



Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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The Association for Molecular Pathology (AMP) would like to provide comments to the Food and Drug Administration on the recently issued draft guidance: ***In Vitro Diagnostic Multivariate Index Assays (IVDMIA)*** (Docket #2006D-0347), published on September 7, 2006

AMP is an international not-for-profit educational society representing over 1,400 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity, AMP members are involved in every aspect of molecular diagnostic testing: administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

AMP's Mission Statement identifies the Society as "dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics." Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

AMP acknowledges what we believe to be FDA's stated intent in issuing this guidance. AMP supports the development of tests and test systems for *in vitro* diagnostic use (IVDs) and encourages industry to pursue FDA clearance and approval where current regulations require. AMP, however, is very concerned that this guidance, if enforced in its broadest sense, could severely reduce the availability of certain reagents and laboratory developed testing services, and compromise the quality of molecular test development by laboratories under CLIA, which have become the diagnostic or prognostic standard of care for many diseases or conditions. Reduced availability of testing services would limit a healthcare provider's ability to manage patient care, and ultimately limit patient access to new or improved molecular tests. AMP requests that for significant changes to the ASR rules or interpretation of those rules, the rulemaking process be used in an open, public forum.

When the ASR rule was published in 1997, FDA believed that the director of a CLIA-certified high complexity laboratory was qualified to design and validate new molecular diagnostic tests. However, in the IVDMIA guidance, FDA asserts that IVDMIA's are not within the ordinary "expertise and ability of laboratories" and therefore "raise safety and effectiveness concerns" necessitating that they meet pre- and post-market review requirements for class II and III devices. AMP questions the agency's interest in regulating medical algorithms, particularly those that are disclosed by the manufacturer and are transparent to both the laboratory and clinician. Such interpretations are and have been longstanding standards in the practice of medicine. Algorithms using patient information (tumor size, extent of malignancy, node involvement, etc) have long been used to determine risk of recurrence of cancer, and of classification of particular cancers. Many laboratory tests cannot be properly interpreted unless patient data is collected (i.e., interpretation of a glucose reading in the absence of knowledge of a patient's last meal). Reference ranges (one element a laboratory has to validate for a laboratory developed test regardless of whether a commercial ASR is used in the development) are often laboratory measurements that are normalized to specific patient parameters based on the population in the laboratory's testing jurisdiction as required by CLIA regulations.

In addition, FDA identifies IVDMIA's not as laboratory-developed tests but as test "systems" that combine data derived from the laboratory assay with an algorithm or calculation to reach a patient-specific result. This definition is neither found in the Federal Food, Drug, and Cosmetic Act, nor in any regulation from the FDA and was not developed through notice and comment rulemaking. Within this proposed definition, the laboratory is the manufacturer of a test system that is subject to FDA regulation as a medical device. However, there is no such definition in any FDA regulation. This area of laboratory operation currently is regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). As our members routinely design and perform many molecular tests in oncology, hematology, human genetics and infectious disease, we are particularly concerned about the broad language in the document.

AMP respectfully requests that:

- **FDA apply restrictions requiring PMA or 510(k) clearance of an IVDMIA only when the interpretive algorithm remains undisclosed by the manufacturer.**
- **FDA provide the scientific rationale for their new concerns over the safety and effectiveness of laboratory-developed tests, as well as a justification for their jurisdiction over medical testing algorithms.**
- **FDA convene a classification panel (e.g., as was done in the reclassification of immunohistochemistry tests) so that criteria for determining which tests will be subject to FDA regulation will be transparent to laboratories developing such tests.**

- **FDA clearly and specifically define the scope of IVDMIA that it intends to regulate.**
- **FDA ensure that any new guidance does not insert FDA into the purview of CMS' regulation of laboratories under CLIA.**
- **FDA clarify the scope of its regulations that renders laboratories responsible for meeting criteria as medical device manufacturers, i.e., pre-market review only or all general controls (registration and listing, quality systems, labeling, medical device reporting).**

Thank you for the opportunity to comment on these very important documents. AMP, whose members are routine users of ASRs, is ready to work with FDA to develop clear, reasonable guidelines that will promote the development of molecular pathology. AMP supports FDA's mission to "promote and protect" public health, balancing safety concerns with access and availability of exciting new medical breakthroughs. Please do not hesitate to contact Wayne Grody, MD, PhD, AMP Professional Relations Committee Chair at WGrody@mednet.ucla.edu if we can be of further assistance.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Ferreira-Gonzalez', with a long horizontal line extending from the bottom of the signature.

Andrea Ferreira-Gonzalez, PhD
President