COLLEGE of AMERICAN PATHOLOGISTS

June 30, 2023

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

Re: Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions DRAFT GUIDANCE [Docket No. FDA -2022-D-2628]

Submitted via Electronic Submission to www.regulations.gov

Dear Dr. Califf:

The College of American Pathologists (CAP) appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance entitled, *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions (ML-DSFs).* 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. Our members have extensive expertise in providing and directing laboratory services under the Clinical Laboratory Improvement Amendments (CLIA) regulations, which require compliance with requirements through a quality system approach for overall operations and administration of the clinical laboratory. This includes the verification and validation of any new or modified tests or devices. It is important to note that there are quality practices in the laboratory specified by CLIA that are separate from operational requirements defined by a manufacturer of a medical device and approved by the FDA. While CLIA regulations are not directly applicable to other medical specialties, they may inform thinking about performance quality goals in ways that strengthen current PCCP recommendations and improve the consistency of their application across medical specialties.

The CAP anticipates that in the near future AI/ML-based technologies will power highly useful ML-DSF applications in a broad range of medical settings including some that are performance-critical. For success and safe operation, the performance quality of these applications must be verified after installation and monitored over time. Performance

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problems may occur if there are differences in the details of local data in comparison with the data used to train the ML-DSF or if the characteristics of local data drift over time. Updates to ML-DSF affecting the machine learning components inherently re-define the relationship between the training and local data and require a practical and appropriate re-verification of performance to ensure safe and effective operation. Hence, ML-DSF are analogous to high complexity diagnostic testing in requiring verification at installation and robust quality control/quality assurance procedures. Because of the partial analogy of these new technologies with current diagnostic testing, the expected impact of these technologies on the practice of pathology and laboratory medicine, and the need to adhere to CLIA in the laboratory setting, the CAP has a keen interest in the regulatory approach for AI/ML technologies. The CAP supports the concepts proposed within the current draft guidance, most notably:

1. A risk-based categorization framework that conveys the potential impact of software (and changes made to software) on the patient. The CAP recognizes that a manufacturers risk assessment may differ significantly from a local risk assessment, and this may represent a gap in the current guidance.
2. A predetermined change control plan (PCCP) that contains a detailed description of modifications, a step-by-step modification protocol, and an impact assessment. This information not only empowers the FDA to perform an informed review, it is also critical for local site implementation and verification of performance.
3. Following establish pathways for premarket authorization of devices with ML-DSFs with a PCCP to avoid adding complexity to the existing regulatory framework.
4. Promoting labeling requirements so that users are aware that the device may be updated in the future, understand the nature of the changes made in an update, and document the steps that users must perform to test, maintain, and document a device's performance. Declaring data management practices also aids in conveying the potential impact of modifications to both the FDA and users. The CAP recognizes the possibility that despite these efforts, users may not be fully prepared for impacts of modifications or unexpected real-world behavior at a local site.
5. Clarifying that modifications that are appropriate for a PCCP are those intended to maintain or improve the safety or effectiveness of the device. Modifications for other motivations may impose undue risk and validation burden on users.
6. Recognizing that modifications to a device with an authorized PCCP should be able to be verified and validated within the existing manufacturer published quality system of the device. Modifications beyond this would not be appropriately covered by the existing PCCP. Of note, laboratories have quality systems in place to comply with CLIA regulations that can go beyond the quality system published by the manufacturer. Such systems (such as the requirement for proficiency testing for many lab tests) are not addressed in the draft guidance and may represent a gap.
7. Recommending that each modification be linked to a specific performance evaluation activity within the Modification Protocol. This will ensure that users follow

a standard procedure for performance evaluation and better understand the potential impact of the modification in patient care. This guidance assumes that the manufacturer will be able to predict failure modes of the device for a given modification. The CAP recognizes the challenges involved and that this might not always be possible. For changes to software used in laboratories in the care of patients, the CAP currently recommends performance evaluation under the management of the laboratory director, who is in the best position to assess risks and impact in the local environment.

8. Reiterating that all modifications included in a PCCP must maintain the device within the device's intended use. This is a prudent course. The CAP recognizes that even within the device's intended use, a modification may lead to unanticipated degradation of performance at a local user's site that may go unrecognized and/or not be well understood. This may be a gap and remains an area of concern.
9. Ensuring that a Modification Protocol describes how manufacturers will update their devices to implement modifications, provide transparency to users with appropriate user training, and perform real-world monitoring, including notification requirements if the device does not function as intended following modification. The CAP has significant experience in providing real world monitoring of laboratory testing quality and recognizes the complexity and investment required for such monitoring. It is unclear if manufacturers will be able to provide robust and meaningful real world monitoring guidance, tools, and/or services to ensure local quality control. The CAP would be happy to describe quality management services and real-world monitoring tools and services that currently empower laboratories to ensure high quality laboratory testing that may be directly applicable to pragmatic monitoring of ML-DSFs both within and potentially outside the laboratory.
10. Providing excellent examples of issues to be addressed in components of a Modification Protocol. The guidance supposes that manufacturers will be able to sufficiently anticipate local site conditions and constraints that may impact ML-DSF performance, but this may not always be possible. In a setting where it is not possible to identify all local factors that could impact performance of new technology, real world performance monitoring is critical for identifying problem situations as they arise.

In summary, the CAP supports the FDA's efforts to develop innovative approaches to regulation of devices that will use AI/ML medical software by leveraging the predetermined change control plan (PCCP), within a general performance assurance strategy, to ensure that iterative modifications are safe and effective. However, for clinical laboratories to meet CLIA requirements, manufacturers should provide robust guidance in the PCCP on the verification steps that should occur at the local site under lab director supervision. Further, those steps should be clearly delineated from validation activity that occurs at the manufacturer. The CAP believes that those principles should also be extended to PCCPs used in non-CLIA settings and wishes to emphasize the

importance of having the PCCP reflect the need for local verification using local data and the role of the local medical director to oversee implementation and monitor performance over time using standard operating procedures. Furthermore, the local sites' responsibilities in the PCCP should be communicated effectively in the product information so that sites are aware of all information related to the likelihood, frequency, and requirements of re-verification prior to acquisition of a product with ML-DSF.

The CAP recognizes the challenge in predicting what information a local medical director may need for local verification given variance in local data and the variety of ways in which a ML-DSF may be incorporated into a device. For this reason, we recommend that verification plans within PCCPs include both the verification process and a set of target verification metrics that have a clear relationship to clinical performance and are tailored to what is practical for local sites including data volume and number of cases. Because of the variety of settings possible and the lack of generally accepted best practices for local verification of AI/ML, the CAP does not recommend particular metrics, but that the metrics and verification process be optimized for each ML-DSF. The metrics should be expressed as "expected performance" of the modified product at local sites rather than acceptance criteria, because acceptance criteria depend partly on-site characteristics and are defined by the local medical director.

Finally, with respect to the PCCP's Impact Assessment, early efforts strongly suggest ML algorithms will require significant effort for validation and performance monitoring. This likely includes new and additive work for a healthcare organization beyond simple verification of a manufacturer's claims. The clinical labor of validation using local data will most significantly impact small sites, such as those that serve remote, vulnerable populations critical to the nation: rural farming regions, mining regions, island territories, prison communities, and military installations. Paradoxically, these vulnerable populations will also stand to benefit the most from their physicians having access to high quality devices with ML-DSF. The CAP recognizes the FDA wishes to minimize the regulatory burden on manufacturers. However, this should not occur at the expense of healthcare providers. For devices with ML-DSF deployed in the laboratory, post-marketing data accrual responsibilities are within the pathologist's purview. A distinct process in the PCCP should ensure post-market ML-DSF performance monitoring responsibilities do not place undue burden on pathologists or other physicians. Again, the best balance may be found through guidance in the PCCP which addresses structured collaboration between the manufacturer and local medical director to reduce risks and optimize device performance at a local site.

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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.

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