

In Vitro Diagnostic Multivariate Index Assays

Public Meeting

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My name is Paul Radensky. I am an internist and a health law attorney with McDermott, Will, & Emery, LLP. McDermott, Will & Emery represents several laboratories that may be affected by the policies announced in the draft guidance, however this presentation does not represent the policies or opinions of McDermott, Will & Emery or its clients.

The draft guidance “In Vitro Diagnostic Multivariate Index Assays” raises a large number of issues, many of which are being covered by other speakers at today’s public meeting. These include concerns over FDA’s legal authority to regulate clinical laboratories, the definition of an in vitro diagnostic multivariate index assay, identifying the elements of an IVDMA that comprise a medical device subject to FDA regulation versus those that are the laboratory service regulated under the Clinical Laboratory Improvement Amendments (CLIA), pathways for pre-market review of such assays, compliance with FDA’s Quality System Regulations, and conflicts between FDA limitations on labeling and promotional statements versus CLIA requirements for laboratory reporting. These concerns are more than “interesting questions” for the FDA to consider for the future. These are critical questions which must be answered before any clinical laboratory can be required to comply with the substantial, new regulatory burdens being imposed by FDA.

Definition of an IVDMA. Laboratories considering the development of a novel assay must have clear and predictable criteria by which they can determine whether or not FDA pre-market review will be required. Good science is part of the development of any novel diagnostic test service regardless of the pathway chosen for commercialization—CLIA or FDA, but the scope of the development program and the documentation requirements can be quite different between the two pathways. Laboratories that elect a CLIA pathway must be able to move forward confident that the FDA will not suddenly change course and expand the scope of tests that it considers “too novel” to fit under its long-standing policy of not requiring pre-market review for laboratory-developed tests. Investors will not finance the development of novel tests

unless they can be confident that the underlying regulatory structure will not change suddenly with the release of a new draft guidance document from FDA.

Identifying the medical device within the laboratory service. Preparation of a pre-market submission, developing procedures to comply with QSRs, and drafting of product labeling—all start with an understanding of what is the medical device subject to regulation. The draft guidance identifies the entire “test system” as the medical device but does not explain how the test system medical device is distinguished from the test system of the clinical laboratory. The draft guidance asserts that the term “test system” for the purposes of FDA regulation is not the same as the term “test system” used under the CLIA regulations, but the FDA does not provide any guidance as to how this common term differs between the two regulatory frameworks. Laboratories must have clear instructions identifying which elements are subject to FDA regulation and which are subject to CLIA before they can proceed to prepare pre-market submissions, design programs for compliance with QSRs or develop product labeling.

Pathways for pre-market review. FDA regulation of medical devices is risk-based. The draft guidance indicates that most IVDMIAs would be class II devices requiring 510(k) clearance or class III devices requiring pre-market approval. The draft guidance further suggests that prognostic claims would likely fall under class II and predictive claims would fall under class III. However, FDA does not specify what risks are inherent in prognostic claims and why these would be addressed with class II special controls nor does the Agency identify the risks involved with predictive claims and why class II special controls would not be sufficient for laboratory services making these claims. Moreover, the draft guidance does not articulate how laboratories can distinguish prognostic claims, such as likelihood of an untoward event (on some therapy), with predictive claims, which similarly may involve likelihood of an untoward event on some therapy. Laboratories must have a clear understanding of the pre-market pathways that must be followed for commercialization of IVDMIA tests so they can assess what resources they will need to develop and commercialize a novel test and what the timeline will be before these tests will be available to assist physicians with clinical decision making.

Compliance with QSRs. Many in the clinical laboratory community have brought to FDA’s attention concerns about how clinical laboratories, which are structured and operate under

CLIA quality regulations intended to assure the reliability and accuracy of test results, can comply with the FDA's QSRs, which are intended to assure the manufacture of effective and safe medical devices. Clinical laboratories operating in compliance with CLIA requirements may incur substantial costs to modify their operations to come into compliance with FDA QSRs. They need to understand—with particularity—what steps will be required to conform laboratory quality processes with the QSRs. It is not sufficient to say that FDA will allow laboratories time to come into compliance—they must also have a roadmap to follow.

Conflicts between FDA and CLIA requirements. FDA limits labeling and promotion to claims cleared or approved by the Agency. By contrast, CLIA regulations require laboratories to furnish physicians with up-to-date information necessary for interpretation of their tests. These rules are in conflict. FDA and CMS must work through leadership at HHS to set out clearly how laboratories can meet these conflicting requirements among the regulations of sister HHS agencies.

Transition. What FDA is proposing under the draft IVDMIA guidance is a substantial departure from long-established FDA policy not to enforce the medical device regulations against clinical laboratories offering laboratory-developed tests. If implemented, the new policy will have a major impact on those laboratories that become subject to FDA regulation. If FDA proceeds, the Agency must allow sufficient time for laboratories to (1) determine which of their portfolio tests are subject to FDA regulation, (2) determine what elements of the tests will be subject to FDA regulation as a medical devices, (3) determine what pre-market review pathways will be required and proceed with preparation of the required pre-market submissions, and (4) conform laboratory operations to FDA QSRs, as needed. For products that will require 510(k) pre-market notice submissions, a transition period of at least 2 years should be allowed following release of a final policy document until required submission of the pre-market notice. For products that require pre-market approval, a period of at least 4 years should be allowed from publication of a final policy until PMA submission.

FDA must not begin enforcement until this necessary transition period is completed. In the interim, if FDA believes that testing by certain laboratories raises public health concerns or

that some laboratories are promoting claims that the Agency believes are deceptive, FDA can refer these cases to CMS and/or the Federal Trade Commission.

FDA has not articulated what concerns it has about IVDMIAs (other than the fact that these are novel), why established regulatory controls under CLIA and the FTC Act are insufficient to address these concerns, nor how regulation under the Medical Device Amendments would be the least burdensome approach to address the Agency's concerns. We would urge the FDA to explain the findings that led the Agency to conclude that it should extend jurisdiction to clinical laboratories performing certain laboratory-developed tests. Before FDA seeks to enforce medical device requirements against clinical laboratories performing IVDMIAs, the Agency must provide, through notice and comment rulemaking, clear answers to critical questions to which laboratories need answers in order for them to comply with medical device requirements. Following the release of any final policy through such rulemaking, FDA must allow sufficient time for laboratories to adopt policies and procedures to comply before FDA begins enforcement of these significant, new rules.