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February 28, 2007

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

Re: Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: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

Dear Sir or Madam:

The American Society of Clinical Oncology (ASCO) submits these comments concerning the September 7, 2006, draft guidance from the Food and Drug Administration (FDA) on in vitro diagnostic multivariate index assays (IVDMIA). As the leading medical society for physicians involved in cancer treatment and research, ASCO has a profound interest in the availability and reliability of these laboratory-developed test systems, as they are increasingly important tools in the management of patients with cancer. While ASCO supports enhanced regulatory oversight of these products, the approach reflected in the draft guidance is subject to question on legal, practical and policy grounds.

Regulatory Background

IVDMIA are theoretically regulated under the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (Public Law 100-578). However, the Centers for Medicare & Medicaid Services (CMS), which has been delegated regulatory authority for CLIA from the Secretary of Health & Human Services, has done little to develop the expertise necessary to review genetic tests like those apparently covered by FDA's draft guidance. In fact, on September 26, 2006, nonprofit organizations interested in genetic testing submitted a petition to CMS urging creation of a regulatory framework adequate for the oversight of genetic testing.¹

As FDA notes in the draft guidance, it has historically taken the position that "clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act."² But, as FDA admits, IVDMIA do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion."³ Indeed, FDA's policy has been to exempt these tests, also known as "home brew" tests, from active regulation. The draft guidance thus represents an abrupt reversal in regulatory policy regarding these tests.

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¹ Petition Requesting a Genetic Testing Specialty and Standards for Proficiency Testing, submitted to CMS Administrator from the Genetics and Public Policy Center, Public Citizen's Health Research Group and the Genetic Alliance, September 26, 2006.

² Draft guidance at p. 2, quoting from 62 Fed. Reg. 62249.

³ Id. at 3.

ASCO Concerns

The draft guidance gives very little notice of FDA’s specific regulatory intentions, but, based on the relatively sparse information available, ASCO has the following general concerns:

- Breadth of Definition of IVDMIA—

The definition of IVDMIAs—i.e., use of clinical data and an algorithm requiring interpretation to reach a patient-specific result—seems extraordinarily broad, likely going well beyond the genetic tests that are the presumed targets of FDA’s regulatory intent. Even if one could rely on FDA’s sound judgment to limit inappropriate or overreaching regulatory action, the uncertainty about FDA’s intent will no doubt serve as a deterrent to investment in any area even arguably subject to FDA regulatory initiatives.

- Lack of Information Regarding Regulatory Pathways—

While the draft guidance promises to address “pre-market pathways and post-market requirements,”¹ there is virtually no detail presented on those topics. In fact, the draft guidance, perhaps recognizing the inadequacy of the information provided, states that sponsors should “contact the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) if [they] have questions regarding the classification of your IVDMI assay and for the type of information [they] need to submit for pre-market clearance or approval.”² This “black box” approach to regulation may eventually meet the needs of sponsors of these products, but it does nothing to inform or reassure patients and providers as to the applicable standards for marketing, and the lack of clarity also is not conducive to investment in development of future products in this arena. Effective regulation that inspires widespread public confidence requires much greater transparency than is reflected in the draft guidance document.

- Threat to Access—

Consistent with the agency’s abrupt assertion of regulatory authority over these products, FDA states that they must be labeled: “For Investigational Use Only. The performance characteristics of this product have not been established.”³ The reimbursement environment for medical devices, including diagnostics, is already challenging, even without this requirement. Mandatory labeling of the products as “investigational” will undermine whatever limited reimbursement and access they currently enjoy. Accordingly, both patients and providers can anticipate serious new problems of access to these useful tools.

¹ Id. at 1.

² Id. at 4.

³ Id.

- **Conflicting Regulatory Jurisdiction—**

At present, jurisdiction to regulate these tests seems to reside with CMS under CLIA. Further uncertainty about the regulatory pathway for these products will derive from FDA’s sudden assertion of seemingly overlapping regulatory authority. ASCO does not take the position that FDA necessarily lacks statutory authority to regulate IVDMIAs as medical devices.⁴ Such authority should not be asserted by FDA, however, while CMS seems to be covering the same regulatory terrain. Sound management of these important issues requires a consistent and clear regulatory framework, leaving no doubt as to who is in charge. The Secretary should specifically designate which tests are under the jurisdiction of CMS and which are to be regulated as devices by FDA, with the decision based on the degree of risk involved in administering the test. Criteria for the decision to assign oversight to FDA as opposed to CMS should be transparent and science-based.

- **Undermining Investment Incentives—**

The extreme uncertainty generated by the draft guidance, together with the clarification that this entire class of diagnostics—previously considered exempt from regulation but now labeled “investigational”—will be subject to enhanced regulatory scrutiny, will likely discourage new investment across the product class. The use of genetic information to guide treatment choices for cancer patients is a very promising field of research inquiry, and it would be unfortunate if instability in the regulatory environment undermined incentives to invest in that research.

Legal Issues

Given the significance of the products at issue, the magnitude of the changes in FDA’s regulatory agenda and the potential consequences of those changes, ASCO believes the process could benefit from enhanced public participation consistent with the requirements of the Administrative Procedure Act (APA), 5 U.S.C. §553. Notwithstanding FDA’s assertion that the draft guidance represents suggestions or recommendations, rather than requirements, it is difficult to accept that the new regulatory regime will not be considered binding on sponsors of IVDMIA products and that APA requirements should not apply.

Aside from the obvious point that the draft guidance will almost certainly be binding on those who would market these products, there are additional reasons why the APA should apply:

1. The draft guidance sets forth a policy that is dramatically different from that which currently governs these products.
2. FDA’s new policy is seemingly inconsistent with an existing regulatory scheme under CLIA, an inconsistency which should be resolved through the rulemaking process.
3. The lack of specificity in the draft guidance can be addressed through notice-and-comment rulemaking in which the public—patients, providers, researchers, and others—can contribute their perspectives on the issues raised by the new regulatory initiative.

⁴ Compare Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests, submitted to FDA by Washington Legal Foundation, September 28, 2006.

Under these circumstances, we do not see any ground for failing to comply with the requirements of the APA, and ASCO would urge FDA to develop a proposed regulation setting forth the specifics of the new regulatory program and giving interested members of the public an opportunity to provide comment.

Practical Considerations

The tests covered by the draft guidance have been used by physicians for years to diagnose their patients and to refine their treatment options. Sudden imposition of new restrictions on those tests could create significant disruptions in patterns of care. FDA should not undertake precipitate changes in regulation of potentially life-extending products without taking into account these very concrete concerns.

Policy Concerns

For many years, companies seeking to develop valuable genetic testing systems for cancer and other diseases have relied on FDA's assurance that they were exempt from regulation under the Food, Drug and Cosmetic Act, and have invested their capital and other resources accordingly. The sudden and seemingly unexpected reversal of that regulatory position is not only disruptive to the business planning of those entities, but it also sends a strong signal of regulatory instability to those investors who might contemplate entering the market in the future. For the benefit of patients and their caregivers, FDA's policy should encourage rather than hinder investment in potentially beneficial interventions like the genetic tests subject to the draft guidance.

CONCLUSION

ASCO endorses FDA regulation of the laboratory-developed tests that are referred to as IVDMIAs, but believes that the agency may not competently or legitimately assert that regulatory authority absent notice-and-comment rulemaking. Informed members of the public, including both physicians and patient advocates, can provide guidance to FDA in fashioning a final regulatory framework, but only if they are allowed to participate in a meaningful manner. If FDA is to proceed with its assertion of regulatory authority over these important tests, it must do so through an orderly process that involves prior notice of the regulatory approach to the public and a full opportunity for public comment.

Aside from these legal and procedural considerations, it is important to recognize that any assertion of regulatory authority by FDA will represent a dramatic shift from prior requirements, under which these IVDMIAs were exempt from regulation. All parties—physicians and other providers, patients and the purveyors of the tests themselves—have relied on prior FDA guidance in assuming that these tests were not under FDA jurisdiction. If such jurisdiction is to be asserted now, there should be consideration of appropriate transition measures to ensure that these tests, now widely used in practice, not become unavailable to those who rely on them. Some concept of “grandfathering” of existing tests where sponsors have reasonably relied on prior FDA advice should be incorporated into the final revised guidance.



Thus, we believe it is entirely appropriate to impose regulatory requirements, including well-controlled clinical trials, on these IVDMA tests, but, while such tests are underway, the current availability of the tests, including their reimbursement status, should not be threatened. We understand the potential inconsistency of an approach that recognizes the inadequacy of current clinical information but that insists that the current status be maintained for the time being. However, it seems that this conflict is inevitable, given the abrupt shift in FDA's regulatory stance regarding these products. ASCO would welcome the opportunity to discuss with FDA how this regulatory conundrum could best be resolved.

Sincerely,

A handwritten signature in black ink, appearing to read "G. Hortobagyi", written in a cursive style.

Gabriel Hortobagyi, MD, FACP
ASCO President

GNH:cs

CC: Courtney Harper (via email)