

Life Sciences Management Group  
Suite 625  
7201 Wisconsin Avenue  
Bethesda, MD 20814

March 5, 2007

Division of Dockets Management  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

**VIA ELECTRONIC SUBMISSION**

**Re: 2006D-0347**  
**Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro**  
**Diagnostic Multivariate Index Assays**

**2006D-0336**  
**Draft Guidance for Industry and FDA Staff: Commercially Distributed**  
**Analyte Specific Reagents (ASRs): Frequently Asked Questions**

Dear Sir or Madam:

I am writing to comment on the Food and Drug Administration's (FDA) proposed guidelines regarding In Vitro Diagnostic Multivariate Index Assays (IVDMIA) and Analyte Specific Reagents (ASRs), both released on September 7, 2006. Based on my 28 years working with device, drug, and biologic companies, as well as in my current capacity as an advisor to venture capitalist and financing groups and as an immunologist who has previously done laboratory research, I am very troubled by both of these documents, which could have a profound chilling effect on the development and characterization of potential biomarkers. Provided below are some of my concerns related to various aspects of the two 'draft' documents.

(1) Although the two documents cover different topics, they operate together to reduce the kinds of useful laboratory developed tests (LDTs) that would be available. It is reasonable to believe that a reduction in the availability of LDTs would negatively impact the ability to identify LDTs and to get the diagnoses they need, the practice of medicine, and the development of new tests, as well as the Agency's and the National Institutes of Health's (NIH) initiative to identify and characterize biomarkers of clinical value. Clinical researchers alone cannot develop, characterize and validate LDTs of clinical significance as biomarkers without a relationship with clinical laboratories under the Clinical Laboratory Improvement Amendments (CLIA), which can perform expanded studies and are validated pursuant to CLIA regulations.

FDA has said that it expects the IVD MIA draft guidance document to affect only a few dozen tests, which I believe understates the reality of its impact. Based on my review of the literature and my work with companies and venture capital groups, I believe that many more tests than that will be regulated as medical devices. Research articles describing new LDTs that would be considered IVD MIAs are commonplace. (See Diagnosis, Prognosis, and Therapy Selection, Genetic Engineering News, Feb. 1, 2007.) Even if only a relatively small number of IVD MIAs are now being offered, the draft guidance document would affect scores of tests that are being researched now, as well as future tests that will be discovered in the next few years. The ability to combine the results of multiple biomarkers is a critical step in the evolution of laboratory research in terms of potential clinical relevance. Biology is complicated; single markers often won't provide the answers we need. Even FDA now recognizes and has approved groups of markers as having clinical relevance. The IVD MIA draft guidance document will chill the transition of research into clinical validation and also negate venture capital investment in this area to fund such efforts, thus preventing, or at best, significantly delaying many promising new tests from ever reaching fruition and clinical application. Such an outcome would be contrary to the intended goals of FDA.

Similarly, the limitations imposed in the ASR draft guidance document also threaten the ability of laboratories to develop new tests, which inherently conflicts with its operational freedom under the CLIA regulations. FDA created the ASR category to ensure that laboratories have high quality building blocks. That regulation worked – ASRs have led to a wide variety of materials manufactured under the Good Manufacturing Practice (GMP) regulations that laboratories can incorporate into the tests they develop. Many of the ASRs are particularly important for molecular biology diagnostic tests. The limits on “multiple moieties” under the ASR draft guidance document means that many of these ASRs would suddenly become unavailable. That would reduce the quality of laboratory testing right now, and would make it more difficult for laboratories to develop new tests in the future. This could become particularly problematic when confronted with outbreaks of new diseases or bioterrorism; “multiple moiety” ASRs would be critically important in helping to develop new CLIA compliant laboratory based tests, and in making them rapidly available to physicians and public health authorities.

These draft guidances will also impact on and escalate the laboratory overhead costs, driving up the cost of laboratory diagnostic services. I believe that FDA should do a cost analysis impact of their draft regulations, before any implementation. The argument that these are merely ‘draft’ guidances is essentially a fiction, because in essence the OIVD uses these as regulations and even threatens enforcement based on these ‘draft’ guidances. In responding to these comments, will FDA indicate whether it will conduct such an impact analysis of these draft guidances?

(2) The two draft guidance documents, if implemented, would have the effect of depressing investment in diagnostics. In fact, since their publication, several venture groups have reconsidered investments in this area. When it comes to attracting investment, the IVD industry has always been the stepchild. Based on my personal experience, I know that venture capitalists and other funders are much more likely to direct their capital funds toward drugs, biologics, and conventional devices than IVDs, given the regulatory uncertainties that these regulations have introduced. Funding is critical to innovation. Because the IVD market is so different from these other categories in terms of return on investment and size of market, the new

regulatory requirements that would be imposed by the two draft guidance documents will deter investment.

Ironically, CDRH could, in the future, experience a decrease in the amount of user fees it receives, because of diminished research and supportive venture capital investment to drive LDTs development and eventual product submissions.

(3) The two draft guidance documents significantly change the regulatory requirements for both LDTs that would be regulated as IVDMIAs and ASRs. FDA should implement these changes through notice-and-comment rulemaking, not through draft guidances which they then implement as if they are established rules. Given that FDA is establishing substantive new requirements on laboratories and ASRs, this needs to be done through the formal rulemaking process, not through an informal guidance document. Rulemaking is the only way to ensure that the public can fully participate, that a record is created, that FDA's rationale for its actions is set forth in detail, that FDA considers and responds to the public's comments, and that FDA takes into consideration the economic impact and other impacts of its actions. FDA would also need to clearly explain the reason(s) for regulating these products this way. That clear articulation of a rationale would provide for a better understanding of FDA's objectives, and how well the regulatory actions fit those objectives. Issuing a draft guidance document followed by public comment is simply not a substitute for rulemaking. While holding a public meeting is helpful, it does not replace rulemaking. If anything, the comments at the February 8th public meeting on IVDMIAs, with the multiple references to lack of clarity and multiple pleas for notice and comment, only reinforce the need for FDA to go through rulemaking. (Given that the meeting did provide a useful forum for publicly airing comments on the IVDMIA document, it is puzzling, why FDA has not held a similar forum for ASRs, to drive an interchange.)

The ASR regulation was adopted through rulemaking. The draft guidance document significantly affects the kinds of products that can be sold as ASRs, as well as the information that laboratories can receive about ASRs. FDA cannot modify the terms of a regulation through a 'draft' guidance document, which it is now implementing. As for IVDMIAs, FDA is creating a whole new regulatory classification. Over the years, FDA has established new classifications by regulation. IVDMIAs should not be treated differently, particularly given that FDA has never regulated LDTs before. To make this fundamental change in regulatory practice via such a casual method is inappropriate.

(4) Both draft guidance documents need a significant amount of clarification. For example, as has been evident over the past six months from public comments, FDA's definition of an IVDMIA has confused many stakeholders. When so many people in the industry are uncertain as to what is intended, it means that much greater clarity is needed. I believe that the notion that regulatory status can hinge on the knowledge of physicians is fundamentally flawed. It sets up a regulatory scheme which is akin to "I know it when I see it." That gives too little guidance to regulated industry and to FDA itself. There are also many practical aspects of the IVDMIA draft guidance document that go unaddressed, such as the relationship between GMPs and CLIA, how modifications of the test would be regulated, and what is the device that is being regulated. (Defining an IVDMIA as the algorithm and the related software/hardware would mitigate many of these issues.) These are crucial questions that fundamentally affect the level and nature of regulation, but they are not addressed in the draft guidance document. They are

inextricably intertwined with the concept of an IVD MIA, and therefore cannot be deferred to some later, separate document.

If, as many of us perceive, the underlying intent of these IVD MIA and ASR guidances is to encourage CLIA regulated laboratories and their suppliers to submit marketing applications for the 'home brews,' OIVD should consider providing 'draft' guidance as to the utility of CLIA generated clinical laboratory data to support marketing applications. This approach could achieve their underlying intent without the negative impact of the current 'draft' guidances. Will FDA address this recommendation in their responses to the comments they receive on these two 'draft' guidances?

The ASR draft guidance document also needs clarifications to avoid confusion. For example, the terms "multiple moieties" and "endpoint" are not in FDA's existing regulations governing ASRs, and are not defined in the draft guidance document. Having established a very detailed definition of an ASR in the regulation, FDA needs to take equal care to define new terms which will alter the scope of ASRs.

(5) Whatever FDA ultimately does, an adequate transition period is needed before any changes to the existing regulatory scheme are imposed. Laboratories, in reliance on FDA's practices and statements, have developed IVD MIAs without any expectation that they would be subject to regulation. Investors funded these projects based on similar expectations. Manufacturers have developed ASRs that contain multiple probes and primers, and that identify multiple proteins or markers, without any reason to believe that this was improper. Laboratories now rely upon these types of materials to develop tests. If FDA were to finalize the draft guidance documents (which, for the reasons stated above, I believe it should not) and the new requirements took effect in, for example, 90 or 180 days, it would cause massive disruption to the established diagnostic system and research to develop new biomarkers, a mandate from the Agency's Critical Path Initiative and the NIH. Therefore, any final document needs to include an ample transition period to mitigate the harm that these new regulatory requirements would cause by making tests unavailable. FDA needs to comment on why its 'draft' guidances would not be disruptive and/or delay achieving the FDA intent on developing new biomarkers for the Critical Path Initiative.

I support the concept to create a registry of IVD MIAs along with OIVD providing written guidance on how clinical data from CLIA compliant laboratories could be used to support marketing applications for LDTs. This would be a more reasonable approach to mitigate this problem and address their underlying intent. It would allow FDA and other regulators to get a better understanding of what is available, as well as what data support these tests. This foundation would, in turn, permit much more focused, informed regulation.

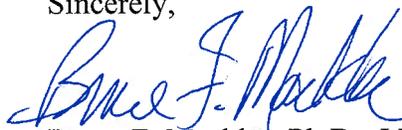
(6) The United States has a robust and innovative diagnostic industry that contributes to economic growth and better health care. Given the significant advances in various fields, such as genomics, proteomics, molecular diagnostics, etc., the pace of important new diagnostic tests is poised to accelerate. However, neither innovation, nor the investment in innovation, flourish when there is unreasonable regulatory uncertainty. Financial markets tend to be risk adverse where there is perceived regulatory uncertainty, such as that being introduced by the two 'draft' guidances. As someone who has spent his career working first in the research laboratory and

then with FDA-regulated companies and now with venture funding groups, I appreciate the importance of reasonable regulation and how financial groups invest in biomedical products. By the same token, companies need to be able to make long-range plans, and require a reasonably predictable regulatory environment in order to raise capital, as well as use their capital to fund developmental projects in this area. Although regulatory change is necessary and inevitable, this is not the way to go about making these changes, which create more uncertainty and raise fundamental legal questions that are likely to be challenged by others. Provoking such legal challenges feeds uncertainty and constrains research and CLIA laboratory development of new biomarkers.

The issuing of these two draft guidance documents on the same day that overturn so many plans and understandings, without soliciting any prior input from industry, is both deeply troubling and indicates that FDA does not appreciate the chilling effect it has on research, application of this research and the investments to bring these product into the laboratory. The release of the two draft guidance documents does not augur well for the diagnostic industry. The precedent set by this action will reverberate and affect other components of the diagnostic industry beyond IVDMIAAs and ASRs. I, therefore, urge FDA to reconsider and withdraw both draft guidance documents, then begin the process through rulemaking. Many of the comments you are now receiving can facilitate your rulemaking efforts

Thank you for providing this chance to offer these comments.

Sincerely,

A handwritten signature in blue ink that reads "Bruce F. Mackler". The signature is fluid and cursive, with the first name being the most prominent.

Bruce F. Mackler, Ph.D., J.D.  
Life Sciences Management Group, Inc

cc: 2006P-0402  
Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests