College of American Pathologists

Comments to the
Food and Drug Administration
on the draft guidance
“In Vitro Companion Diagnostics Devices”

October 12, 2011
The College of American Pathologists appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance entitled "In Vitro Companion Diagnostic Devices". The College of American Pathologists (CAP), celebrating 50 years as the gold standard in laboratory accreditation, is a medical society serving more than 17,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The College advocates accountable, high-quality, and cost-effective patient care. CAP Laboratory Accreditation Program is responsible for accrediting more than 7,000 clinical laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and also serve as inspectors in the CMS-deemed CAP accreditation program. CAP also provides laboratories with a wide variety of proficiency testing programs and has the responsibility to evaluate the accuracy of test performance and interpretation in more than 23,000 laboratories worldwide.

GENERAL COMMENTS
CAP shares the FDA's commitment to public health and supports its efforts to ensure consistency and reliability of diagnostic tests. High quality laboratory developed tests (LDTs) have been in clinical use for many years and represent some of the most innovative tests offered to patients today. CAP believes that as written this guidance will negatively affect the ability of pathologists to continue to provide these innovative high quality tests to their patients. As physicians specializing in the diagnosis of disease through laboratory methods, pathologists have a long track record of delivering high quality diagnostic services to patients and other physicians and have a keen interest in ensuring that access to these services is not unduly restricted. Molecular evaluation of tumors is one of a pathologist's responsibilities to patients. The purpose of testing for the individual patient is not to identify "sub populations" or "subsets of populations" which might benefit from a particular therapy as noted in the draft guidance, but to better define the therapeutic options available for that individual. Whether those options are exercised or not is a decision reserved for the patient in consultation with his or her physicians. We believe this to be the essence of the practice of medicine. When viewed in that sense, the results of companion diagnostic testing are only one component in determining a patient's treatment regimen. Although it is true that certain tests that inform about cellular molecules and signaling pathways, particularly those targeted by specific agents, can have particular significance in assembling an optimized course of therapy, such tests must be recognized as only part of that tumor's full characterization and only one element in choosing how that patient will be treated.

Physicians who treat cancer patients (surgical oncologists, medical oncologists, radiation oncologists, radiologists) and pathologists in particular devote considerable professional expertise in characterizing every individual tumor. This is apparent in the American Joint Committee on Cancer (AJCC) Cancer Staging Protocols that define each tumor by various features including size, differentiation, invasiveness, proliferation, location, and metastatic spread. In conjunction with clinical, radiologic, and surgical findings, this pathologic staging helps determine which therapeutic options are available to that patient. As regimented as this practice endeavors to be, those who treat cancer patients recognize the great variability with which tumors can present, their biological heterogeneity, and the need for professional knowledge and insight in how to best classify an individual tumor. The situation with biomarkers related to neoplasms, however, is considerably complex. Each tumor has unique biological characteristics, behavior and genome. Overlying this variability in tumor biology is the critical issue of
tissue sampling, an area demanding the professional expertise of a pathologist. A diagnosis may be achieved by cytologic evaluation of cellular material, fine needle aspiration, fine needle biopsy, endoscopically obtained biopsy, excisional biopsy, or therapeutic resection, all methods which produce different, and often limiting, amounts of tumor tissue which must be used for appropriate characterization. It is the pathologist’s responsibility to evaluate any of these specimens appropriately using the best ancillary methods and tests available to secure a reliable diagnosis for each individual patient.

It is also the responsibility of the pathologist not only to convey the nuances of the tumor’s pathology to the oncologist, but also to convey information that could influence the interpretation of any adjunctive test results. The draft guidance, in attempting to define a regimented approach for the approval of each companion diagnostic tying it to every specific clinical indication and specimen type, is unrealistic in its view of how these tests are used by the pathologist and the oncologist clinician. Indeed, in rigorously defining and linking clinical indication, test result, and a specific therapeutic, this policy may falsely assure users that a particular test result conveys a greater level of significance than is warranted.

**SPECIFIC COMMENTS ON THE DRAFT GUIDANCE SECTIONS**

**Definition and Use of an IVD Companion Diagnostic**

FDA defines an IVD companion diagnostic device as an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. (Generally, this means that the use of the IVD companion diagnostic device with the therapeutic product allows the therapeutic product’s benefits to exceed its risks.)

The draft does not distinguish between tests which assess individual metabolic capabilities (e.g. pharmacogenomic tests) from those which assess characteristics of specific neoplasms (e.g. KRAS, HER2). Failure to make this distinction will be problematic. Typical pharmacogenomic tests might assess the presence of specific polymorphism in genes that are reflected in the metabolic pathways necessary for the activation or inactivation of a particular therapeutic agent. Such tests can be standardized relatively easily since they are performed using a consistent substrate (nucleated blood cells) and well defined, narrow performance requirements.

FDA has indicated that a laboratory test could be essential to identify patients most likely to benefit from or have an adverse reaction to the therapeutic. CAP believes this definition needs further clarification. One could argue that any biopsy result indicative of cancer is essential to identify patients likely to benefit from a chemotherapeutic regimen and as most of such therapeutics have potentially significant side effects and possible adverse reactions, a proper diagnosis is essential to avoid those side effects and potential adverse reactions. In addition, FDA has noted it may be essential to use a diagnostic test to monitor the response to treatment for purposes of dosage adjustment or other treatment modifications. Typically, these tests are not interpreted alone but rather are used in the context of the patient’s physical response and other laboratory testing.

**Review and Approval of IVD Companion Diagnostic Devices and Therapeutic Products**

This draft guidance poses a major concern for clinical laboratories performing LDTs because of the implication that LDTs have ‘unproven performance characteristics’ and may mislead healthcare
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providers and cause serious adverse health consequences to patients. Clinical laboratory tests in accredited laboratories are closely regulated to ensure that all testing meets accepted performance characteristics. Each clinical laboratory is required under CLIA to verify the analytic validity of every diagnostic test. In doing so, the laboratory establishes analytic sensitivity, analytic specificity, accuracy, precision, reportable range and reference intervals. Further, for CAP-accredited laboratories, all molecular testing systems must have clinical validity established as well. CLIA-certified laboratories are required to have a system of continuous quality improvement in place and monitoring is achieved through laboratory inspections and the performance of proficiency testing. CAP believes that clinical laboratories offering tests used to guide therapeutic decision making can recognize the potential problems and through strict adherence to quality management and assay validation establish a high degree of assurance of test quality.

Overall, clinical laboratories perform very well, with evidence that US labs are performing even better than the overall average derived from national and international labs combined.

Labeling

In the section on therapeutic product labeling, the guidance states “When appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared IVD companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer’s IVD companion diagnostic device.” CAP strongly believes that the label should indicate the biological pathway or target of testing rather than a specific test or test process and that the label should not restrict testing methodologies to only FDA approved or cleared devices but rather specify the analyte to be tested. In no case, should a brand name be indicated. As noted above, LDTs have provided benefits to patients and clinicians for decades and are currently used in clinical practice to guide therapeutic decision-making. Restricting through labeling of therapeutic products to FDA approved or cleared IVD companion diagnostic tests and their defined limitations will necessarily limit patient access to valuable tests, restrict pathologists’ ability to provide the most thorough evaluations for their patients, and affect coverage and reimbursement decisions. Further, implementation of the guidance may impede the incorporation of new scientific evidence of disease pathobiology and technical advances in device methodology.

CONCLUSIONS

The College fears that a strict interpretation of the draft guidance entitled, “In Vitro Companion Diagnostic Devices” will disrupt patient care. Many LDTs currently employed in clinical laboratories have well established and determinative roles in clinical care and guide therapeutic decision making. The role that LDTs have played in the advancement of modern medicine should be recognized: virtually all new laboratory tests are developed as laboratory developed tests before being commercially developed. The significance of this function of the LDT for the advancement of medicine cannot be overstated, and any regulatory guidance should address the very serious consequences of restricting that role. The College is seriously concerned that interpretation of the draft that does not take this into account will reverse many recent gains in laboratory medicine, hinder innovation and reduce the speed of test development, and generally subvert a long standing tradition of advancement in medicine.
Understanding that any companion diagnostic cannot be formally evaluated in every conceivable clinical setting, strict enforcement of the draft recommendations will constrain the use of many diagnostic assays used in the evaluation of tumor specimens. While it is important for FDA to set clear expectations of vendors who develop and market tests, it is equally important that the guidance not hamstring the ability of pathologists and oncologists to use these assays for an individual patient.

We understand your purpose for developing such guidance for the manufacturers of those tests that meet the definition of companion diagnostics, but it should be clear that their purpose is intended to safeguard against undue claims by device manufacturers for such tests, and not impose restriction on medical practice, or redefine what the practice of medicine means. As written, the draft guideline will do that, if implemented, and will likely negatively influence the use and availability of these assays and possibly raise questions of medical liability.

**CAP Recommendations**

CAP would like to see the FDA acknowledge that the molecular characterization of tissue is an intrinsic part of the pathologic evaluation of that tissue. While the testing used for that needs to be accurate, its interpretation falls within the responsibilities of the pathologist. FDA should be cautious not to direct or imply specific treatments, which are ultimately medical decisions.

CAP recommends that therapeutic labels refer to the analyte being tested or performance characteristics required rather than to any specific tests that are FDA approved. If an FDA approved test is, in fact, the best test available for the evaluation of a particular specimen, it will be used. However, pathologists, medical directors of laboratories, should be able to continue to choose to use the test that will provide the best diagnostic information for their patients. Often these tests are LDTs.

CAP appreciates this opportunity to submit these comments on the draft guidance document. If you have any questions, please do not hesitate to contact, Fay Shamanski, PhD, Assistant Director, Public Health and Scientific Affairs (202.354.7113/fshaman@cap.org).