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March 5, 2007

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

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Draft Guidance for Industry, Clinical Laboratories and FDA Staff on In Vitro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

Published Date: 07 September 2006

Dear Sir/Madam:

Thank you for the opportunity to comment on the Draft Guidance entitled “**Draft Guidance for Industry, Clinical Laboratories and FDA Staff on In Vitro Diagnostic Multivariate Index Assays,**” issued September 7, 2006. As a leader in understanding genetic based disorders and in developing both tests and therapeutics for such disorders, Genzyme Corporation is in a unique position to comment on this Guidance. Genzyme’s corporate infrastructure includes a Diagnostics business unit and the Genzyme Genetics laboratory services business, allowing the corporation a comprehensive and unique view of the personalized medicine approach to therapy. Genzyme has differentiated its product offerings based on our understanding of particular diseases and the relationship of diagnostic test results to patient response. We also have considerable experience in studying rare genetic disorders and small patient populations. We successfully have launched therapies for four rare genetic disorders and provide diagnostics testing to identify those patients. Recently, Genzyme has expanded its research and development efforts in oncology and pathology.

Our comments derive principally from our belief that because diagnostic testing is increasingly important to healthcare providers for decision-making, full opportunity for stakeholder engagement is crucial to achieving an appropriate regulatory approach. A coordinated deliberative effort involving other relevant Federal Agencies, as well as stakeholders, would be optimal. We believe a robust participatory dialogue process is needed to achieve the objective of creating a framework for oversight of IVDMIAs that is grounded in a thoughtful analysis of new and emerging science and technology and the early evidence of the promise of personalized medicine. Should FDA's Good Guidance Practices, or other administrative or legal requirements, prevent the multidirectional dialogue required (i.e., including the ability for FDA participants to respond and have substantive input into discussions), then Genzyme respectfully requests that the agency withdraw the proposed draft to allow such discussions to take place.

In particular, such a forum also will allow a robust discussion of a critical, but perhaps easy-to-overlook, component of the debate about appropriate oversight or regulation of innovative laboratory tests. And that is the impact on future innovation. All companies make choices about which products to research and develop partly based on determinations about balancing expenditures against potential future gains. This is no less true for laboratories that develop and offer innovative tests than it is for large medical device companies that develop and market test kits. However, in the former case, the tests are more likely to be for quite targeted—and therefore smaller—populations, while the latter test kits are more likely to be for much larger markets. Innovation in testing for small, targeted patient populations is occurring in clinical laboratories, who often are taking the lead from academic researchers whose studies and data have demonstrated the clinical usefulness and importance of tests, and who rely on laboratories to validate the tests further and to make them available to a broader population of physicians than those associated with a particular academic institution. The substantial costs associated with the development and validation of these tests need to be kept in mind, as they often are not reimbursed by third-party payers. If additional requirements associated with FDA clearance or approval were added, with their additional substantial costs, bringing these tests to physicians and patients could become cost-prohibitive for many laboratories and for many tests. Innovation would, as a result, be slowed or, in some cases, stopped altogether.

We strongly urge that this matter be taken fully into account as FDA proceeds with this oversight/regulatory decision-making. We believe that this is one among other important topics that merit fuller and more interactive discussion among stakeholders and FDA.

In addition to recommending a fully participatory process, including an interactive meeting between FDA and relevant stakeholders and experts, we have several specific comments on changes we believe would be important to include in any final Guidance.

The Definition of IVDMIA's Should Be Clarified.

As currently written, the Draft Guidance states that IVDMIA's will be considered Class II or III devices that require premarket clearance. Specifically, the Draft defines IVDMIA's as “test 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.” The Draft also describes the criteria of IVDMIA's—use of clinical data, employment of an algorithm, and a result that cannot be interpreted by a health care provider without the help of the test developer. This definition potentially would capture laboratory operations, mathematical or algebraic formulas, physician decision aids, risk prediction models, panels of standard markers, and a large number of other systems that we do not believe the agency intends to include.

For example, the current definition could encompass:

- Viral genotyping
- Viral strain typing

- Infectious agent screening
- Maternal triple test screen
- Physician decision aids (e.g., Predictive Nonograms & Adjuvant! Online)
- Panel(s) of standard clinical markers

Clarification and narrowing of the definition would be consistent with statements by FDA officials, indicating that the Draft Guidance was not intended to apply to well-established tests, including some of those noted above, that clearly fall within the proposed definition. (It is also unclear if peer-reviewed publication of a transparent algorithm or independent verification would exclude a test from being considered an IVDMA under a refined definition, as that might address the criterion related to physician interpretation without the help of the developer). A clearer and unambiguous definition should be crafted, and there should be additional opportunity for public comment once that is done.

The Potential Confusion Caused by Two Regulatory Schemes, CLIA and FDA, Should Be Taken into Account.

The position that clinical laboratory services historically regulated under the Clinical Laboratory Improvement Act (CLIA) are FDA-defined “test systems” consequently regulated as medical devices raises many questions. Identifying or establishing a new class of FDA-regulated products—genomic/proteomic tests and, by extension, other tests and technologies that employ computers, machine learning, computations, population metadata, reference data sets, and/or derived clinical algorithms—essentially extends to these tests a new scheme of FDA premarket clearance or review. This then implicates for laboratories that offer these test services a series of as-yet undefined new requirements (e.g., Quality Systems Regulations; Good Manufacturing Practices; Design Controls; facility registration and inspections; and product labeling, clinical claims, and postmarket requirements) under the Federal Food, Drug, and Cosmetic Act (FFDCA). The imposition of these new requirements on laboratories would create confusion, at minimum, and potentially result in duplicative and possibly conflicting regulation under CLIA and the FFDCA.

If the regulatory strategy suggested by the Draft Guidance is pursued to the logical conclusion implied by the Draft, we urge that FDA concentrate its efforts on, for example, the validity of technical claims, and not on matters such as GMP or QSR compliance, which are properly applicable to device manufacturers but not to clinical laboratories. In addition, we strongly urge the agency, as it proceeds in its thinking on this issue, to look carefully at both the similarities and differences between FDA’s approach to Quality Systems and that of CLIA, to which laboratories already are subject.

We note specifically, as one example of where FDA requirements for medical devices could run contrary to laboratories’ responsibilities, the strict promotional restrictions and labeling regulations applicable to FDA-regulated devices. If parallel requirements were put in place unaccompanied by specific guidance as to how they would be enforced, consultative services provided to health care

providers by laboratory medical directors could be seriously compromised. These and other potential conflicts between CLIA and FFDCA need further consideration. We urge FDA, before proceeding further on this Guidance or otherwise, to address and reconcile any such conflicts so laboratories performing IVDMIAs have clear, non-redundant, and non-conflicting rules.

An Appropriate Transition Period for Laboratories Should Be Part of Any New Approach.

We believe that, if finalized, this Draft will lead to an entirely new and different approach to the oversight of certain types of laboratory tests, many—or most—of which can be expected to be laboratory-developed rather than device-manufacturer-marketed tests. Because of FDA's long-standing and, to date, well-understood policies and practices regarding the regulation of clinical laboratories and the testing services they offer, laboratories have expected and worked to achieve compliance with all applicable requirements under CLIA. They have not established processes or operating approaches designed to comply with the requirements for medical device manufacturers under the FFDCA. Immediate implementation and enforcement of any new approach which, either directly or in effect, brings laboratories under an FDA compliance regimen could have perhaps unintended effects that will jeopardize patient and physician access to necessary diagnostic testing. For example, reimbursement could be placed into a questionable status if third-party payers determine that new or unpredictable and non-transparent FDA regulation of certain tests places those tests in a category of "investigational" or "experimental," meaning that reimbursement could be denied and patients thereby could be denied access to testing that physicians believe is necessary to make critical medical decisions. In addition, some laboratories may need to suspend or curtail some operations, until such time as they believe they can re-tool their processes, record-keeping, etc., to ensure compliance with new FDA requirements. Such possibilities, and others, would lead to disruptions in a crucial link in the medical care chain and would not be in the best interest of patients. Thus, we urge FDA not only to ensure that any new approach taken by the agency be the least burdensome to achieve the goals, but also to provide an adequate transition period for implementation.

Genzyme was pleased to participate in the recent public meeting on the Draft Guidance, thanks the agency for extending the comment period, and appreciates the opportunity to comment on the Draft. Please contact me at 617-768-6275 or Linda Temple at 617-768-9290 should you have any questions regarding this letter.

Cordially,



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