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Attorney-Client Communication;
Privileged and Confidential

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

Re: Docket No. 2006D-0347
Draft Guidance for Industry, Clinical Laboratories,
and FDA Staff on In Vitro Diagnostic Multivariate Index Assays

Dear Sir or Madam:

CardioDx, Inc. ("CardioDx") appreciates the opportunity to comment on FDA's draft guidance on In Vitro Diagnostic Multivariate Index Assays ("IVD MIA"). We believe that the federal government has an important role in overseeing the quality of laboratory tests. We further believe that the federal government should take care to exercise its oversight in a way that does not retard the development of useful innovation, that does not prevent physicians and patients from having access to useful diagnostic tools, and that does not unnecessarily drive up the costs of health care. These comments are offered with the intention of assisting the government to accomplish these objectives.

The choices that FDA makes about oversight of IVD MIAs will have a profound effect on whether particular tests are developed in the future, what entities will be capable of developing tests, and what kinds of tests will be developed. We ask that FDA carefully consider how its regulation will affect future test development in this area of rapidly progressing science and substantial importance for improving public health.

Background on CardioDx

CardioDx is a small molecular diagnostics company based in Palo Alto, California. We are developing tests to better target cardiovascular therapies. For example, we are developing a test to identify patients at highest risk for plaque progression and/or acute events, so that they can be monitored and treated accordingly. We are also developing a test to identify patients most likely to benefit from beta blockers, and one to identify patients at high risk for arrhythmias, and, therefore, most likely to benefit from an implantable defibrillator. In developing these tests, we are conducting large, carefully developed clinical studies using samples obtained from our own sample bank and samples provided by physicians using appropriate ethical safeguards.

If our studies validate our tests, we expect to offer our tests as laboratory services to physicians. Our intention is to build a lab for CLIA certification by the end of 2008. We do not expect to initially sell test kits or ASRs, and we will offer our services only on the order of a physician.

Comments on Draft IVD MIA Guidance

1. The draft guidance appears to create duplicative federal regulation.

Regulation of IVD MIAs by two federal agencies, as well as the FTC, seems unnecessary. If the federal government believes that CLIA regulation is missing some essential element of necessary oversight, it would seem appropriate to build that element into CLIA. CLIA has a proven track record of success, and adding a regulator would seem to be wasteful of scarce resources – both private sector and government resources. FDA and CMS/CLIA have worked collaboratively before to implement CLIA, and could do so again.

2. The draft guidance could discourage innovation, limit flexibility, and keep important discoveries from being used for the benefit of the public.

Scientists are just beginning to realize the potential of molecular diagnostics. There is no well-worn development path for these tests. With so little information available, developers must be allowed flexibility in the development process. Further, because the science is progressing so fast, one can expect that even marketed tests will be regularly improved. FDA's classic regulatory process has not been structured to accommodate the pace of change in this area. If FDA is to regulate IVD MIAs, the agency should consider in advance how it will design its process so as to encourage innovation and change, and communicate that information to test developers.

3. Physicians need access to data and can understand and adjust to uncertainty.

Even if a test has not been clinically validated with precision, it may be valuable to physicians. Physicians need access to medical information as it develops. They have been trained to accumulate multiple kinds of data, including clinical history, signs and symptoms, and test results, in counseling patients. In this context, physicians can cope with the uncertainties that may be presented by certain tests. Further, they can evaluate the science that supports tests in making judgments about test utility and are unlikely to embrace tests if the science, including the basic elements of any associated algorithms, is not made available to them. FDA will do patients no service if it restricts the flow of information to physicians as quickly as the information is gathered.

4. The draft guidance should be clarified.

The draft guidance appears to assert jurisdiction over some home brew tests but not others. As we understand it, a test is covered if it is a test system that uses an algorithm that cannot be readily reproduced by another lab or interpreted by a physician without information on its performance and effectiveness. We cannot determine whether our tests will be test systems, and we cannot evaluate whether FDA would consider our algorithm sufficiently reproducible and our test sufficiently interpretable.. We believe that they can be, but some further guidance is needed, at least on these two points. Clarification should be provided in advance of implementing the guidance, rather than have FDA make determinations on a case-by-case basis, so that test developers can make planning decisions well in advance.

In addition, we cannot determine what data would be required to support an FDA application. FDA has neither explained why IVD MIAs required more regulation than other home brew tests, nor has it established any criteria for determining the level of regulation to be applied to any particular IVD MIA. In CardioDx's view, the extent of regulation should depend primarily on the risk associated with the test rather than on the test's complexity or novelty. For example, a test that is the sole determinant of whether to select a treatment is more risky than one that is just one part of selecting a treatment regimen. In addition, there are numerous possible ways to establish the clinical validity of a test, e.g., clinical studies, peer reviewed literature. We need some additional guidance on FDA's data expectations before requirements are put in place.

5. The draft guidance should accommodate tests for which development is already underway.

To establish the clinical validity of CardioDx's tests, we have developed protocols in conjunction with experts in trial design, clinicians and statisticians. We have spent millions of dollars to design and conduct our studies. If all goes well, we anticipate that our first test will be fully validated at some time in 2008. If, however, our tests were to require FDA approval, and our trial design or execution did not comport with FDA's views, we could be forced to begin again, at great cost to the company and the public. Developers of medical devices generally have the opportunity to meet with FDA throughout the development of their products, beginning with pre-IDE meetings. CardioDx had no expectation of FDA involvement and has therefore not included FDA in its planning. It would be manifestly unfair to force the company to meet an FDA standard that it had no reason to anticipate.

This is true especially in the area of molecular diagnostics, which offers some unusual challenges. For example, genetic tests may have different predictive value in

different subpopulations. It will not be possible to quantify the predictive value in each subpopulation. Test developers need to know in advance of beginning studies how FDA will treat this and other unusual aspects of qualifying genetic tests.

6. Implementation of the draft guidance would add significant cost in time and money to test development.

There are significant costs associated with FDA regulation. We would anticipate both a delay of at least a year in our lead program and a substantial financial cost to obtain approval, even if we were not required to do additional studies. Equally important, we have planned to comply with CLIA and not to install a QSR system. The cost of installing and maintaining QSR compliance, with its extensive documentation requirements, would be substantial. We are not entirely sure how QSR would or even whether it could be applied to a service such as ours.

CardioDx is a very small company dependent entirely on venture financing. We cannot be sure that we would be able to secure the financing to absorb these delays and costs. These costs would be even more burdensome for developers who are interested in tests for rare disease or conditions.

Recommendations

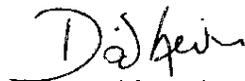
1. FDA should rethink its role and coordinate with CMS/CLIA to avoid waste and duplication. FDA should begin with the premise that one regulatory agency is preferable to two, and consider whether the CLIA program could be strengthened to achieve the federal government's objectives. If it is determined that FDA involvement is required, that involvement should be structured to complement, not duplicate, CLIA, and the role of each agency should be clearly specified.
2. Whatever FDA involvement is adopted, FDA should establish an orderly transition plan. The plan should recognize and accommodate the fact that many tests are already well along in development.
3. FDA should state publicly how it will determine the level of regulation to be applied to particular tests. The level of regulation should depend principally on the risk to patients posed by the test. It should further state the kinds and quality of data that would be required for approval/clearance of tests well before any requirements take effect.
4. FDA should state with greater precision and clarity what tests will be covered by the new policy.

5. FDA should adopt a policy that CLIA compliance will satisfy QSR requirements, or, alternatively, define the “device” portion of the test narrowly, so that the QSR applies narrowly to a subset of the test that is actually manufactured.
6. FDA should consider the effects of its policies on tests for rare disease and conditions, and on the availability of tests for subpopulations, with the goal of establishing a system that will not make development of such tests commercially infeasible.
7. Before imposing requirements, FDA should collect information about tests offered now, and their strengths and weaknesses, with the goal of determining if there is a problem to be solved, and how FDA’s oversight might be narrowly targeted to solve the identified problem. The registry proposed by the Coalition for 21st Century Medicine would be an appropriate way to do that. There is no reason to impose costly and burdensome requirements on all test developers simple to prevent a few marketers from defrauding the public. FDA’s current system provides ample enforcement authority to deal with those who abuse the system.
8. Because the choices that FDA makes now are so important to the public health, FDA should make sure that it considers all viewpoints and all of the available choices. This can only be accomplished through rulemaking.

Conclusion

CardioDx appreciates the opportunity to comment on the draft guidance. We cannot overemphasize the effect of the choices that FDA makes now on the availability of tests in the future. Each of us, and our children and grandchildren, deserve the best that science has to offer. As an agency dedicated to the public health, we ask that FDA fully consider the impact of its actions and make choices that will best protect the public.

Sincerely,



David Levison

President and Chief Executive Officer