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Advancing Excellence

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February 12, 2007

Andrew C. von Eschenbach, MD
Acting Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2006D-0347- Draft Guidance for Industry, Clinical Laboratories and FDA Staff: In Vitro Diagnostic Multivariate Index Assays

Dear Commissioner von Eschenbach:

The College of American Pathologists (CAP) is providing the following written response to the Food and Drug Administration's (FDA) request for public comment on the *Draft Guidance for Industry, Clinical Laboratories and FDA Staff: In Vitro Diagnostic Multivariate Index Assays*. The College of American Pathologists is a national medical specialty society representing more than 16,000 pathologists who practice pathology and laboratory medicine. Therefore, the CAP has a profound interest and extensive experience in this topic.

The CAP's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories worldwide. College members have extensive expertise in providing and directing laboratory services and serve as inspectors in the accreditation program. In addition, the CAP provides laboratories with a wide variety of proficiency testing programs and educational solutions to assist in the improvement of the laboratory's performance and its positive impact on patient care. These programs are designed to improve the quality of laboratory services and to ensure the accuracy and reliability of test results.

SUPPORT FOR FDA GOALS

The CAP shares the FDA goal of protecting the public's health by ensuring safe and effective diagnostic tests to inform clinical decision-making. We help laboratories achieve the highest standards of excellence to impact positively patient care through our Laboratory Accreditation Program which exceeds the regulatory compliance required by the Clinical Laboratory Improvement Amendments (CLIA). As in other areas of medicine, laboratory medicine is improved in incremental steps as new information about clinical targets and test performance become available. As such, unnecessary impediments to the process of diagnostic test development are not necessarily in the interest of promoting high quality patient care.

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The CAP recognizes the interest of the FDA in developing a guidance document that takes into account the increasing complexity of laboratory-developed tests, and we agree that complex diagnostic tests are being developed and made available that are not subject to traditional peer review and independent verification. While the CAP supports the FDA goal of ensuring safe and efficacious diagnostic tests, we believe that this goal can best be achieved through the enhancement of CLIA. Laboratories now have extensive experience working with the Centers for Medicare & Medicaid Services' (CMS) Division of Laboratory Services to comply with stringent quality control mechanisms in place through CLIA. Given the established relationships with CMS through its administration of CLIA and the positive effect this has had on laboratory quality and ultimately on patient care, CAP believes the goal of ensuring clinical validity of the complex laboratory testing described in the IVDMA guidance can best be achieved if laboratories demonstrate clinical validity of their tests through the CLIA inspection process.

Laboratory-developed tests that guide treatment decisions in serious conditions or diseases and that cannot be independently verified increase the risk that an erroneous result may cause real patient harm. With an understanding of the FDA goal of ensuring patient safety through the regulation of IVDMIAs, the CAP requests that the proposed regulatory framework outlined in the *Draft Guidance for Industry, Clinical Laboratories and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* be reconsidered. If the FDA continues on this path, CAP urges the FDA to clarify the definition of an IVDMA, emphasize the need for transparency in laboratory-developed tests, and reduce impediments to the rapid development of laboratory-developed tests.

The CAP offers the following specific comments on the proposed Draft Guidance:

IVDMIA DEFINITION

Clarification

The CAP asks for clarification of the definition of an IVDMA as there is room for misinterpretation in the current definition. The FDA's stated goal for issuing the draft guidance is "to dispel the existing confusion and clarify its approach to regulation of IVDMIAs." Yet, laboratories remain unsure whether tests currently being offered would be considered IVDMIAs under the current definition in the draft guidance. The document would benefit from concrete examples of currently offered tests that would be expected to go through FDA premarket review and those tests currently offered by laboratories that would not be considered IVDMIAs. For example, the CAP believes that DNA sequence analysis of a gene for a genetic disorder should not be considered an IVDMA. The sequence of exons and adjacent flanking and/or intron sequences are typically determined and a final result reported indicating the presence of any disease-associated sequence variants and perhaps known neutral polymorphisms. The use of software programs which assist in sequence analysis should not be problematic because results can also be unambiguously ascertained by visual review of primary data.

Independent Verification

The CAP believes that independent validation of complex laboratory-developed tests improves patient care, increases standardization, and reduces errors and that a critical component of laboratory-developed testing is transparency. The use of software or an algorithm in a test should not define a test as an IVDMA. We suggest that laboratory-developed tests with published methodologies, algorithms, and clinical validity studies that can be independently evaluated by the broader medical community should not be required to be submitted for FDA pre-market review in addition to the existing quality controls in place through CLIA.

PRE-MARKET AND POST-MARKET REQUIREMENTS FOR IVDMIAS

Reduce Impediments to Diagnostic Test Development

The CAP encourages the FDA to limit the number of impediments to the process of laboratory-developed testing. Rapid test development has greatly benefited the American public's health by reducing the time between research and translation of research findings into clinical use and patient benefit.

We believe that all test procedures used for the diagnosis, prevention, treatment, and assessment of human disease regardless of designated CLIA test complexity, should be subject to a documented quality control program and to proficiency testing. We stand in support of efforts to move forward to develop new and innovative approaches to improve patient care. Additional regulation of laboratories that already have stringent quality control mechanisms in place through CLIA should only be imposed when tests being offered cannot be independently verified and there is reason to believe that the public's health may be at risk. The FDA should take into consideration whether compliance with FDA regulations as well as CLIA regulation is consistent with a least burdensome approach. In addition, as laboratories have not been subject to FDA review of laboratory-developed tests and may be unfamiliar with FDA quality control requirements, further guidance on all FDA requirements is needed before any additional regulation is imposed.

CONCLUSION

The CAP would like to reiterate its support for the general concept that it is appropriate to review those complex diagnostic tests that cannot be independently verified by the larger medical community due to lack of access to proprietary information.

CAP Recommendations

CAP believes that this goal can best be achieved through the enhancement of CLIA such that demonstration of clinical validity of laboratory tests becomes part of the laboratory accreditation process. The CAP' Laboratory Accreditation Program has already taken this step. If the FDA is determined to initiate separate oversight of laboratory-developed tests, further clarification from the FDA on the type of tests it intends to review as well as how laboratories can comply with both FDA Quality Systems Regulations and CLIA regulations is needed. Such clarification is essential before any further FDA enforcement to avoid impeding the progress of laboratory medicine that has benefited the public health

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by allowing rapid development of diagnostic tests through incremental improvement of tests and the traditional routes of peer-reviewed publication.

Thank you for the opportunity to present our views. For questions or comments, please contact Fay Shamanski, Assistant Director of Public Health and Scientific Affairs, at (202) 354-7113 or fshaman@cap.org.

Sincerely,

Handwritten signature of Thomas Sodeman MD FCAP in black ink.

Thomas Sodeman, MD, FCAP
President

CC: Steven I. Gutman, MD, PhD, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA