

# 21<sup>st</sup> centurymedicine

March 2, 2007

**VIA Electronic Submission** ([www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments))

Dockets Management Branch—HFA-305

Food and Drug Administration

5630 Fishers Lane—Room 1061

Rockville, Maryland 20852

**RE: 2006D-0347**

**Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on *In Vitro*  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

Dear Sir or Madam:

On behalf of the Coalition for 21st Century Medicine (the “Coalition”), we are pleased to submit comments in response to the above-captioned draft guidance on In Vitro Diagnostic Multivariate Index Assays (IVDMIA)s(the “Draft Guidance”). The Coalition comprises some of the world's most innovative diagnostic technology companies, clinical laboratories, physicians, venture capitalists, and patient advocacy groups and was founded last Fall with a mission to improve the quality of healthcare by encouraging the research, development and commercialization of innovative new diagnostic technologies. We believe our mission is fully consistent with the goals and objectives of the Food and Drug Administration (FDA). We also believe that working with the FDA on key policy considerations raised by the Draft Guidance will advance our mission and the goals and objectives we share with the FDA.

As explained more fully below, we would respectfully request that FDA consider the following recommendations:

1. If the FDA determines that regulation of IVDMIA)s as medical devices<sup>1</sup> is the most appropriate pathway to address concerns the Agency has about these assays, we would urge FDA to proceed only under the full protections of notice-and-comment rulemaking. Prior to publication of a proposed regulation, we would encourage the FDA to convene a public workshop where stakeholders and regulators can discuss critical issues about regulation of IVDMIA)s in an interactive fashion.

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<sup>1</sup> The Coalition is aware that some groups have questioned whether or not FDA has the authority under the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et seq.*) to regulate laboratory-developed tests, including IVDMIA)s, as medical devices. The Coalition does not address this question. These comments include the Coalition's recommendations as to how FDA should proceed if it makes a final policy determination to regulate these laboratory services as medical devices. The Coalition's comments supportive of certain approaches to regulation should not be considered an acknowledgement by the Coalition or any of its members 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 IVDMIA does not represent an admission by the Coalition or any of its members 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)).

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2. FDA should work with the Centers for Medicare & Medicaid Services (CMS) through the Department of Health and Human Services (HHS) to determine the most appropriate regulatory framework for IVDMIAs to assure that patients and physicians have timely access to accurate, reliable and safe advanced diagnostic information. This should include enhancing and strengthening existing requirements under the Clinical Laboratory Improvement Amendments (CLIA), wherever appropriate, to address concerns FDA may have about the accuracy, reliability or safety of IVDMIAs. A first step could involve the creation of a registry to assess the number and type of IVDMIAs currently in clinical use and to gather information regarding the data supporting these IVDMIAs. The Coalition also supports CMS's proceeding with proposed rulemaking on the development of a new genetic specialty under CLIA.
3. FDA's regulation of any laboratory-developed tests should be risk-based rather than technology-based and should be grounded in intended use claims pursued by laboratories:
  - Analytical performance claims should be regulated as Class I exempt from pre-market review and Quality System Regulations other than complaint files and medical device reporting requirements.
  - Prognostic or predictive claims that are not intended to produce binary results and that would not be intended for use definitively to make a diagnosis or to make a "yes/no" treatment decision should be regulated as Class II subject to clearance under 510(k).
  - Predictive claims based upon binary results that are intended to be used to make a definitive diagnosis or a yes/no treatment decision should be regulated as Class III subject to pre-market approval.
  - There should be an exemption for tests intended for use in the diagnosis, monitoring or management of patients with rare disorders.
4. FDA's criteria for evaluating pre-market review submissions of in vitro diagnostic tests introduced in the 21st century must reflect 21st century advances in scientific methods. IVDMIAs supported by data from studies following methods that are accepted by experts in the relevant fields (as evidenced by peer-reviewed publications) should be cleared or approved even if uncertainty remains about the clinical utility of the tests in specific populations. Uncertainty about clinical utility can be addressed through transparency and disclosure in labeling.
5. FDA has defined IVDMIAs by their incorporation of algorithms that are not well-known to physicians. Therefore, FDA should identify the algorithm (and any associated software or hardware) as the medical device subject to regulation. Identifying the algorithm as the medical device will clarify the distinction between the FDA-regulated device and the CLIA-regulated laboratory service, and will provide an established, clear regulatory pathway for modifications to the cleared/approved device and the laboratory service.
6. FDA should allow a reasonable transition period following publication of its final policy regarding regulation of IVDMIAs to allow laboratories to come into compliance with the substantial new regulatory burdens that would be imposed. This includes transition periods before the Agency would enforce compliance with pre-market review as well as post-market controls, such as QSRs. Pending release of any final policy on IVDMIAs and an appropriate transition period, FDA should allow

laboratories to continue to offer tests that are lawfully performed under CLIA and state licensure laws and should not require laboratories to mark these tests as “Investigational Use Only.”

Further explanation of these recommendations and the rationale for proposing these is provided below.

**I. The Draft Guidance, If Implemented, Would Impose Substantial New Obligations on Clinical Laboratories and Represents Substantive Rulemaking—not Guidance. The Terms Used in the Draft Guidance are Novel and Ambiguous, and Many Key Issues are Not Addressed in the Draft Guidance. This Creates Significant Uncertainty for Laboratories and Other Stakeholders. Therefore, the Coalition Strongly Urges that, If FDA Proceeds with Regulation of IVDMIAs, the Agency Should Proceed Under Formal Notice-and-Comment Rulemaking. The Coalition also Requests that FDA Hold a Public Workshop Prior to Issuing a Proposed Rule**

**A. The Draft Guidance, If Implemented, Would Impose Substantial New Obligations on Clinical Laboratories and, Therefore, Represents Substantive Rulemaking—not Guidance.**

The FDA’s release of the Draft Guidance in September 2006 provided the first public notice to clinical laboratories that FDA was intending to require pre-market submissions and compliance with post-market controls on any segment of laboratory-developed testing. Prior to the release of the Draft Guidance, clinical laboratories proceeded with the development of new tests confident that they had a choice of the regulatory pathway they could select: (1) A company could choose to create and distribute a new test to clinical laboratories for the laboratories’ use. Such a test was clearly subject to FDA regulation as a “device.” (2) Alternatively, a laboratory that developed a new test could choose to be a clinical laboratory regulated under federal CLIA regulations performing the new test only in its own clinical laboratory. Laboratories choosing to do business as a clinical laboratory were not subject to FDA’s medical device regulations, so long as they did not sell the test, or components of the laboratory procedures, to other medical laboratories. By contrast, the Draft Guidance, if implemented, would restrict the pathway available to clinical laboratories who develop assays fitting FDA’s definition of an IVDMIA to the first pathway—pre-market submission and regulation as a medical device. As such, the Draft Guidance, if finalized, would be binding on clinical laboratories and is, therefore, a rule within the meaning of the Administrative Procedure Act.<sup>2</sup>

Although termed a “guidance,” the Draft Guidance does not fit under FDA’s Good Guidance Practice (GGP) Regulations. Under the GGP Regulations: “Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or the FDA.”<sup>3</sup> As noted above, the Draft Guidance does impose legally binding obligations on clinical laboratories. Nowhere in the

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<sup>2</sup> Under the Administrative Procedure Act: “[R]ule’ means the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency and includes the approval or prescription for the future of rates, wages, corporate or financial structures or reorganizations thereof, prices, facilities, appliances, services or allowances therefore or of valuations, costs, or accounting, or practices bearing on any of the foregoing; . . .” (5 U.S.C. § 551(4).) Similarly, under Executive Order 12866 “Regulatory Planning and Review,” the Executive Branch defines a regulation as “an agency statement of general applicability and future effect, which the agency intends to have the force and effect of law, that is designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency. \* \* \*” (E.O. 12866 [Sept. 30, 1993] as amended by E.O. 13258 [Feb. 26, 2002] and E.O. 13422 [Jan. 18, 2007].)

<sup>3</sup> 21 C.F.R. § 10.115(d)(1).

Federal Food, Drug and Cosmetic Act<sup>4</sup> or the regulations promulgated thereunder is the term “IVDMIA” identified. The Draft Guidance is the only document that identifies these services as medical devices subject to pre-market submission and post-market controls. Absent the Draft Guidance, clinical laboratories would not have to fulfill these requirements for IVDMIA. The Draft Guidance therefore changes the regulatory obligations and burdens of laboratories.

In addition, the GGP Regulations state that “[one] may choose to use an approach other than the one set forth in a guidance document.”<sup>5</sup> However, it is not clear how laboratories can comply with the requirements enumerated in the Draft Guidance by any means other than following the Draft Guidance and submitting to pre-market review and post-market controls as a medical device manufacturer.

Because the Draft Guidance imposes substantial new regulatory requirements on clinical laboratories that are not anywhere addressed in the FDCA or its regulations and because the Draft Guidance provides no pathway for compliance by laboratories offering IVDMIA other than by submission to FDA’s pre-market review and post-market controls, the Draft Guidance represents substantive rulemaking. Should FDA decide to finalize the policies announced in the Draft Guidance, it should do so only through formal notice-and-comment rulemaking.

**B. The Term IVDMIA as Used in the Draft Guidance is Novel and Ambiguous. Many Key Issues are Not Addressed in the Draft Guidance. This Creates Significant Uncertainty for Laboratories and Other Stakeholders.**

The term “In Vitro Diagnostic Multivariate Index Assay” is a novel term that is not set forth anywhere in the FDCA or in FDA’s regulations. Since the publication of the Draft Guidance, many stakeholders have expressed to FDA their concerns about the lack of clarity of the IVDMIA definition (this concern was mentioned repeatedly at the FDA public meeting on February 8, 2007). Laboratories simply cannot determine which test services fit within the definition and which do not. This leaves laboratories in a very precarious position of uncertainty as to whether they are operating as medical device manufacturers and whether the tests they offer are or are not considered by FDA to be medical devices subject to pre-market review and post-market controls.

The Draft Guidance provides both a definition of IVDMIA as well as criteria that describe an IVDMIA. IVDMIA are defined as: “[T]est systems that employ data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease.”<sup>6</sup> In the Draft Guidance, FDA notes that “Use of the term ‘test system’ in this guidance document is not linked with use of the term in [the CLIA regulations].”<sup>7</sup> FDA does not explain, however, how the term test system differs between the FDA and CLIA regulatory frameworks. Laboratories must understand these distinctions if they are going to be held accountable to both FDA and CLIA requirements for their test systems.

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<sup>4</sup> 21 U.S.C. § 301 *et seq.*

<sup>5</sup> 21 C.F.R. § 10.115(d)(2).

<sup>6</sup> Draft Guidance, at 3.

<sup>7</sup> *Id.*, footnote 2. The CLIA regulations define test systems as “the instructions and all of the instrumentation, equipment, reagents, and supplies needed to perform an assay or examination and generate test results.” (42 C.F.R. § 493.2.)

The Draft Guidance provides the following criteria to describe an IVDMIA:

“IVDMIA reflect the following characteristics:

1. Use clinical data -- including data from one or more in vitro assays and, in some cases, demographic data -- to empirically identify variables and to derive weights or coefficients employed in an algorithm;
2. Employ the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test; and
3. Report this result, which cannot be interpreted by the well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.”<sup>8</sup>

Many stakeholders have identified long-established test measures involving algorithmic transformations of clinical laboratory data, such as creatinine clearance, cholesterol ratios, and triple marker screening for fetal neural tube defects, that would fit under these criteria and would appear to be IVDMIAs. FDA has indicated in public meetings, however, that it does not intend to regulate these long-established tests. It is unclear, however, if modifications to such tests (e.g., the quadruple marker screen currently used for neural tube defects) would render the modified tests subject to FDA regulation.

Although the first criterion is reasonably straightforward, the second and third criteria are ambiguous and subjective. It is unclear what would be required to assess whether an algorithm can be independently confirmed under the second criterion. If the algorithm has been published in the peer-reviewed literature is this sufficient to allow for independent validation such that a test would not be considered an IVDMIA? If a laboratory unrelated to the laboratory that develops a test conducts a study on its own which supports the validity of the test algorithm, is this sufficient to remove the test from being an IVDMIA? The third criterion involves an inherently subjective assessment of what a well-trained healthcare practitioner can or cannot interpret. Who determines whether or not practitioners can interpret the test results? By what objective standard? If health care practitioners can interpret the results based upon findings from clinical studies published in peer-reviewed journals would this be sufficient to take a test out of the definition of an IVDMIA? If not, what standard would apply? If a test initially fits under the definition of an IVDMIA because it is determined that healthcare practitioners cannot interpret the result independently, will the IVDMIA no longer be subject to FDA regulation once a sufficient number of practitioners become familiar with the assay measurement?

The lack of clarity around the definition of an IVDMIA has important implications for laboratories and those who fund the development of new tests in those laboratories. If a test is subject to FDA pre-market review and post-market controls, the cost of development and the ongoing cost of compliance with QSRs will be substantially higher and the time to commercial release significantly longer than would be the case under the CLIA pathway. Laboratories and their sponsors must be confident of the likely costs and timeline to commercialization or they may find that projects may need to be halted mid-course for lack of funding. Uncertainty about the regulatory pathway will give funders pause before investing in novel

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<sup>8</sup> Id.

tests, and higher costs and longer times to market will mean that sponsors will invest only in those tests that are less risky and/or have larger patient populations to justify the increased investment expenditures.

It is not simply the lack of clarity around the definition of an IVDMA that concerns laboratories and their financial sponsors. Many key issues that must be addressed for laboratories to be in compliance with the requirements to be imposed on IVDMA manufacturers are left as open issues. These include: identifying the elements of an IVDMA that comprise a medical device subject to FDA regulation versus those that are the laboratory service regulated under CLIA, pathways for pre-market review of such assays, compliance with FDA's QSRs, 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. We respectfully submit that these are critical questions which must be clearly and publicly answered before any clinical laboratory can be required to comply with the substantial, new regulatory burdens being imposed by FDA. Although we believe that the regulatory framework under which these questions are addressed should be accomplished through notice-and-comment rulemaking, we would agree that many of the details about compliance with FDA requirements can be set out in sub-regulatory guidance.

**C. Therefore, the Coalition Strongly Urges that If FDA Proceeds with Regulation of IVDMA's, the Agency Should Proceed Under Formal Notice-and-Comment Rulemaking. The Coalition also Requests that FDA Hold a Public Workshop Prior to Issuing a Notice of Proposed Rulemaking**

The burdens to be imposed on clinical laboratories by the policies announced in the Draft Guidance are significant and warrant the full protections afforded by on-the-record notice and comment rulemaking. Although FDA's GGP approach does allow for notice and comment from stakeholders, it falls short of formal rulemaking in several key areas:

- First, formal rulemaking requires agencies, like FDA, to respond to comments on-the-record in a final rulemaking. Given the large number of questions that have been raised and comments submitted in response to the Draft Guidance, having an opportunity to review FDA's on-the-record responses to these questions and comments will be very important. These responses will also help provide useful guidance to affected parties.
- Second, formal rulemaking involves a statement of justification and performance of impact analyses, such as those under the Regulatory Flexibility Act, when required. Because the policies presented in the Draft Guidance are new and likely to have a significant impact on at least one sector of the clinical laboratory community (laboratories that conduct high complexity testing), it is not inappropriate to ask FDA to provide a clear justification for regulation of IVDMA's and to assess the burdens that regulation will impose on laboratories, referring physicians and patients.<sup>9</sup>
- Third, formal rulemaking allows for oversight by the Office of Management and Budget (OMB) to assess how rulemaking by one agency may affect regulatory policies by another agency. In the case of laboratory testing, regulatory policies by CMS (CLIA) and the Federal Trade Commission (FTC)

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<sup>9</sup> This is also consistent with the Regulatory Philosophy and Principles presented under Executive Order 12866 "Regulatory Planning and Review"—"each agency shall identify in writing the specific market failure . . . or other specific problem that it intends to address . . . that warrant new agency action, as well as assess the significance of that problem to enable assessment of whether any new regulation is warranted." (E.O. 12866 as amended, *supra*.)

already govern the operations of clinical laboratories. New and additional regulation by FDA should be evaluated in the context of those established regulatory frameworks to make sure the objectives and burdens of regulation are consistent. Rulemaking would ensure that FDA has assessed whether and how concerns it may have about IVDMIAs may be addressed more effectively or efficiently through enhancement of CLIA or enforcement by the FTC.<sup>10</sup>

- Formal rulemaking also includes the opportunity for congressional oversight, access to judicial review, when appropriate, and codification in the Code of Federal Regulations.<sup>11</sup>

Because the Draft Guidance describes a category of medical device not described elsewhere in the FDCA or FDA regulations, would impose substantial new burdens on clinical laboratories, is ambiguous in identifying which laboratories and which test services will be subject to regulation as medical device manufacturers and medical devices, respectively, we would urge FDA to withdraw the Draft Guidance at this time. Following withdrawal of the Draft Guidance, we would recommend that FDA hold a public workshop at which all stakeholders and Agency representatives can discuss at length and in an interactive fashion the concerns the Agency has with IVDMIAs and the full range of regulatory options to address those concerns. Following such a meeting, if FDA determines that regulation of IVDMIAs as medical devices represents the most effective and efficient approach to address the Agency's concerns, then we would recommend that the Agency proceed under formal notice-and-comment rulemaking. By following this process, FDA can assure that the new regulatory framework will meet the Agency's objectives in the least burdensome fashion while protecting patients and assuring access to innovative new tests.

## **II. FDA Should Work Through HHS to Enhance and Strengthen Regulation of IVDMIAs and Other Laboratory-Developed Tests Under CLIA Where Appropriate. FDA and/or CMS Should Consider Creating A Registry of IVDMIAs to Assess the Nature and Scope of Established IVDMIAs. The Coalition Supports the Call for CMS to Proceed with Consideration of Proposed Rulemaking to Create a Genetic Specialty Under CLIA.**

### **A. FDA Should Work Through HHS to Enhance and Strengthen Regulation of IVDMIAs and Other Laboratory-Developed Tests Under CLIA.**

IVDMIAs are clinical laboratory test services. As such they already are subject to substantial levels of regulation under federal and state law. The federal regulatory framework created by Congress to assure the consistent performance by laboratories of valid and reliable testing is CLIA.<sup>12</sup> CLIA is a comprehensive regulatory system covering the pre-analytic (including sample requisition and accession), analytic and post-analytic (including reporting) phases of laboratory testing. CLIA regulations include

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<sup>10</sup> E.O. 12866 directs agencies to consider the effect of regulation by other agencies: "Each agency shall examine whether existing regulations (or other law) have created, or contributed to, the problem that a new regulation is intended to correct and whether those regulations (or other law) should be modified to achieve the intended foal of regulation more effectively." (E.O. 12866 as amended, *supra*.)

<sup>11</sup> See Office of Management and Budget, Final Bulletin for Agency Good Guidance Practices, 72 Fed. Reg. 3242 (Jan. 25, 2007).

<sup>12</sup> Under CLIA: "No person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a certificate issued by the Secretary [of HHS] under this section applicable to the category of examinations or procedures which includes such examination or procedure." (42 U.S.C. § 263a(b).) CLIA requires the Secretary to "issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations and other procedures." (42 U.S.C. § 263a(f)(1).)

standards covering registration, personnel, facility administration, proficiency testing, quality systems, and enforcement.

We understand that some believe that CLIA regulations address only analytical performance (can the test measure what it is purported to measure) and do not cover clinical validity (accuracy at predicting a clinical condition or predisposition) or clinical utility (value of the information to patient management).<sup>13</sup> This is not an accurate reading of the CLIA regulations. CLIA regulations require that laboratories validate clinical tests for their intended uses before patient use.<sup>14</sup> In the context of IVDMIAs, if the result reported by the laboratory is the product of a computational algorithm, then CLIA would require that the laboratory establish performance characteristics for that result. If the result is a predictive score, then CLIA would require clinical validation of such score.

Beyond the requirement for establishing performance specifications—including clinical validation when inherent in the reportable result—other provisions under CLIA also pertain to the clinical validity and clinical utility of laboratory testing. CLIA regulations require that the laboratory director “ensure that reports of test results include pertinent information required for interpretation” and that “consultation is available to the laboratory’s clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions.”<sup>15</sup> Laboratories are also required to have a clinical consultant who, among other things, must be available to assist the laboratory’s clients in “ensuring that appropriate tests are ordered to meet the clinical expectations.”<sup>16</sup> These regulations show that a comprehensive framework exists to assure that clinical testing is relevant to patient management.

The purpose of laboratory testing is to provide information to physicians and patients to assist with patient management decisions. For tests that are professional use only (testing ordered by and results reported back to a treating physician), concerns that the FDA may have about lack of pre-market review by a third party of IVDMIAs should be addressable through clarifications and enhancements to the CLIA regulatory framework, such as requiring transparency about the validation of a novel test to support intended use claims and about limitations in the data supporting such claims. This could include a requirement to provide citations to peer-reviewed publications that evidence the validation performed and posting of summaries of validation data that have not been published in a peer-reviewed venue (e.g., through posting on the lab’s website and by inclusion of references in the laboratory report).<sup>17</sup>

**B. FDA and/or CMS Should Consider Creating A Registry of IVDMIAs to Assess the Nature and Scope of Established IVDMIAs.**

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<sup>13</sup> Staff of the Secretary’s Advisory Committee for Genetics in Health and Society, Federal Oversight of Genetic Tests and Genetic Testing Laboratories Nov. 2006, at 2, footnotes 3-5.

<sup>14</sup> CLIA requires laboratories to establish performance specifications for test systems other than unmodified FDA-cleared or approved test systems: “Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house . . . ) or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: (i) Accuracy. (ii) Precision. (iii) Analytical sensitivity. (iv) Analytical specificity to include interfering substances. (v) Reportable range of test results for the test system. (vi) Reference intervals (normal values). (vii) Any other performance characteristic required for test performance. (42 C.F.R. § 493.1253(b)(2).)

<sup>15</sup> 42 C.F.R. § 493.1245(e)(8), (9).

<sup>16</sup> 42 C.F.R. § 493.1257(b).

<sup>17</sup> Such refinements and enhancements may be adopted through revision to the Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services (Appendix C of the State Operations Manual).

IVDMIA's represent a leading edge of new diagnostic technologies aimed at personalizing healthcare to improve patient outcomes and reduce health care costs. The number and nature of tests that are currently in clinical use across academic laboratories and private commercial laboratories is unclear. FDA has indicated at various meetings that it believes the number of IVDMIA's to be relatively small, but it is unclear on what basis FDA has made such an estimate. Our own informal analysis suggests that there are approximately 200 novel tests that involve in vitro diagnostic data incorporated into algorithms to produce patient-specific results which are in development or have recently been introduced clinically. Our review of the literature suggests that this number will grow significantly in the near future.

In order to obtain a clearer picture of the scope of testing that would fit under an IVDMIA definition, we would recommend that FDA or CMS (under CLIA) consider the establishment of a registry. If a robust database of tests is developed, this would help inform FDA as well as CMS, HHS and FTC of the number and nature of tests being performed, the claims being made, and the potential risks involved. Such data could help inform policymakers across these agencies as well as those in Congress to identify the most appropriate regulatory framework to assure that patients have timely access to accurate and reliable tests that can improve patient outcomes.

A registry could be set up through FDA on a voluntary basis initially, much like the FDA's voluntary pharmacogenomic submission project.<sup>18</sup> Alternatively, a registry could be set up through CMS under the CLIA program, which already surveys all laboratories that perform high complexity testing. Regardless which agency sets up and maintains such a database, we would recommend that it be set up initially on a pilot basis (1) to assure that the data fields are relevant and will produce useful data for analysis and (2) to allow an assessment of the resources required for laboratories to report into the database and FDA, CMS or other entities to maintain and analyze the data held in the database.

**C. CMS Should Proceed with Consideration of Proposed Rulemaking to Create a Genetic Specialty Under CLIA.**

In September 2006, a Citizen Petition was submitted to CMS asking CMS to create a genetic testing specialty under CLIA and to establish standards for proficiency testing.<sup>19</sup> The petitioners noted that although the Centers for Disease Control and Prevention issued a Notice of Intent in 2000 that CMS would issue a Proposed Rule to create a genetic testing specialty and that as late as June 2006, a CMS official testified before the Secretary's Advisory Committee on Genetics, Health and Society that a Proposed Rule was in the process of being cleared at CMS, CMS indicated in August 2006 that it had abandoned this rulemaking activity. CMS indicated that it was abandoning the new regulatory effort because current regulations are adequate to ensure the accuracy and reliability of genetic testing laboratories.<sup>20</sup>

The Coalition believes that it is appropriate for CMS to consider proceeding with rulemaking regarding creation of a genetic specialty under CLIA. Although we appreciate CMS's concern that new regulation may inhibit innovation in a rapidly changing field, like genetic and genomic testing, we believe these considerations can be taken into account during a rulemaking proceeding. The rulemaking exercise under

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<sup>18</sup> See <http://www.fda.gov/cder/genomics/VGDS.htm>

<sup>19</sup> Petition for Rulemaking Requesting a Genetic Testing Specialty and Standards for Proficiency Testing submitted by the Genetics and Public Policy Center, the Genetic Alliance and Public Citizen's Health Research Group (Sept. 26, 2006).

<sup>20</sup> *Id.*

CLIA should consider existing regulatory requirements, and any new regulatory requirements should be appropriately targeted to address identified concerns in the most effective and efficient means possible.

**III. FDA Regulation of Laboratory-Developed Tests Should be Risk-Based Rather Than Technology-Based. FDA Regulation of In Vitro Diagnostics Should be Based Upon the Sponsor's Claimed Intended Use(s).**

**A. FDA Regulation of Laboratory-Developed Tests Should be Risked-Based Rather Than Technology-Based.**

We were concerned by FDA's decision to move forward with regulation of a segment of laboratory-developed tests identified by a technological feature—a computational algorithm—rather than by consideration of the nature and extent of risk associated with novel testing. Although we would agree that technological advances sometimes may correlate with risk, technological changes are not the best proxy for risk. FDA has not identified why tests incorporating algorithms raise significantly greater risks than tests that do not incorporate such computations. Although the level of regulation of IVDMIAs may vary depending on risk, the threshold decision of whether to regulate is based on technology, not risk.

When any novel test is first introduced, its performance characteristics and its appropriate role in patient management are generally not well understood by health care practitioners based upon their prior knowledge of medicine. Data from the laboratory(ies) that develop the test as published in peer-reviewed literature or provided directly by the laboratory are necessary to inform practitioners about the performance and use of the test. There is nothing inherent in a computational algorithm that makes a test more or less understandable to practitioners. It is the novelty of a test—not an algorithm—that is relevant in assessing physician understanding.

Whether or not physicians understand a test report is itself only a weak proxy for risk. If a novel test is used directly to make a definitive diagnosis or to direct a “yes/no” decision about selecting a particular therapy, then there can be significant risk if the test report is not understood by the physician. The risk is much less, however, when a diagnostic test is simply one of many pieces of information used by a physician to make a diagnosis or to select treatment. The nature of the disease and treatment are also important. FDA should consider these risk-related factors in developing a regulatory framework for diagnostic tests rather than triggering regulation based upon the presence or absence of an algorithm or the Agency's assessment as to whether the test report can be interpreted by practitioners.

**B. FDA Regulation of In Vitro Diagnostic Tests Should be Based Upon the Sponsor's Claimed Intended Use**

When assessing the potential risks associated with a novel test for purposes of determining the appropriate pre-market review pathway and the extent of data required for clearance or approval, FDA should focus on the claims made by the sponsor. If a sponsor claims that a novel test reports a particular result, but makes no claim as to how the results may be used to make a diagnosis or to select treatment, FDA should not infer such broader claims. Physicians order tests based upon their determination as to how the information obtained from the test report will be used in patient management. That determination may be informed by the laboratory's claims, but also may be based upon other information available to the physician as well as the physician's own clinical experience. Rather than inferring claims that may involve greater risk and requiring the sponsor to clear higher regulatory hurdles, FDA may

address the potential for greater risk through appropriate statements set out in labeling about the limitations of the test.

**C. Recommendations for a Risk-Based Framework for Regulation of IVDMIAs**

We would offer the following recommendations for a risk-based regulatory framework for IVDMIAs:

- Analytical performance claims should be assigned to Class I, exempt from pre-market review and exempt from QSR requirements (with the exception of recordkeeping and complaint files)
- Claims of clinical validity that are non-binary and are not intended to make a definitive diagnosis or to make a “yes/no” treatment determination should be assigned to Class II with clearance under 510(k) premarket notification.
- Claims of clinical utility that are binary and are intended to make a definitive diagnosis of a disease presenting a high risk or to make a “yes/no” treatment determination should be assigned to Class III, premarket approval.
- Tests intended to assist with diagnosis or management of patients with rare disorders (other than tests that produce binary results intended to make a definitive diagnosis or “yes/no” treatment determination) should be assigned to Class I, exempt from pre-market review and exempt from QSR requirements (with the exception of recordkeeping and complaint files).

Intended use statements that are limited to describing the intent to produce a reportable result within specified performance limits and that do not make any particular claim of clinical validity or utility represent low risk to patients. Physicians will order such tests based upon their own understanding and knowledge of how the particular reportable result can be used in patient management. FDA’s inferring intended use, clinical validity or clinical utility claims that are not, in fact, made by the laboratory would be interfering with the practice of medicine. Class I general controls, such a registration and listing and maintenance of records and complaint files should be sufficient to protect patients and should provide FDA sufficient information to assess whether the test poses risks that would require higher levels of controls.

Claims that are limited to providing information about clinical validity that physicians will use in conjunction with other information when making a diagnosis or selecting treatment involve greater risk than analytical performance claims because physicians will rely on the claim, in part, in making a diagnosis or selecting treatment. However, because the results are intended to be adjunctive only, the risk is moderated by the availability of other information to support or challenge the findings from the diagnostic test. Physicians should not act on the basis of information from these tests alone. If other information is contradictory, the physicians should explore further before making a diagnosis or selecting treatment. Class II special controls should be sufficient to protect patients with these types of tests.

Claims that are binary in nature—yes/no determinations about diagnosis or treatment selection for conditions or diseases presenting a high risk—involve the highest level of risk because these are intended to be used directly in patient management. Class III premarket approval controls are appropriate for these highest risk claims. This type of risk-stratified approach is consistent with the least burdensome provision.

Proceeding under FDA regulation will involve substantially greater costs and longer times to commercialization than proceeding under a CLIA pathway. Laboratories and those who fund them will

only invest in novel tests if they determine that the potential return on investment is reasonable and consistent with other potential applications of their investment dollars. Tests targeted to patients with rare disorders inherently have a low potential market return unless the unit revenues are adequate to justify the investment. If the investment costs are increased substantially by proceeding under an FDA clearance or approval pathway, it is likely that laboratories will not invest their resources in the development of tests for rare disorders. The only other option would be for the price of such tests to increase substantially to reflect the increase in development and ongoing compliance costs. As prices are constrained by third party payer policies, which often are quite restrictive for diagnostic tests, the ability of labs to obtain a reasonable return on investment for these tests will likewise be constrained. For these reasons, we would recommend that tests targeted to patients with rare disorders (except those that represent binary determinations) should be assigned to Class I exempt from pre-market review and QSR compliance except for recordkeeping and complaint files.

**IV. FDA Pre-market Review of a 21st Century Diagnostic Should Adopt 21st Century Scientific Methods. Scientific Methods Accepted by Experts in the Relevant Field Should be Sufficient to Support Pre-market Clearance/Approval of Novel Diagnostics. Uncertainty about Clinical Utility Can be Addressed Through Transparency in Labeling.**

FDA's Critical Path Initiative recognizes the potential value of novel biomarkers to help physicians and patients select therapies which are best suited to the individual patient. This is intended to improve patient outcomes and save healthcare resources. As such, biomarker diagnostics in the 21st Century are called upon to perform in ways that older diagnostics were not used. Many novel tests require consideration of multiple markers in order to provide useful information for physicians and patients. To facilitate physician interpretation of results from multiple markers, computational algorithms are not infrequently incorporated into tests to produce reportable results. These are the tests on which FDA appears to be focusing with its IVDMA regulatory initiative.

Whenever one combines results from multiple markers into a single outcome measure, there is the potential for uncertainty in the outcome measure based upon the ways in which the underlying measures may combine to produce the reported results. The potential relationships among the markers increase factorially with the number of markers. The potential uncertainty inherent in these outcome measures is unlike that with which the Agency has been comfortable with traditional in vitro diagnostics. As long as sponsors proceed with validation studies consistent with established methods for validation accepted by experts,<sup>21</sup> FDA should allow these tests to be cleared or to obtain pre-market approval despite uncertainty about the clinical utility of the test. As standards in methodology evolve over time, FDA's criteria for clearance or approval should adapt accordingly. Otherwise, FDA reviewers will not be equipped to handle the types of submissions they will be asked to review. We would also note that concerns about uncertainty can best be addressed through limitations included in labeling.

**V. If FDA Proceeds with Regulation of IVDMIAs, it Should Specify that the "Device" is the Algorithm—not the Laboratory Procedure, which is Regulated by CLIA.**

Under the Draft Guidance, the key feature which identifies an IVDMA is the presence of a computational algorithm, which as the Agency correctly observes, usually runs on software. As we understand the Draft Guidance, a laboratory-developed test that does not incorporate an algorithm to

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<sup>21</sup> See, e.g., Simon R. Development and evaluation of therapeutically relevant predictive classifiers using gene expression profiling. *J Natl Cancer Inst.* 2006;98(17):1169-1171.

produce a reportable result will not fit the definition of an IVD MIA.<sup>22</sup> Therefore, we would recommend that, if FDA proceeds with regulation of IVDMIAs, the Agency should define the “device” subject to regulation as the algorithm along with any associated software and hardware involved with running the algorithm. Under this definition, FDA regulation would comprise whatever level of pre-market review is required (based upon risk-based assignment to Class I, II, or III), labeling consistent with the intended use statements cleared or approved by FDA, compliance with QSRs, and MDR reporting.

Defining the algorithm as the medical device would address many questions and concerns that commenters have raised about how clinical laboratories can simultaneously meet laboratory licensure and certification requirements under CLIA and state laws (and voluntary accreditation where applicable) and fulfill FDA pre-market and post-market control regulations as medical device manufacturers. During the February 8<sup>th</sup> meeting, many speakers noted the problems created by overlap between CLIA and QSRs. Drawing this line would largely eliminate these issues. The clinical laboratory would perform pre-analytical, analytical and post-analytical steps under CLIA and state law, subject to test validation, personnel, quality system and proficiency testing requirements to which the laboratory has always been subject. There would be the added step that the laboratory would be acquiring and using an FDA-regulated device—the algorithm—the labeling and instructions for use of which would be incorporated into the laboratory’s procedure manuals. FDA inspectors evaluating compliance with QSRs would look at compliance with required controls as these pertain to the algorithm, but would not need to address the operations of the lab, which the CLIA/state/accrediting bodies cover in their inspections.

Defining the device as the algorithm would also make the regulatory requirements for modifications much clearer as these would follow well-established pathways under CDRH and OIVD guidance.

**VI. If FDA Proceeds with Regulation of IVDMIAs, it Should Allow Sufficient Time for Laboratories to Come into Compliance with the Substantial New Burdens Imposed by These New Rules. Pending Release of any Final Policy on IVDMIAs and an Appropriate Transition Period, FDA Should Not Require Laboratories to Label IVDMIAs as “Investigational Use Only.”**

**A. If FDA Proceeds with Regulation of IVDMIAs, it Should Allow a Sufficient Transition Period for Clinical Laboratories to Come Into Compliance with the New Rules**

Two themes were clear among essentially all presenters at the FDA’s Public Meeting on the Draft Guidance, which was held on February 8: (1) extending medical device jurisdiction to IVDMIAs represents a major change in FDA policy that will impose significant new burdens on clinical laboratories offering these tests, and (2) there remains significant confusion among stakeholders about what and how FDA intends to regulate under the IVD MIA initiative. Given these concerns, the Coalition would strongly urge FDA to allow clinical laboratories adequate time following release of a final policy document<sup>23</sup> to come into compliance with the new rules. Fundamental fairness requires that such transition periods be allowed because laboratories cannot know until a final document is released who, what, how or when they will need to come into compliance.

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<sup>22</sup> We understand that the FDA has indicated that not all tests that incorporate algorithms would be considered IVDMIAs.

<sup>23</sup> As above, the Coalition urges FDA to proceed with formal notice-and-comment rulemaking. However, regardless of the format of release of any final policy, we would also urge FDA to allow for a transition period before enforcement of the new rules begins.

As the burdens to come into compliance differ significantly depending upon the regulatory class to which tests may be assigned, we would propose the following transition periods—

- All IVDMIAs—1 year for establishment registration, listing of IVDMIAs, and compliance with complaint recordkeeping and MDR reporting requirements.
- Class II IVDMIAs—2 years for submission of 510(k) pre-market notifications.
- Class III IVDMIAs—4 years for submission of pre-market approval applications.

We would note that phased transition of a major new regulatory framework is consistent with previous Agency practice, such as the regulation of reproducers of single use medical devices, as well as FDA's proposal for research use only products.<sup>24</sup>

We would also note, that pending release of a final policy document and passage of an appropriate transition period, if FDA has concerns about the performance of any particular IVDMIA, it can contact CLIA program officials and/or state regulators, who can take appropriate action against laboratories performing testing that fails to meet required performance standards. If FDA has concerns about labeling or promotion, it can contact FTC officials and/or parallel state agencies, who can take appropriate action against laboratories making unfair or deceptive claims.

**B. Pending Release of any Final Policy on IVDMIAs and an Appropriate Transition Period, FDA Should Not Require Laboratories to Label IVDMIAs as "Investigational Use Only."**

Many IVDMIAs are well-established in clinical practice and are being covered by health plans and payers across the U.S. If FDA were to require that these tests be labeled for "Investigational Use Only" pending clearance or approval by FDA, then there is a high likelihood that health plans and payers would discontinue providing coverage for these tests. If that occurs, only patients with sufficient wealth to self-pay for these tests will have access to them. In addition, if FDA labels the tests as investigational, this may put physicians who order and use the tests and laboratories that perform and report the results of the tests at risk for professional discipline charges or malpractice actions. This would be the result of a regulatory label—not due to any change in the performance of the assay.

Therefore, we would ask that the Agency not require laboratories offering IVDMIAs to label these as "Investigational Use Only" until after a final policy document is released and a reasonable transition period (as proposed above) is completed.

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The Coalition supports FDA's goal of working to assure that patients have access to timely, accurate and reliable testing that can improve patient outcomes and reduce healthcare resource utilization. We agree that novel test systems raise new challenges for existing regulatory frameworks, and that those regulatory systems must adapt to these challenges. We look forward to working with FDA to understand the nature and scope of novel tests that incorporate computational algorithms and to evaluate the most appropriate

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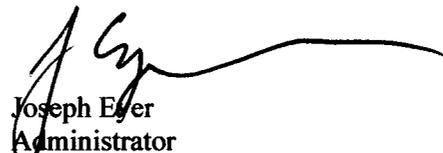
<sup>24</sup> See <http://www.fda.gov/cdrh/reuse/reuse-documents.html#6> (links to documents announcing FDA's enforcement of pre-market requirements for reproducers of single use devices as these policies evolved over time).

regulatory framework to promote development of innovative tests while assuring these are safe and effective. In response to the Draft Guidance, we respectfully make the following recommendations:

1. If the FDA determines that regulation of IVDMIAs as medical devices is the most appropriate pathway to address concerns the Agency may have, we would urge FDA to proceed under notice-and-comment rulemaking. Prior to publication of a Proposed Rule, we would encourage the FDA to convene a public workshop where stakeholders and regulators can have frank, interactive discussions about these issues.
2. FDA should work with the CMS through HHS to determine the most appropriate regulatory framework for IVDMIAs, including enhancements to CLIA, wherever appropriate. A first step could involve the creation of a registry to assess the number and type of IVDMIAs currently in clinical use. We would also support CMS's proceeding with proposed rulemaking on the development of a new genetic specialty under CLIA.
3. FDA pre-market review of any laboratory-developed tests should be risk-based rather than technology-based; should provide an exemption for tests for rare disorders and for analytical performance claims; should assign claims not involving binary determinations to class II; and should leave claims involving high risk binary determinations in class III.
4. FDA pre-market review of in vitro diagnostic tests should allow clearance/approval when supported by data from studies following methods accepted by experts in the relevant field. Uncertainty about clinical utility can be addressed through transparency in labeling.
5. If FDA proceeds with regulation of IVDMIAs, FDA should identify the algorithm and associated hardware/software as the medical device subject to regulation.
6. FDA should allow a reasonable transition period following publication of final policy regarding regulation of IVDMIAs to allow laboratories to come into compliance. Pending release of any final policy on IVDMIAs and an appropriate transition period, FDA should not require laboratories to mark these tests for "Investigation Use Only."

We look forward to continuing our dialogue with the Agency on this important matter. If you have any questions about our comments, please contact me at 202-879-5590. Thank you for consideration of these comments.

Sincerely,



Joseph E. Eger  
Administrator  
Coalition for 21<sup>st</sup> Century Medicine