



IVDMIA Toolkit for Commenting on FDA Draft Guidance

Executive Summary

On September 7, 2006, the Food and Drug Administration (FDA) issued Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (the IVDMIA Draft Guidance).¹ This guidance introduces additional regulation into an area that is currently regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

The Coalition for 21st Century Medicine was formed by some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, venture capitalists, and patient advocacy groups – all linked by a common mission to develop advanced diagnostics that improve the quality of healthcare for patients. We will be submitting comments on the FDA guidance which consider the following key points:

- 1) IVDMIA regulation as proposed in the draft guidance may delay access to new technology and medical information and decrease incentives to develop new tests.
- 2) FDA should first consider recommending improvements to the existing CLIA system to improve quality of care without disrupting the current regulatory process.
- 3) Should FDA move forward, the current guidance needs to be substantially modified to better define the regulatory path and to ensure timely development of laboratory developed tests. This would be best done through formal notice and comment rulemaking.

We as a coalition would like to work with FDA to insure that the potential for 21st Century Medicine is realized in a timely fashion with appropriate regulation and care.

What are we requesting?

¹ A copy of the IVDMIA Draft Guidance is attached and available on line at <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.

The Coalition for 21st Century Medicine requests that your company, organization, or an affiliated organization file comments with FDA addressing key issues in the IVDMA Draft Guidance and urging the Agency to consider the potential impact on major stakeholders including patients, physicians, and the innovators who serve them. The points included in this document represent a consensus among many members of the Coalition. Parties submitting comments should, of course, select the points that they would like to make to FDA and frame them in their own individual fashion, based on the experience and requirements of each individual commenter.

Summary Points for Consideration

- 1. FDA should consider working with CLIA to address their concerns by improving the current CLIA regulatory system rather than adding a new regulatory infrastructure with overlapping jurisdiction between FDA and CMS (the governing body with oversight of CLIA).**
- 2. If FDA moves forward with regulation of IVDMIAs it should do so through a formal process of notice and comment rulemaking. The current IVDMA Draft Guidance is relatively short, FDA needs to provide a formal and detailed regulatory path, establish timelines for the regulatory transition, and review the potential unintended consequences for patients and physicians with key stakeholders before proceeding.**

We urge you to provide specific cases and examples that demonstrate ways in which you or your organization might be impacted if the IVDMA Draft Guidance is implemented and help us insure a thoughtful, careful regulatory process.

Background & Key Points

Here are some important issues raised by the IVDMA Draft Guidance that you may want to consider for your FDA filing.

Background

FDA was granted authority to regulate medical devices in 1976. Diagnostic test kits that are manufactured by companies for sale to third party laboratories constitute medical devices that must obtain clearance or approval from FDA. Laboratory developed tests (LDTs) that are developed and provided by a single laboratory as a medical service (i.e., not sold to third party laboratories), have been historically outside the scope of FDA's regulatory authority. FDA regulation of IVDMIAs represents a substantial policy change.

- FDA has established three requirements for an IVDMA:

A) An IVDMA uses clinical data (from one or more IVDs, assays, and sometimes demographic data) to empirically identify an algorithm

AND

B) An IVDMA employs the algorithm to integrate these different data points in order to calculate a patient-specific result (e.g., a "classification," "score," or "index")

AND

C) The IVDMA result cannot be interpreted by clinicians using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.

- This definition is broader than FDA intended and likely overlaps standard medical practices, such as maternal testing for Down's Syndrome and the broad use of medical treatment algorithms.
- FDA's definition requires a subjective assessment as to whether a physician can interpret test reports which would be difficult to define and enforce.
- The Draft Guidance bases regulation on technology (multivariate analysis) rather than on health risks to patients. FDA should consider a risk based alternative.
- Currently CLIA accredited laboratories can make newly discovered genetic tests, mutations or improvements available in a timely fashion via the CLIA regulatory

framework. With FDA regulation patients and physicians may experience significant delays in access to state of the art tests.

- If LDTs are subject to FDA regulation as medical devices, then laboratories themselves become medical device manufacturers. Laboratories would be simultaneously subject to potentially overlapping FDA and CLIA regulations and standards.

We Would Encourage You to Consider Some or all of the Following Alternatives

1) We would like to request a more formal FDA Process

- Instead of issuing and finalizing guidance documents, FDA should propose new regulations that are detailed, clear, predictable, and practical in light of the actual risks and benefits of particular tests. Proposed regulations would then be subject to a period of notice and comment.

2) We would like FDA to consider strengthening CLIA as an alternative

- A reasonable and effective regulatory approach would be to strengthen CLIA and its regulations. CLIA should be strengthened through harmonizing quality standards and by the creation of a genetics sub-specialty under CLIA that addresses FDA's concerns regarding IVDMIAs.
- If FDA does move forward, it would be more efficient to maintain all laboratory service regulation, inspections, and proficiency testing under CLIA and FDA regulation should be limited to the actual test design and validation (i.e., the manufacturing components of the process development) and the marketing claims.

3) We would like FDA to consider a public registry as an alternative

- Instead of requiring clearance or approval, FDA could institute a disclosure program (akin to a registry) to provide reliable information about the strengths and limitations of IVDMIAs to all stakeholders. All IVDMIAs could be required to be registered and listed with FDA and validated by CLIA-certified laboratories. Tests could be required to be labeled to reflect the absence of FDA clearance or approval.

4) If FDA proceeds we would like FDA to narrow the definition of an IVDMIA and better define and clarify the regulatory process in a way that encourages innovation:

- The definition of IVDMIAs should 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 and what elements constitute the clinical laboratory service that uses the device.
- If FDA regulates IVDMIAs, the Agency should only require clearance or approval of laboratory tests that are used for high risk health situations and that reach a substantial test volume. Tests that serve small patient populations, have a low volume of usage, or are low risk, should be exempt from regulation. Such tests could be maintained in a registry as described above.
- If FDA regulates IVDMIAs, the regulatory review should focus on whether the evidence supports the intended claims as established by the company. A PMA should be required only for those predictive tests that are high risk and result in a binary therapy recommendation based solely on the test outcome. All other tests that are used in conjunction with other clinical parameters as decision aids or tools, should, at most, require 510(k) clearance. If a test with only analytical performance claims is an IVDMIA, it should be Class I, 510(k)-exempt.
- If FDA regulates IVDMIAs, we recommend a transition period of two years for submission of applications for IVDMIAs deemed to require a 510(k) and four years for submission of applications for IVDMIAs deemed to require a PMA. We also recommend a transition period for GMP compliance requirements. During the transition period, FDA should not require that laboratories label their tests as “investigational.”
- If FDA is going to oversee IVDMIAs, there should be clear delineation of responsibility and authority between FDA and CMS to avoid overlapping regulations and inspections and to facilitate compliance.

Where do I direct comments?

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20850

RE: 2006D-0347

 *(this is the FDA docket number)*

If you have questions or suggestions about this document, please contact David Barnhart at 202-638-5616.

DRAFT

1/23/2007

To read more about the draft guidance, please go to:

IVDMIA Draft Guidance: <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>

To submit your comments on these FDA documents electronically before the **March 5, 2007** deadline, refer comments to Docket ID Numbers below:

Docket ID: [2006D-0347](#)

Title: Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays;

Availability: 09/04/06

Deadline: 03/05/07