



THE RESOURCE FOR LABORATORY PROFESSIONALS

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March 1, 2007

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

Re: Docket No. 2006D-0347-Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on Analyte Specific Reagents.

Re: Docket No. 2006D-0336- Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays

Dear Sirs:

On behalf of the Clinical Laboratory Management Association ("CLMA"), an organization of approximately 4,500 clinical laboratory professionals and consultants representing hospitals, independent clinical laboratories, physician office laboratories, skilled nursing facilities, and medical device companies, I am submitting comments regarding the Draft Guidance for Industry, Clinical Laboratories, and Food and Drug Administration ("FDA") Staff on Analyte Specific Reagents ("ASRs") (Docket No. 2006D-0347) and the Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays ("IVDMIA") (Docket No. 2006D-0036). CLMA looks forward to working with the FDA and hopes that the following comments will assist you in the drafting of guidance regarding FDA oversight of ASRs and IVDMIA.

The ASR and IVDMIA Draft Guidance could stifle scientific advances and innovations.

Advances in science hold promise for better diagnostic and therapeutic information provided by laboratory professionals at every point of the health care continuum and these advances must not be stifled by more regulatory burdens. Historically, reimbursement for clinical laboratory services does not recognize the value to the patient or the practice of health care. This is due largely to the current reimbursement structure that fails to address the value of clinical laboratory services and is solely focused on cost of producing a result.

Therefore, increasing FDA regulatory requirements, such as those proposed in the IVDMIA & ASR draft guidance, could further stifle innovation by substantially increasing both the costs and time required to develop multivariate diagnostics. Presently, clinical laboratories have been able to produce revenue from in-house assays and have been able to rely on this funding to further data collection studies that have been used for advances in science and to collect valuable data for potential FDA submission. CLMA recommends that any continued regulation of IVDMIA remain under the Clinical Laboratory Improvement Act of 1988 (CLIA) administered through the Centers for Medicare and Medicaid Services. This would help in alleviating the possibility of stifling scientific burdens.

Laboratory tests are services not commodities

Clinical laboratory tests are services, not commodities. These complex medical services require significant training and expertise to perform and interpret tests accurately, with the end goal of positively affecting patient outcomes. FDA has taken the position that clinical laboratories that develop tests in-house are considered "manufacturers", but that the agency has opted, in the past, not to exercise its right to regulate these labs. FDA has long been concerned that practitioners ordering these in-house tests or "home-brews" made from ASRs may be unaware of the clinical performance characteristics of these tests and unassumingly think they had been regulated by the FDA. This could not be further from the truth because practitioners are aware of CLIA's strict regulatory process already in place and have relied on this regulatory process when ordering in-house tests for their patients.

2006D-0347

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Currently, CLIA requires the director of the clinical laboratory to ensure that the tests results are effective for patient care, require the laboratory to have a clinical consultant who is responsible for communicating clinical context information, require the laboratory to validate the performance characteristics of LDTs – including algorithms, and require the laboratory director to ensure the clinician can interpret the test result. Clinical Laboratory Services do not fit into FDA's medical device regulatory system. Enhancement and better enforcement of CLIA is consistent with FDA's emphasis on "smart regulation" and "least burdensome approach"

The language in the IVDMA & ASR guidance requires significant clarification on FDA's definition of an IVDMA and ASR.

The FDA's presumed goal of regulating IVD tests is to verify their clinical and analytical performance to ensure that these tests are safe and effective for future patients. Therefore, if FDA concludes that further regulation of IVDMA's beyond the regulatory requirements of CLIA is necessary, then we suggest clarification of the characteristics of those assays that should be deemed IVDMA's and subject to FDA regulation as contrasted to those assays meeting specified criteria that would not be deemed to be IVDMA's and hence not subject to FDA regulation.

CLMA recommends that the agency provide specific examples of tests which employ algorithms that would be considered IVDMA's,¹ and specific examples of tests that would not be considered under the scope of IVDMA FDA regulation.² Furthermore, CLMA would also like to recommend that the FDA provide examples of class II and III devices because the current document does not provide enough guidance for laboratory professionals to predict the class of their test.

FDA should provide a "field-tested" template as guidance

On February 6, 2007, FDA, cleared for marketing the Agendia MammaPrint Test that determines the likelihood of breast cancer returning within five to ten years after a woman's initial cancer. It is the first cleared IVDMA test that has claims for genetic profiling for breast cancer. CLMA takes the position that FDA should use this approved test as a "field-tested" template for future regulatory review of IVDMA's. This would provide laboratories with a template to follow when going through the newly instituted IVDMA FDA regulatory process and some consistency to the IVDMA regulatory process that has been lacking in the past.

Laboratory input on FDA regulations is necessary

There needs to be a transition period to enable labs with IVDMA's to adjust from the current CLIA regulatory path to the CLIA-plus-FDA regulatory regime. The lack of a transition period, where clinical professionals provide input to the FDA, could seriously disrupt the availability of tests. If FDA imposes the device requirements on labs without any transition/input period it could halt the use and development of tests, as well as improvements to existing tests. If an IVDMA is subject to FDA regulation based on risk, a laboratory should have between two to four years to submit an application to FDA. In 1998, FDA allowed a transition period for its draft compliance policy guide entitled "Commercialization of IVDs Labeled for Research Use Only and Investigational Research"

¹ 1) a new single-source test system; 2) uses patient/or clinical data derived from one or more in vitro diagnostic assays together with a proprietary, non-published algorithm; 3) generates a patient-specific, binary result that is intended definitively to diagnose a condition or to direct behavior for the cure, mitigation, treatment, or prevention of disease; and 4) presents significant safety and effectiveness risks not present in test systems which have become a part of the standard of care.

² 1) low-risk consequences of invalid or inaccurate test results; 2) independent verification by one or more laboratories; 3) support of clinical relevance in peer reviewed literature; 4) transparent algorithms; 5) interpretation support for clinicians; 6) support in clinical guidelines; 7) established use; or 8) CPT code assignment and payer recognition.



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which permitted companies/labs to come into compliance with the agency's pre-market submission requirements. Therefore, a similar transition period should be allowed for IVDMIAs because laboratories have a stake in these regulations, CLMA recommends that FDA institute a disclosure program/registry where laboratories would be able to provide reliable information about the strengths and limitations of particular IVDMIAs. This would give FDA the opportunity to have a better understanding of the scope of IVDMIAs and therefore create a more specific definition and regulation of IVDMIAs.

FDA should focus on clarifying its definition of "marketing"

In the past, FDA regulation of ASRs has been to exempt all Class I devices from pre-market review while regulating a small number of Class II and III devices upon which FDA has placed restrictions on their sale and use. ASRs are Class I devices subject to general controls under section 513(a)(1) of the Act, which requires ASR manufacturers to register and list their devices, submit medical device reports, follow labeling requirements, and follow GMPs.

The ASR rule also restricts the sale, use, distribution, labeling, advertising and promotion of ASRs. One of the restrictions is that only physicians and other persons authorized by applicable State law may order-in-house tests that are developed using ASRs. The second restriction requires the laboratory that develops an in-house test using an ASR to add a statement disclosing that the laboratory developed the test and it has not been cleared/approved by FDA when reporting the test result to the practitioner. Finally, there are restrictions prohibiting advertising and promotional materials from manufacturers' of ASRs from making any claims for clinical or analytical performance. As a result, ASRs must bear the statement, "Analyte Specific Reagent: Analytical and performance characteristics are not established." This then triggers FDA's pre-market approval requirement process for the manufacturer of the ASR even though the manufacturer/clinical laboratory has not included the ASR as part of a kit test.

FDA has stated that when ASRs are used exclusively by a clinical laboratory for an in-house test that there need not be FDA clearance or approval provided for the test if no marketing or claims are made regarding medical results. This is in direct contrast to the preamble of the ASR Rule where an ASR is used as part of a "kit or system for 'in vitro diagnostic use'" and that has proposed intended use, indications for use, and performance characteristics. Presumably, FDA designed the rule so that: 1) manufacturers would take certain actions, such as following GMPs, to help ensure safety and effectiveness and 2) clinical laboratories would develop and verify the validity of test in which the ASR is used. However, FDA still asserts that a test kit which includes an ASR must be approved by the FDA if the clinical laboratory engages in the distribution, advertising or promotion of the test.

CLMA would like to see FDA narrow the scope of its definition of "marketing" when determining pre-market approval for ASRs. The agency has not addressed the issue of "home brewed" tests and when the activities of a clinical laboratory utilizing an ASR causes it to become a "manufacturer" by the activities in which it engages using the ASR in a laboratory developed assay. Furthermore, there is no discussion within the guidance as to how a clinical laboratory might reflect a laboratory developed test that includes an ASR in a test catalogue, web site or other information that it circulates about the assay. CLMA would also like to see examples given by the agency on how clinical laboratories may disseminate information on assays to practitioners without being considered "marketing" and therefore, falling under FDA's manufacturer regulatory qualifications.

Thank you for your attention to this matter.

Sincerely,

Judy Lien
President