AMERICAN CLINICAL LABORATORY ASSOCIATION

November 1, 2024

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

Re: ACLA Comments on Draft Guidance: Predetermined Change Control Plans for Medical Devices ("PCCP Draft Guidance") (Docket No. FDA-2024-D-2338)

The American Clinical Laboratory Association (ACLA) submits the following comments on FDA's PCCP Draft Guidance. ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers by advocating for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized care. ACLA member laboratories are at the forefront of developing tests to respond to emerging health issues, and they frequently innovate new areas of science. Laboratory developed testing services offered by ACLA members play an indispensable role in delivering healthcare to patients.

As an initial matter, ACLA maintains that FDA lacks authority to regulate laboratory developed testing services (LDTs) under its medical device authorities.[1] No statement or proposal in these comments is intended to be inconsistent with this position, nor shall any such statement or proposal be interpreted or construed as such. Nonetheless, in the event that FDA's final rule to regulate LDTs as medical devices is implemented and deemed lawful in a court of law, we submit these comments to ensure that PCCPs can be leveraged by laboratories to support continued rapid innovation of diagnostics to meet patient needs. As explained below, the modifications that would be appropriate for a PCCP under the Draft Guidance are too narrow to encourage meaningful iterative improvement of diagnostics without repeated cycles of premarket review. The types of modifications that are appropriate for a PCCP must be expanded. The guidance also should clarify that a PCCP may allow modifications to a cleared or approved IVD test kit to be implemented by high-complexity clinical laboratories, rather than the manufacturer of the IVD test kit, without FDA premarket review. Finally, the statutory standard for evaluating a PCCP does not include an evaluation of the regulatory history of the subject device nor of the submitter, and accordingly, FDA should not take such histories into consideration.

[1] As explained in ACLA's comments to FDA's proposed rule to regulate laboratory developed testing services as medical devices, and in a complaint filed against the FDA to enjoin implementation of such rule, laboratory developed testing services are not devices, and FDA lacks legal authority to regulate them as such. *See* ACLA Comments on Proposed Rule, "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177) (Dec. 4, 2023), https://www.acla.com/wp-content/uploads/2023/12/Comments-of-the-American-Clinical-Laboratory-Association-on-LDT-Proposed-Rule-Docket-No.-FDA-2023-N-2177.pdf; Complaint, ACLA and HealthTrackRX v. FDA, HHS, Becerra, and Califf, Case No. 4:24-cv-479, https://www.acla.com/wp-content/uploads/2024/05/ACLA-LDT-Complaint.pdf.

I. Greater Flexibility in Scope of Modifications Appropriate for PCCPs

One of ACLA's many concerns with FDA device regulation of LDTs is that device regulation is rigid and burdensome in a way that would lead to less innovation and slower development timelines, often without corresponding benefit to patients. Although PCCPs potentially could encourage the iterative innovation that is a trademark of diagnostic development, the PCCP Draft Guidance would restrict the pathway such that any meaningful improvement of a diagnostic would still require 510(k) clearance or PMA approval, thereby defeating its purpose.

For example, under the PCCP Draft Guidance, modifications to a device's indications for use generally would not be appropriate for inclusion in a PCCP because they "would be difficult for FDA to assess prospectively." ACLA firmly disagrees that modifications to indications for use should be categorically excluded from eligibility for PCCPs and urges the Agency to develop methods for prospectively assessing such changes. Modifications to the indications for use of diagnostics are a key aspect of iterative improvement of tests. For example, oncologists have relied on LDTs to deliver diagnostic information consistent with emerging science, and new scientific discoveries are being made—and new clinical care guidelines are being published—faster than FDA can review and approve marketing submissions for diagnostics. By the time an oncology assay obtains approval or clearance for a new clinical claim, that claim may not reflect the latest advances in patient care. If FDA insists on approving or clearing every new clinical claim for a test, diagnostic innovation will slow to the detriment of patients.

The limited exceptions to this general exclusion, for changes "to describe a specific subset of a patient population within the originally indicated patient population," "to specify use of the device with an additional ... human genetic variant," or, for cleared devices only, "regarding use in the home setting" are too narrow to meaningfully advance diagnostic innovation without repeated cycles of premarket review. ACLA agrees that these changes could be addressed through a PCCP, but additional changes are appropriate, as well. Specifically, addition of copy number variants, new genes, changes in sample type, changes in collection devices, and changes to incorporate automation *all* should be appropriate for inclusion in a PCCP, in contrast to the guidance in Examples 1, 2, 6, 7 and 9. Requiring these changes to go through individual premarket review would limit and slow patient and provider access to important diagnostic information.

In particular, ACLA disagrees that there is a categorical difference between changes to address additional genetic variants and changes to address additional genes, especially when the general intended use of the test is the same. First, the method for analytically validating changes to address additional genetic variants and changes to address additional genes is largely the same, so there is no basis for distinguishing these changes due to their technological characteristics. The clinical validation for these changes also is similar, especially in the context of panel tests for a general intended use, such as tumor profiling, where the tests already measure dozens or hundreds of genes. For such tests, additional genes do not change the general intended use of the test, and the method for determining clinical significance of the additional genes is highly similar to the method for determining clinical significance of additional genetic variants. Indeed, not all human genetic variants of a single gene have clinical significance, and accordingly, laboratories do not add every variant to the indication for a test. Rather, there is a process for determining clinical significance. The same process often is followed when determining whether to add a gene to a panel test.

Additionally, ACLA disagrees with the limitations in the PCCP Draft Guidance that modifications that could introduce new risks for a cleared device, or modifications are not "minor"

or manufacturing changes generally would not be appropriate for inclusion in a 510(k) PCCP or PMA PCCP, respectively. These types of changes are incredibly narrow and undermine the goals of encouraging iterative improvements of diagnostics. As the PCCP Draft Guidance notes, for PMAs, permissible modifications would include only those changes that could otherwise be reviewed under a real-time PMA supplement or 30-day notice for an approved device, i.e., those changes that would be reviewed in an expedited manner under existing processes. Accordingly, the PCCP process would not present a meaningful advantage over submitting additional premarket submissions. Moreover, the provided justification, that "the risks of implementing the modification are likely not adequately mitigated by the existing risk management framework of the device and the manufacturer's quality system" prejudges the applicable risk management framework and quality system. Laboratory quality systems are adept at evaluating the risks of test modifications – CLIA has permitted high-complexity laboratories to modify cleared and approved IVD test kits for decades.

Finally, we note that limiting the scope of "appropriate" modifications for PCCPs is an entirely artificial restriction that is not reflected in the statute. Rather, section 515C of the FDCA authorizes FDA to approve or clear a PCCP when applicable standards are met, and we urge FDA to develop methods for evaluating a broad range of modifications to encourage use of the PCCP pathway and support rapid innovation of diagnostics.

II. Flexibility for Laboratory Modifications Consistent with Cleared and Approved PCCPs

Additionally, we encourage FDA to revise the guidance to clarify that a PCCP may allow modifications to a cleared or approved IVD test kit to be implemented by high-complexity clinical laboratories, rather than the manufacturer of the IVD test kit, without FDA premarket review. Such modifications, when validated according to the methodology included in a cleared or approved PCCP, would be consistent with the clearance or approval for the test kit.

We note that in the LDT Final Rule, FDA adopted a policy under which it would not require premarket review when a high-complexity clinical laboratory modifies a manufacturer's 510(k)-cleared or De Novo authorized test in a way that would not trigger premarket review requirements if the manufacturer made the modification themselves. FDA stated that this policy was appropriate "to promote more efficient and effective use of Agency resources and because it understands laboratories may make such changes to, for example, integrate a test into its operations, accommodate local conditions (*e.g.*, storage conditions), or address supply shortages." The PCCP guidance should likewise reflect that high-complexity clinical laboratories can modify a cleared or approved IVD test kit without premarket review if the manufacturer of that test kit could make the same modification without premarket review consistent with a cleared or approved PCCP.

III. Equal Treatment of PCCP Applicants

Finally, Congress set forth a standard for clearing or approving a PCCP in section 515C of the FDCA, and that standard does not include evaluation of the regulatory history of a specific device nor of the applicant submitting the PCCP. Nonetheless, under the PCCP Draft Guidance, FDA's "guiding principles" for reviewing a PCCP include that FDA will consider "the regulatory history of the specific device ... and manufacturer." These considerations would likely slow innovation, however, particularly for novel tests and new developers that lack a specific regulatory history. For example, many laboratory test developers do not have a regulatory history with the Agency because their tests were not previously regulated. To ensure equal treatment of all

developers, we urge the Agency to strike this language from the guiding principles and to clarify that any PCCP meeting the standard set forth in section 515C of the FDCA will be cleared or approved.

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Thank you for your consideration of these comments. If you have any questions, please contact Vice President of Government Affairs and Policy, Mary Lee Watts, at mlwatts@acla.com.

Sincerely,

Susan Van Meter
President