



Division of Dockets Management
HFA-305
Food & 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Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on *In Vitro* Diagnostic Multivariate Index Assays

Dear Sir or Madam:

XDx, Inc. (XDx) appreciates this opportunity to comment on the draft guidance issued by the Food and Drug Administration (FDA) on September 7, 2006 indicating FDA's intention to regulate certain laboratory developed tests (LDTs) as medical devices. XDx is a molecular diagnostics company based in South San Francisco, CA and a leader in the new era of personalized medicine. XDx offers the AlloMap molecular expression test to monitor acute cellular rejection in cardiac transplant recipients. The test has been clinically validated in prospective, blinded, multi-center clinical trials.

XDx supports the intentions of the draft guidance, but we are concerned that in its current form, the draft guidance does not make it clear how a regulated clinical lab would comply with both FDA regulations and the Clinical Laboratory Improvement Amendments (CLIA). In addition, we are concerned that the draft guidance will impede the development of new molecular tests that offer the potential to significantly improve the quality of life for patients with a variety of diseases. We have focused our comments on discussing the difficulties of complying with both FDA and CLIA requirements, and have offered suggestions to clarify and eliminate these difficulties, while providing a framework supportive of innovative methods of improving public health.

XDx's first concern is that FDA's Quality Systems Regulations (QSRs), 21 C.F.R. § 820, would be difficult to apply to LDTs. QSRs are designed for traditional medical device manufacturers to ensure the production of standardized, uniform products. QSRs require that device manufacturers have in place quality systems for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution. Applying QSRs to clinical laboratories may not be the most effective pathway to ensure quality control since CLIA regulations already require laboratories to build systems that

guarantee accurate, reproducible testing. In addition, CLIA clearly states that the Laboratory Director of a high complexity lab is responsible for ensuring the “accuracy, precision, and other pertinent performance characteristics” of testing for the populations their laboratories serve, necessitating both analytical and clinical validation. 42 C.F.R § 493.1445.

Rather than implementing prescriptive design controls for the device itself (as with QSRs), CLIA focuses on regulating the clinical laboratory and the service to ensure standard, quality test results. A primary goal of CLIA oversight of laboratory testing is the promulgation of sound laboratory practices. In the context of LDTs, the CLIA system is equally, if not more, effective in guaranteeing quality results and in fact, appears to make more sense than the QSR scheme. Regulating the quality of the clinical lab services, rather than the end product, ensures quality testing, but without the confusing and conflicting application of QSRs.

XDx is equally apprehensive about the application of medical device labeling requirements to LDTs. 21 C.F.R. § 809.10 requires a medical device label to include the proprietary name, the intended use, warnings or precautions, the statement “For In Vitro Diagnostic Use,” the name and place of business of the manufacturer, a lot or control number, and a package insert with various information to accompany the device. A number of practical problems arise with these requirements as applied to LDTs, including:

- Where is the label to be affixed since the test is not packaged or distributed?;
- What constitutes a lot number? Each individual run of the test?;
- To whom should the package insert be shipped? The prescribing physician? The patient? How should it be shipped? With the test results?

XDx suggests that FDA offer further guidance on labeling for IVDMIAs to eliminate potential confusion.

Finally, XDx believes that continuous improvement of IVDMIAs will be difficult under the draft guidance in its current form. Under CLIA regulations, laboratories may modify cleared or approved test systems, provided the laboratory establishes performance specifications for each test system before reporting patient test results. These performance specifications include validation requirements for accuracy, precision, analytical sensitivity and specificity, a reportable range of test results, reference indicators, and any other relevant performance characteristic. This scheme allows the flexibility needed to improve test performance in rapidly emerging fields of medicine with the end result being that patients have rapid access to the best diagnostic testing methods available. However, under the draft guidance in its current form, it is not clear if modifications to IVDMIAs would be permitted or whether a supplemental premarket submission would be required for any modified IVDMIA.

XDx encourages FDA to consider the value of a flexible regulatory pathway to allow innovative new diagnostics to reach the healthcare system quickly. First, if there are concerns about the effectiveness of CLIA oversight, steps should be taken to strengthen the regulations and inspection processes, which could improve all LDTs, not just IVDMIAs. Second, if the FDA continues to question CLIA oversight of IVDMIAs, we ask that FDA consider limiting its review to IVDMIA algorithms and associated clinical data, with laboratory operation remaining under CLIA review. In conjunction with initial regulation of the algorithm by the FDA, the

CLIA performance specification system could provide a framework for getting innovative, modified devices to market safely and quickly.

Given these concerns, X Dx suggests that the FDA should work closely with the Centers for Medicare and Medicaid Services (CMS) to clearly delineate each agency's role in the regulation of IVDMIAs. FDA and CMS should collaborate to avoid duplicative and inconsistent regulations, and FDA should provide clear guidance to clinical laboratories on which regulations will apply to IVDMIAs and what would constitute compliance. FDA should not discount the role of CMS, under CLIA, to adequately regulate certain aspects of IVDMIAs and should work to make the transition for clinical laboratories as seamless as possible.

X Dx appreciates the opportunity to submit these comments to the Draft Guidance and looks forward to working with you and the agency on these issues. LDTs are an essential part of diagnostic medicine; any attempt to regulate them more stringently should be carefully considered by all stakeholders to ensure the safest, least burdensome approach possible.

Sincerely,



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