



CLARIANT

**DIVISION OF DOCKETS MANAGEMENT
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FOOD AND DRUG ADMINISTRATION
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RE: 2006D-0347

As a clinical laboratory with a mission to be the leader in cancer diagnostics by dedicating ourselves to collaborative relationships with the healthcare community as we translate cancer discovery and information into better patient care, we have a number of serious concerns about the recent IVDMA Draft Guidance.¹ We believe that it will have many sweeping consequences – delaying patient and physician access to important new technology and medical information across many diseases – should the FDA move forward and implement the policies announced in this document as currently written. We would like to respectfully submit our concerns and recommendations. Further, we urge the Agency to contemplate the potential negative impact on the physicians as well as the patients that are served by clinical laboratories should the Draft Guidance be finalized as written and consider less burdensome methods as required by law.

Innovation at laboratories will be seriously reduced.

- Laboratories have been the source of many innovations for decades. LDTs have been used to identify novel diseases and health conditions and are an essential part of public health. In particular, LDTs are a very important element of advances in the assessment and characterization of cancers of all types. Often, LDTs are developed to incorporate the rapidly evolving knowledge about the molecular basis of cancer and to guide treatment decisions based on this assessment.
- If laboratories are required to undergo premarket review and to comply with post-market controls for all LDTs meeting FDA's definition of IVDMA, the ability of laboratories to attract funding from outside sources or obtain Board approval to invest in the development of innovative new tests will be seriously reduced. Only those tests with the largest market potential will be developed. For products that do obtain clearance or approval, the science will be frozen at the point of the first clearance in many cases unless the market is sufficiently large to justify the additional investment to obtain supplemental clearances/approvals.

Laboratories would bear an excessive regulatory burden that would make the development of innovative tests cost-prohibitive.

- If LDTs are subject to FDA regulation as medical devices, then laboratories would be considered as medical device manufacturers and subject to both FDA and CLIA regulations and standards.

¹ Clariant's comments supportive of certain approaches to regulation should not be considered an acknowledgement by Clariant that FDA has the authority to regulate laboratory services as medical devices. In addition, our reference to tests that may fit under FDA's definition of an IVDMA does not represent an admission by Clariant that any particular laboratory test is a device as that term is defined under Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 321(h)).

- To expand and adapt from CLIA quality systems to the development and implementation systems that would comply with FDA's device requirements, such as Quality System Regulation (QSR) compliance would be very costly and could take years. The Draft Guidance also does not address the overlap and inconsistencies between CLIA and QSR's.

The definition of an IVDMIA and the regulatory path is unclear.

- The outlined definition of an IVDMIA is broad, containing new and ambiguous terms that create uncertainty. Laboratories need clearer parameters to clearly distinguish between an IVDMIA subject to FDA regulation and all other LDTs not subject to FDA regulation. The definition should also clarify what components constitute the medical device subject to FDA premarket review and post market controls as well as the elements that represent the clinical laboratory service using the device, which remains subject to CLIA requirements.
- Treating the entire test system from sample acquisition to final report would create significant problems for laboratories, particularly with respect to the ability to modify test processes and regularly improve their test systems.
- The document states that most IVDMIAs will either require 510(k) clearance or premarket application (PMA) approval. It is not clear when a 510(k) or a PMA will be required. Given the huge differences in the regulatory burden between the two, FDA needs to more clearly define the standards for evidence for distinguishing the two regulatory groups.
- The 510(k) and PMA processes require additional Agency review for many modifications. LDTs are frequently modified by laboratories to enhance the performance of these tests. There are often relatively short time periods between process improvements. Therefore, the FDA needs to clearly establish the criteria specifically for IVDMIAs as to when premarket review is needed in these situations. Because of the differences between IVDMIAs and products now regulated as devices, the current guidelines are not applicable. Requiring review of every change to an LDT will hinder improvements or freeze the development of many existing tests. Laboratories should retain the ability to rapidly innovate existing tests as currently exists under CLIA (which requires validation of modified tests prior to patient use).

The restrictions on labeling and promotion conflict with CLIA's requirements for provide information necessary for the interpretation of test results.

- Since laboratory reporting consists of a physician to physician report, the IVDMIA Draft Guidance could intrude into the practice of medicine by physicians by restricting content and conflicting with CLIA. This is an important area that needs to be resolved.

Should FDA move forward to regulate IVDMIAs, we would like to propose some options that should improve oversight in this area without impacting access to critical tests and services. Clearly, there is no simple solution to these issues and any solution will require further clarification and refinement.

Establish a CLIA laboratory-validated test registry.

- Instead of requiring clearance or approval, FDA could institute a public disclosure program (such as a registry) to provide reliable information about the strengths and limitations of particular tests.
- This registry could include information on analytical performance characteristics of each test, clinical data in the form of publications, laboratory experience, adverse events and other relevant informational items to ensure transparency.
- By reviewing and analyzing the data in such a registry, the FDA and other regulatory bodies (such as CMS and CDC for the CLIA program) would have an opportunity to assess these registered

IVDMIA. This would provide a better knowledge base from which to establish a regulatory framework.

- Registration of all IVDMIA with FDA and validation by CLIA-certified laboratories would be required once a testing volume threshold (based on tests performed) is exceeded. Also, labeling would be required to reflect the absence of FDA clearance or approval.

Strengthen the existing CLIA regulations relative to LDTs.

- We believe that improvements to the existing CLIA system would provide a clear path to improving quality care and encouraging innovative new laboratory developed tests that are crucial for the practice of medicine – both today and in the future. This might serve as a viable alternative to adding regulatory burden and creating conflicting dual jurisdiction between FDA and CMS.
- The current CLIA regulations could be expanded to more directly require clinical validity for tests that assess outcomes. While many LDTs do have clinical validation data, the approach to gathering the data and data requirements could be standardized. Quality standards for genetic-based LDTs could be defined through the creation of a genetics sub-specialty under CLIA, particularly related to the appropriate conditions for clinical validation of diagnostic or predictive claims as well as performance standards and proficiency testing standards.
- All laboratory service regulation, inspections, and proficiency testing should remain under CLIA. FDA regulation should be limited to the actual test design and validation and the marketing claims.

Limit Regulation Based on Risk and Test Volume

- Tests that are used at a low volume or that serve small patient populations should be exempt from regulation (beyond establishment registration and listing of the test assay). Otherwise, many of these patient groups will be underserved. In addition, the regulation of higher volume tests should be risk based.
- A PMA should be required only for high risk, predictive tests that result in a binary therapy recommendation based solely on the test outcome. All other IVDMIA that are advisory and do not give a binary therapy recommendation as well as predictive tests that have multiple peer-reviewed publications should be exempt from pre-clearance or only require clearance through a 510(k).
- A test classified as an IVDMIA with only analytical performance claims should be Class I, 510(k)-exempt from premarket review and from post-market controls other than record keeping requirements, MDR reporting, and complaint file requirements.

Establish A Transition Period

- A transition period is essential to provide companies with time to adapt and bring IVDMIA from the current CLIA regulatory path to a new CLIA + FDA regulatory path. Laboratories cannot instantly comply with FDA's regulatory requirements.
- FDA should incorporate a transition period of two years for submission of applications for IVDMIA requiring a 510(k) and four years for submission of applications for IVDMIA requiring a PMA into any final document to minimize disruption in the availability of tests.
- There should also be a transition period for any applicable QSR compliance requirements.
- Many IVDMIA are well-established tests being used in clinical practice and are covered and paid by health plans. If FDA were to require that laboratories suddenly begin to label these tests

"investigational," This could have a very detrimental effect on patient access due to reimbursement issues. Payers may withdraw coverage, physicians and patients may become confused, and there may be additional concerns from professional licensure and malpractice perspectives. To avoid these negative consequences, we would urge that during the transition period and pending determination on any submission required at the end of the transition period, FDA should not require that laboratories label their tests as "investigational." Further, IDEs should not be required for the studies performed to provide data for these submissions.

- This transition or "grace" period of two to four years should begin on the date that the IVDMIA exceeds a volume threshold.
- The classification of an IVDMIA into a 510(k) or PMA path should be dependent on the health risk as determined by the intended use(s) claimed by the laboratory. FDA should provide guidance on their criteria for assessing the health risk of an IVDMIA.

Division of Authority

- There should be clear delineation of responsibility and authority between FDA and CMS to avoid overlapping or conflicting regulations and inspections.

Should FDA move forward to regulate IVDMIAs, we believe the current guidelines need to be modified substantially in order to better define this new regulatory path and to encourage the development of important new laboratory tests. If FDA proceeds to extend premarket review and post-market control requirements on any LDTs, we would request that the Agency should proceed only through formal rulemaking procedures. As the comments at the February 8 Public Meeting showed, the Draft Guidance provides inadequate clarity. The best way to ensure that these numerous critical issues are addressed is through rulemaking as mentioned above. FDA should propose new regulations that are detailed, clear, predictable and practical relative to the actual risks / benefits of particular tests instead of issuing or finalizing the current IVDMIA Draft Guidance. Proposed regulations would then be subject to the formal rule making process of notice period of and comment. Thank you for your consideration of our perspective.

Best regards,

A handwritten signature in black ink, appearing to read "Kenneth J. Bloom". The signature is fluid and cursive, with a large initial "K" and "J".

Kenneth J. Bloom, M.D., F.C.A.P.
Chief Medical Officer
Clariant, Inc.