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AMP Comments Regarding FDA Draft Guidance for “In Vitro Companion Diagnostic Devices”

I. Introduction

The Association for Molecular Pathology (“AMP”) is pleased to provide comments to the Food and Drug Administration (“FDA”) regarding its July 14, 2011 Draft Guidance addressing “In Vitro Companion Diagnostic Devices” (“Draft Guidance”). AMP is an international medical and professional association representing approximately 2,000 physicians, doctoral scientists, and medical laboratory scientists who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Our members are dedicated to the development and implementation of molecular pathology testing for the benefit of our patients in a manner consistent with the highest standards established by the Clinical Laboratory Improvement Amendments (CLIA), the College of American Pathologists (CAP), the American College of Medical Genetics (ACMG), and the Food & Drug Administration (FDA). AMP members populate the majority of clinical molecular diagnostics laboratories in the United States, and our efforts are central to the generation of novel, high quality, molecular tests that are applied daily in medical decision-making. Assays designed and validated within our laboratories are used for diagnosis, prognosis and patient management in all medical areas including cancer, infectious diseases, heritable disorders, and histocompatibility testing. In addition to developing and implementing such tests, AMP members are experts in the interpretation of these assays. The Draft Guidance has important implications for AMP members, who are responsible for the evaluation of relevant patient specimens and the oversight, interpretation, and consultation related to specimen-associated laboratory testing.

II. AMP applauds FDA discouraging the inclusion of test brand names or manufacturers in therapeutic product labeling

AMP applauds FDA for its recognition of the untoward effects of therapeutic product labeling that specifies a particular manufacturer’s IVD. By emphasizing testing rather than vendor, FDA will encourage the development and advancement of diagnostics that will be useful not only in association with the particular therapeutic product at issue, but also in conjunction with other drugs and biologics that will be linked to a given biomarker.

For example, mutations in codon 600 (predominantly V600E) of the gene *BRAF* serve as a companion biomarker to the targeted biologic vemurafenib, which was recently approved for use in patients with

melanoma. However, the *BRAF* V600E mutation has for several years served as a surrogate marker for *MLH1* promoter methylation in colon cancer and a prognostic marker in thyroid cancer, among other applications. Moreover, alternative mutations in the same codon, or a variety of mutations in multiple codons may eventually prove to be differentially clinically relevant to a number of disease entities. Such is the case with various mutations in the gene *KIT*, for example, which have medical significance in conditions as diverse as gastrointestinal stromal tumors (GISTs) and acute myeloid leukemia (AML). It is to be expected that many biomarkers will in the future be linked to a variety of disease entities and therapeutic products. It is, of course, not feasible for laboratories to maintain multiple platforms and methods to test for the same biomarker for alternative therapeutic products within the same class, drugs and biologics from different classes, and a potentially wide range of other possible clinical applications. Therefore, FDA's support for the subsequent introduction and use of alternative test products is important in promoting laboratory efficiency and enhancing assay performance, and thereby improving the care of our patients.

IVD manufacturers and pharmaceutical companies appear unlikely to validate companion biomarker assays on the full range of specimens typically encountered in a clinical laboratory. These samples include, for example, core biopsies, needle biopsies, and an array of body fluids. From the laboratory and CLIA perspectives, performing an FDA cleared or approved test on specimens not validated by the manufacturer constitutes an "off-label" use, converting the assay to a laboratory developed test, irrespective of the kit's cleared or approved intended use.

Off label use presents unique challenges for pathologists and other laboratory professionals, whose roles are very different from those of physicians who prescribe approved therapeutic drugs for uses other than their approved indications. During the off label prescription of drugs, the physician simply writes an order for a drug for a patient in whom he believes administration of the therapy is consistent with appropriate medical practice, and for which the potential benefits are likely to exceed the possible harms. By contrast, CLIA requires clinical laboratories to validate the off label use of FDA-cleared or approved tests as if they were laboratory developed tests.

However, molecular pathology assays often have reliable, well established, and robust technical performance characteristics, rendering unnecessary extensive validation solely because of expanded intended use. Technical performance of many tests will be identical or equivalent, irrespective of the context in which it is offered. For example, assays to detect the *BRAF* V600E mutation are likely to perform equivalently on an array of sample types for a variety of indications. Implementations of new medical uses for a diagnostic test are typically added, as appropriate, after collaborative discussions that include review of published literature with treating physicians about the clinical utility of the application. Using an FDA-cleared assay off-label for additional sample types and applications may be a medical decision between the treating physician and the pathologist or other laboratory professional. Nevertheless, the absence of such alternative uses from the diagnostic label would appear to mandate full and complete validations for each and every use.

III. FDA's primary focus should be the companion biomarker rather than specific tests to measure it.

AMP believes FDA's primary focus should be on the companion biomarker, rather than associated diagnostic tests. From a medical and physiologic standpoint, the relevant parameter is the biological relationship between the biomarker at issue and its associated therapeutic product, not the individual test or tests by which the biomarker is detected. Therefore, we propose changing the title of the Draft Guidance to "Companion Biomarkers." The accompanying change in emphasis and scope will provide FDA with an improved framework for regulating targeted therapies that will confer greater benefit to patients.

AMP is an enthusiastic supporter of FDA in its desire to ensure accurate and robust analytical performance and a high level of clinical validity for testing of given biomarkers. However, in many instances the significance of the biomarker and its optimal use will require knowledge of the quantitative relationship of the biomarker to potential therapeutic responsiveness. This is particularly relevant in cancer diagnostics, where the predictive value of the biomarker may vary at different allele proportions in a specimen as well as in relation to regional tumor heterogeneity, the latter of which may be reflected in the morphology of the neoplasm. For many biomarkers our knowledge of these and other neoplastic features and relationships will initially be incomplete and will require clinical judgment. Therefore, it is critical that FDA not inadvertently impede diagnostic advancement or the acquisition of knowledge about biomarker performance including optimal testing approaches, by locking in approved platforms through its promotion of "companion devices."

Consistent with the preceding, it should be noted that maximizing the analytical sensitivity of a test for a biomarker associated with a targeted therapy will expand the market for the drug. Consequently, therapeutic product manufacturers may have limited incentive to pursue research that could demonstrate decreased therapeutic effectiveness in patients with tumors that contain a small allele burden of a relevant mutation. AMP believes any and all claims of superior test performance over alternative methods, when predicated on technical features such as lower limit of detection, should be supported by convincing evidence of clinical, as opposed to merely analytical significance. For example, sponsors should demonstrate that patients with low-level, response-related mutations in properly microdissected tissue specimens have equivalent outcomes to patients with higher mutant allele proportions, not merely that one test detects more such mutations than another. FDA should evaluate the clinical benefits of an enhanced lower limit of detection in relation to its potential benefits and harms, with the goal of preventing inappropriate decision making based upon erroneous beliefs about probable therapeutic responsiveness.

Further, in its definition of a companion diagnostic, FDA on page 7 attempts to exclude tests that provide information that is merely useful, "but that are not a determining factor in the safe and effective use of the product." AMP would like to offer additional perspective regarding the nature and role of

laboratory testing in medical care. A demonstrable relationship between therapeutic product and a biomarker is by definition present for the types of drugs and biologics to which the draft guidance is directed. However, for many therapeutic products, medical information and patient specific characteristics may be determining factors in the safe and effective use of a drug in a given patient. Such information may also include results of other diagnostic tests, which may outweigh the impact of test results for the companion biomarker in the decision-making process.

For example, although FDA mentions serum creatinine as a test that would not constitute a companion diagnostic, the presence of renal failure is an absolute or relative contraindication to the administration of a number of drugs. Many laboratory tests are used to directly inform treatment decisions. Blood glucose levels are used to determine insulin dose, bacterial identification and susceptibility testing directly impact antibiotic selection, and CD20 status is used to guide rituximab selection. However, medical practice typically involves the integration and assimilation of multiple pieces of information, with the isolated impact of a particular factor such as a test falling along a continuum of greater to lesser weight. This suggests the bright line concept of “determining factor in the safe and effective use of the product” may introduce arbitrariness in the application of the Guidance to therapeutics other than those that directly target particular biomarkers.

IV. FDA’s policy of limiting approval of novel therapeutic products linked to biomarkers to those for which an FDA cleared or approved assay is available is too restrictive.

AMP believes that FDA’s proposed policy to limit approval of novel therapeutic products linked to specific biomarkers (or subsequent label changes for already approved products) to those drugs and biologics for which an FDA cleared or approved assay for the biomarker is either concurrently or subsequently available, is too restrictive. Instead, FDA should weigh the benefits and harms of approving the drug for use with laboratory developed tests on a case-by-case basis. In many instances CLIA-certified laboratories may offer laboratory developed assays for a biomarker that utilize standard molecular diagnostic techniques with which there is significant clinical experience. The benefits of such tests will often exceed their risks. FDA should be aware that there are many existing examples of laboratory developed tests for biomarkers that have been applied in connection with therapeutic products to great effect. Such tests include *KRAS* mutation testing in association with anti-*EGFR* therapy in metastatic colon cancer, *EGFR* mutation testing in non-small cell lung cancer, *BCR-ABL* testing in chronic myelogenous leukemia, *PML-RARA* testing in acute promyelocytic leukemia, and flow cytometry testing in association with monoclonal antibody therapies in hematopoietic malignancies. In many cases, FDA approval of a therapeutic product for use with a biomarker measured by a laboratory developed test would likely shorten the timeline for bringing the benefits of the drug to patients, without a significant increase in medical risk. In addition, support for the use of laboratory developed assays as a means of detecting companion biomarkers will encourage investigation into diagnostic methodologies which will yield demonstrable clinical rewards for our patients.

Conversely, AMP believes that the inclusion in therapeutic product labeling of implicit or explicit requirements mandating the use of FDA cleared or approved tests for a biomarker will in many instances be harmful to patients and injurious to their care. We urge FDA to oppose attempts to place these types of restrictions in product labels. Under circumstances in which an FDA cleared or approved test method has been conclusively demonstrated to offer meaningful superiority in *clinical* performance relative to alternative test platforms, the methodology, rather than specific tests, should be included in the label. As previously stated, there are often multiple alternative medical uses for detection of specific genetic variants, or mutations in particular genes. It is not feasible for most laboratories to maintain multiple assays for the identical biomarker, and it would be unreasonable to expect them to do so. Because of the impossibility of complying with a burden of this nature, attempting to force laboratories to implement only FDA cleared tests would decrease test availability, to the detriment of patient care. There is often an inextricable link between pathologic specimen characteristics, including tumor burden and mutation heterogeneity, and the clinical significance of the test result. In addition, there may be important issues relating to the turnaround time of a test. Finally, there may be a need for deliberation among the medical team caring for an individual patient about these and other considerations prior to embarking on a course of therapy. These features of patient care suggest that regulatory actions that force distribution of samples away from the site of patient care may disadvantage patients and compromise their care.

V. Reflexive classification of tests for companion biomarkers as high risk may impede the commercial development of new assay and the advancement of new test methods.

The Draft Guidance in footnote 10 conveys FDA's position that most companion diagnostics will be class III devices. AMP believes that in many cases this bar will be too high. Because class III devices typically require premarket approval rather than a 510(k) determination of substantial equivalence, AMP is concerned that reflexive classification of companion biomarkers as high risk devices will impede the commercial development of new assays and advancement of new test methods. After initial approval of a therapeutic drug and an associated test, subsequent clinical trials with other tests will be difficult and expensive to conduct, and the potential rewards are unlikely to justify the expense. Once the clinical validity of a biomarker has been established, the investigative work usually will not need to be replicated. The technical performance of a test generally does not require clinical trials or intensive study. Therefore, substantial equivalence will typically be a better model for introducing tests for companion biomarkers into medical practice.

VI. Final determination of significant risk for the purposes of compliance with IDE regulations should primarily be made by the institutional review board overseeing the study.

FDA has stated its intention to consider all diagnostic assays used in clinical trials of therapeutic products investigational devices carrying significant risk under 12 C.F.R. 812(m)(3). Such tests will be required to comply with the investigational device exemption regulations. AMP believes that all diagnostic assays used to make treatment decisions whether in investigational or routine clinical settings,

should be performed in CLIA-certified laboratories. However, AMP is concerned that classification of many assays as significant risk devices for the purposes of applicability of and compliance with the IDE regulations may be unnecessary, generating excessive burdens on sponsors while doing little to ensure patient and research subject safety. This seems particularly true when assay results are confirmed by or used in conjunction with a well-validated, well-performing test already in clinical use in a CLIA certified laboratory, even if the test is performed for other clinical reasons, or for many, on clinical specimens outside those encompassed by the intended use under consideration.

For example, an assay that is used to detect the *BRAF* V600E mutation in colon cancer is likely to be readily applied with minimal modification to enable detection of the same mutation in melanoma or thyroid cancer. Such a test is not truly investigational. Although the clinical validity for the new intended use has yet to be proved, the test's analytical performance is well-established. Demonstration of equivalent technical performance in an alternative use will often be straightforward. In such cases, an assay can be safely and effectively used for comparison and confirmation purposes of other molecular pathology tests proposed as companion biomarker assays.

VII. Pharmaceutical and diagnostic sponsors should be required to provide data on the negative predictive value of a test used to predict drug or biologic responsiveness.

Pharmaceutical sponsors should always be required to provide data on the predictive value of a negative result for a drug putatively linked to a biomarker. Pathophysiologic reasoning is inadequate to establish the relationship between a biomarker and a therapeutic product, even one targeted directly to the biomarker. Although universal responsiveness to a therapeutic product has been demonstrated among patients with a disease who have mutations in a particular gene, there may be also be a significant response rate in patients who lack mutations in the gene. In such cases it may be inappropriate to treat based on the presence or absence of the biomarker, despite its high positive predictive value. Again, this enters the realm of medical decision-making.

VIII. Pharmaceutical and diagnostic sponsors should be required to submit studies of all assays for companion biomarkers for peer reviewed publication.

Pharmaceutical and diagnostic sponsors should be required to submit all assays for companion biomarkers for peer reviewed publication, and to make all reasonable efforts necessary to ensure publication of study results.

IX. Conclusion

Thank you very much for the opportunity to participate in discussions about regulatory approaches to companion biomarkers. AMP offers its assistance to FDA as the Agency addresses this important issue, and looks forward to further discussions with you.