to use an AI/ML-based SaMD as a predicate in the manufacturer’s own submission, the manufacturer’s “device must be compared to the version of the predicate device cleared or approved prior to changes made under the PCCP.” In other words, a modified AI/ML SaMD cannot be used as a predicate, even if the modifications to the device were within the scope of the Authorized PCCP.

USING AN AUTHORIZED PCCP

The PCCP Draft Guidance includes the following decision tree for determining if the modification is within the scope of an Authorized PCCP or a new submission is required:



SUPPORT FOR ADAPTIVE LEARNING?

Discussions in various industry forums has speculated that AI/ML guidance issued by FDA would be supportive of algorithms that deploy adaptive learning, i.e., algorithms that provide autonomous updates to the device or function in its use environment without human intervention. The following excerpts from the PCCP Draft Guidance, however, call into question whether FDA will embrace such technology as part of the regulatory framework:

- Section III (Scope): "*This draft guidance is applicable to ML-DSFs that the manufacturer intends to modify over time. This includes ML-DSFs for which modifications to the ML model are implemented automatically (i.e., for which the modifications are implemented automatically by software), as well as for ML-DSFs for which modifications to the ML model are implemented manually (i.e., involving steps that require human input, action, review, and/or decision-making, and therefore are not implemented automatically)*." This language appears to support the use of adaptive learning.
- The very next paragraph, however, raises doubts: "*For the purposes of this guidance, the term 'PCCP' refers to a plan that includes device modifications that would otherwise require a premarket approval supplement, De Novo submission, or a new premarket notification. A plan that contains only minor modifications that would not require a new submission is outside the scope of this guidance*." In many cases, adaptive learning would make autonomous changes to a function or system that would never breach the threshold requiring a submission, but the PCCP Draft Guidance states repeatedly that only those changes that would normally require a submission need an "Authorized PCCP." This suggests that only autonomous changes normally requiring a submission would be covered by the guidance, if at all.
- As shown below, the PCCP Draft Guidance then adds a design verification and design validation burden to every change, which effectively requires a design change as part of design controls to be applied before

release of the change. The burden of following a design change process likely limits the application of the PCCP to locked algorithms that cannot be autonomously changed in the use environment.

    - Section VI.C. (Types of Modifications) states: "*Modifications proposed within the Description of Modifications should be able to be verified and validated within the existing quality system of the device*." And Section VII (Modification Protocol) strengthens this perception: "*Documentation of modifications verified and validated per the Modification Protocol must be compliant with the quality system (QS) regulation. The QS regulation requires manufacturers of finished medical devices to review and approve modifications to device design and production (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record (21 CFR 820.181)*."
    - Appendix A, which includes a series of questions to be answered within the Modification Protocol section of a PCCP, includes four questions (in Paragraph (4)(a)) that discuss the software verification and validation to be performed on proposed changes.

- Appendix B provides examples of five products, with each product including two modification scenarios. The first scenario is a proposed modification that would be covered under an Authorized PCCP and would not require a submission to the FDA. The second scenario is a proposed modification that would not be covered under an Authorized PCCP and therefore would require a submission to the FDA. The final sentence of every "Modification Scenario 1" is: "*The manufacturer should document the modification that was specified in the PCCP in accordance with their quality system*." This language suggests that all five example products include locked AI/ML algorithms.

It may be that FDA intends to be support of adaptive learning within the context of the PCCP Draft Guidance. Indeed, the Agency acknowledges the novel nature of regulating modifications to AI/ML systems: "Understanding that this is an evolving area, FDA is proposing to consider PCCPs for ML-DSFs where modifications are implemented automatically to the extent the Agency can properly review them for substantial equivalence to the predicate or a reasonable assurance of safety and effectiveness."

We believe, however, that clarification is needed. We encourage firms hoping to develop AI/ML-based SaMDs or implement AI/ML technology within their medical devices to review the PCCP Draft Guidance carefully and consider submitting comments to FDA seeking clarity regarding the use of adaptive learning.

THE "ENTIRE" DEVICE?

Although most design change schemes include the use of an impact analysis to tailor design control activities to the elements of the device and its Design History File impacted by the change only, we find this language in Section VII(B)(3) of the draft guidance to be contrary to that principle: "*Performance evaluation should include the plans for verification and validation of the entire device following ML-DSF modifications for each individual modification and in aggregate for all implemented modifications*." Firms should consider submitting comments that seek clarity regarding the design verification and design validation requirements of ML-DSF modifications.

ADDRESSING BIAS

The PCCP Draft Guidance addresses potential bias in the data management practices and re-training practices sections of the PCCP's Modification Protocol. Data management practices will ensure that data sequestration between training and testing data is effectively defined to minimize bias through inappropriate re-use of training data during testing. Likewise, re-training practices reinforce data sequestration and identify "risks related to ML model

bias introduced by re-training a modified ML model," along with planned mitigations.

TRANSPARENCY VS. EXPLAINABILITY

"Explainability," in the context of AI/ML, is a function within the system allowing user to understand how a particular decision was made by the AI/ML system. Explainability seeks to provide confidence in AI/ML decisions by walking any observer through the logical path of each decision so they can understand how the decision was made and agree that the decision was appropriate.

Transparency does not provide an explanation for each decision but instead provides insight into the AI/ML system's logic, model, development, and training process, as well as an overall sense of confidence in the way the system was built. Proponents of transparency argue that AI/ML systems are so complex (increasingly so) that it is impossible to explain each individual decision. Transparency seeks to provide confidence in AI/ML decisions through confidence in the way the AI/ML system was built, trained, and tested.

Industry, academia, the healthcare provider community, and the public at-large have debated whether transparency or explainability is the most appropriate means for increasing confidence in decisions made by AI/ML systems. The PCCP Draft Guidance clearly falls into the transparency camp. FDA will look for evidence of transparency in the PCCP its evaluation of submission, primarily in the update procedures described in the Modification Protocol section. Section VII(B)(3) of the PCCP Draft Guidance states: "*The update procedures in a Modification Protocol should describe how manufacturers will update their devices to implement the modifications, provide appropriate transparency to users, and, if appropriate, updated user training about the modifications and perform real-world monitoring, including notification requirements if the device does not function as intended pursuant to the authorized PCCP*."

There is no mention of explainability in the PCCP Draft Guidance.

FINAL THOUGHTS

The PCCP Draft Guidance is a significant step forward in the FDA's ability to effectively regulate AI/ML-enabled medical devices. Many companies have already begun to implement PCCPs, as they were understood based on FDA's 2019 discussion paper, to better inform FDA's submission evaluation process—and they have done so with some success.

Other than the Chinese Guidelines for Registration Review of Artificial Intelligence Medical Devices, the FDA's draft guidance constitutes the most rigorous treatment of regulating AI/ML-enabled medical devices globally, even given the issues we identified above. Other regulatory bodies and government authorities have works in progress that will provide additional requirements and guidance for these systems, but their status and potential similarities and differences relative to the U.S. regulatory framework is still an open question.

We encourage firms to carefully review the PCCP Draft Guidance, making note of the scope of PCCP application (i.e., changes otherwise requiring submission); if or how the draft guidance supports adaptive learning; and whether the application of design controls to modifications seems appropriate. We further encourage firms to submit comments to FDA before the comment period expires on July 3, 2023. This will ensure that FDA hears from a wide variety of voices and addresses key issues before publishing its final guidance.

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