



December 9, 2009

To: Food and Drug Administration

Re: Comments on Development of Companion Diagnostics and the April 2005 Food and Drug Administration ("FDA") Drug-Diagnostic Co-Development Concept Paper

Dear Sir or Madam:

On behalf of the Personalized Medicine Coalition ("PMC"), thank you for the opportunity to submit comments on the above-captioned concept paper on drug-diagnostic co-development (the "Concept Paper"). The PMC is an independent, non-profit education and advocacy organization that promotes personalized medicine concepts and products for the benefit of patients. Its diverse membership acts as a resource for policy makers, opinion leaders and the public about the issues that shape and accelerate the development of personalized medicine.

We appreciate the opportunity to provide comments and suggestions on the Concept Paper and on the appropriate path by which the Agency should proceed to establish a balanced regulatory approach to encourage investment in therapies used as part of personalized medicine and future diagnostic technologies, as well as those used to prescribe drugs. We believe that working in concert with the FDA on key policy considerations, particularly those raised by the Concept Paper, will advance our mutual goals and objectives. To that end, PMC appreciates the Agency's interest in and willingness to reach out to the broad range of stakeholders represented by PMC. At the suggestion of the Agency, PMC has also attached as an addendum a short list of proposed topics for an FDA public workshop and/or white paper series related to the co-development of drugs and diagnostics to further develop this essential guidance for industry.

Combinations of targeted drug therapies and diagnostics to guide optimal clinical treatment protocols offer great benefit to patients and have the potential to significantly advance public health. These benefits include innovative methods to further individualize therapies such as identification of potential responders, or non-responders, to a specific drug and identify more precisely individuals at risk for adverse events. Although genomic science and technology continue to advance rapidly, innovative companies cannot realize their full potential to co-develop, validate and commercialize drugs and diagnostics to benefit of patients without greater regulatory clarity. In particular, greater clarity is needed with respect to the standards of evidence necessary to validate co-developed and independently developed diagnostics to support a specific reference to or requirement for such testing in therapeutic labeling as well as the process developers should take to develop such evidence.

With respect to labeling of the therapeutic product, while FDA maintains it has discretionary authority over laboratory developed tests ("LDTs")¹ as medical devices² subject to FDA clearance or

¹ A "laboratory developed test" (LDT) is a test developed and performed by a clinical laboratory. The Clinical Laboratory Improvement Amendments (CLIA) of 1988 regulates laboratories and establishes quality standards for all laboratories to certify the accuracy, reliability and timeliness of patient test results. Under CLIA a laboratory is defined as any facility that does laboratory testing on specimens derived from humans to give information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health. Among other requirements, CLIA requires a laboratory to verify and establish analytical performance characteristics of tests offered by that laboratory. The Centers for Medicare & Medicaid Services (CMS) was charged by Congress with the primary responsibility for management of the CLIA program.

approval, FDA has added to the labeling of certain drug products, reference to pharmacogenomic information that is currently only available through LDTs. (These comments do not address any legal debate regarding FDA's authority to regulate LDTs for which PMC takes no position.) We would like to better understand the parameters for including or excluding information about these tests in labeling.

With respect to the process required to obtain FDA approval of therapeutic labeling with reference to validated diagnostics, which also could include imaging and pharmacodynamic and pharmacokinetic tests, development of drugs and companion diagnostics currently requires interaction with FDA through multiple centers and divisions. We strongly support efforts to facilitate optimal and efficient interactions across the Agency. Without a clear regulatory process to navigate the Agency and assurances of reasonable review periods for diagnostics, expansion of personalized medicine will be stymied and therapeutic labeling, based on adequate evidentiary standards in the context of accepted standards of care, will be hampered.

PMC is encouraged by the Agency's renewed focus on and attention to updating and further developing the important issues raised by the Concept Paper. PMC also believes that it is important for the Agency to understand, as it proceeds with crafting guidance for industry, how such personalized medicine industries have developed since the publication of the Concept Paper in 2005. While PMC acknowledges the different perspectives of the industries and entities that comprise its membership, PMC is pleased to submit these consensus-based comments. As more fully explained below, we respectfully request that FDA consider the following overarching recommendations on regulating pharmacogenomics and the section-by-section comments on the Concept Paper as FDA undertakes development of a draft proposed industry guidance on drug-diagnostic co-development and companion diagnostics.

DEVELOPMENTS IN PERSONALIZED MEDICINE:

In April 2005, FDA published the Concept Paper as a means of engaging stakeholders in discussion around the regulatory requirements to support developing a particular diagnostic and particular therapeutic together.³ The Concept Paper acknowledges that pharmacogenomics is "a rapidly evolving science" and points out the effort the Agency has made to better understand the regulatory implications of pharmacogenomics through a variety of interactions with stakeholders, including public meetings and the establishment of an FDA Docket to encourage and enable stakeholder input on the topic.⁴

In April 2007, US Department of Health and Human Services (HHS) Secretary Michael O. Leavitt declared that accelerating the development of personalized health care was one of the Department's top priorities. He established a cross Department personalized health care initiative managed by the highest level of the Department, the Office of the Secretary. The primary objective of this initiative was to accelerate scientific and regulatory advancement of personalized medicine in a more comprehensive and

² A medical device is: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. FDCA § 201(h), 21 U.S.C. § 321(h).

³ FDA *Drug-Diagnostic Co-Development Concept Paper* (hereinafter "*Concept Paper*").

⁴ *Concept Paper* at 2.

cohesive manner.⁵ A pivotal piece of this initiative was the recognition, at the highest level of government, that “[p]ersonalized health care is information-based health care” and “[i]t is not enough merely to develop the knowledge and information that will make personalized health care possible... we must use [this information] correctly.”⁶

Yet, as genomic-based science races forward, enabling more innovative genetic testing and more targeted drug therapies to move beyond the pages of scientific journals to clinical practice (and indeed the increasingly mainstream parlance of patients and providers), the development of regulatory pathways necessary for efficient commercialization and oversight of scientifically robust, genetically targeted therapies has lagged behind. FDA Commissioner Margaret Hamburg has publicly acknowledged that FDA’s current “regulatory schemas” are ill-suited for genetic and genomic testing and the broader field of personalized medicine. She has said that the FDA is “on the cusp of a whole new way of doing business” with respect to when and how it will regulate the building blocks of personalized medicine such as genetic tests and targeted drug therapies.⁷

Diagnostic/drug development models have also been slow to emerge since the publication of the Concept Paper, yet new advances in technology and genomic information are rapidly changing the landscape of investment in personalized medicine, particularly in diagnostics.⁸ This investment has created and will continue to create opportunities for linking innovative diagnostic tests to therapeutics that will enable clinicians to target treatments. Industry and government regulators agree that much remains unknown as they work together to establish reasonable assurances of safety and efficacy. But stakeholders, most importantly patients, cannot afford to wait for absolute certainty.

Regulatory policy must ensure appropriate and timely validation to promote rapid access to new diagnostic information and sustain the continuous innovation necessary to enable timely and accurate information to support clinical diagnosis, prognosis and targeted therapy decisions. Maintaining an appropriate balance between regulation and innovation has long been a challenge. However, unless FDA moves to identify and establish the essential regulatory consistency and clarity necessary to enable commercial equilibrium with respect to co-developed and companion drugs and diagnostics, the future of personalized medicine and its promise to improve health and reduce inefficiency in the health care system through investment in innovative diagnostic and therapeutic products will not thrive.

⁵ Press Release: *HHS Secretary Leavitt Announces Steps Toward A Future of "Personalized Health Care*, <http://www.hhs.gov/news/press/2007pres/20070323a.html>

⁶ *PERSONALIZED HEALTH CARE: OPPORTUNITIES, PATHWAYS, RESOURCES*, <http://www.hhs.gov/myhealthcare/news/presonalized-healthcare-9-2007.html#forward>

⁷ Jessica Bylander, “Personalized Medicine Does Not Fit in FDA’s Current Scheme, Experts Say.” *The Pink Sheet Daily*, Oct. 12, 2009, <http://thepinksheetdaily.elsevierbi.com/>.

⁸ “Diagnostics 2009” published by PricewaterhouseCoopers contends that growing interest in personalized medicine is a key factor driving partnering deals between pharmaceutical companies and diagnostics developers. However, drug/diagnostic collaborations remain challenging and there are still few success stories because drug makers and diagnostic developers have different economic incentives. Consequently, the cost and risk components become critical, and limiting in partnership negotiations. *The Gray Sheet*, September 21, 2009, *Companion Diagnostics Spark Pharma Deals, But Still Mostly For Cancer*.

OVERARCHING COMMENTS ON FDA'S THINKING FOR DRUG-DIAGNOSTIC CODEVELOPMENT:

The scope of the Concept Paper is simply defined: the prospective development of a single *in vitro* diagnostic test in conjunction with a single drug for mandatory use in clinical decision making where both the test and the drug would be used in patient management.⁹ However, PMC believes that this narrowly defined scope is insufficient to provide the appropriate regulatory clarity to advance personalized medicine. Specifically, FDA needs to address:

(1) the variety of models for development and commercialization of diagnostic tests, including independent development and commercialization of diagnostic tests that are used in selection of a drug or biological, where the development of the diagnostic takes place separate from the development and approval of the drug or biological ("companion diagnostics"), as well as co-development models where both the diagnostic and therapeutic are developed at the same time by a single sponsor or sponsors working in collaboration ("co-development");

(2) the regulatory oversight of *in vitro* diagnostic devices (IVDs) and LDTs through a transparent approach to create a forward-looking paradigm for companion diagnostics and co-developed tests; and

(3) the level of evidence necessary to validate any test for purposes of referencing (for non-mandatory use) or requiring (for mandatory use) the test within the therapeutic labeling (including updating information about the required level of evidence as the science evolves over time).

First, the variety of models for development of diagnostics that inform the appropriate use and/or dosing of particular therapeutics is both expanding and shifting through a variety of commercial and scientific models. These models include co-development of a drug and diagnostic test, development of a diagnostic test after the referenced therapeutic or a new indication has been approved (e.g oncology applications), development of a diagnostic test for a use that is not labeled but for which off-label use has become the standard of care for a particular indication, and application of an existing diagnostic test to newly approved or already commercialized therapeutic.

The Concept Paper, as currently drafted, comprehends only a narrow slice of innovative diagnostic development. Overall, the Concept Paper implies that the diagnostic and the drug are manufactured either by the same company or by two companies with common interests. This is often not the case. And, given the different timelines associated with the development of drugs versus diagnostics, many requirements contemplated in the Concept Paper could add significantly to the time required for commercialization of products (both drugs and diagnostics) and hamper the ability of independent diagnostic companies to innovate.

Furthermore, the scope of the Concept Paper may not accommodate ongoing scientific advances as drugs develop. For example, in many cases diagnostic test development cannot begin until a biomarker has been qualified and validated. This can occur at various points along the drug development and regulatory approval continuum, but the Concept Paper does not address this reality and therefore is not representative of most drug development strategies.

Consequently, the Concept Paper should address and distinguish these various scenarios for diagnostic development. Erbitux, for example, was approved on the same day as a diagnostic test. Herceptin is another example of a different dual approval scenario, where a diagnostic (HercepTest) was used on an independent set of samples and found to provide acceptably concordant results with the clinical trial assay that had been used in clinical trials for immunohistochemistry (IHC) detection of Her2 protein over-expression. This was a bridging strategy that is not meaningfully addressed in the Concept

⁹ *Concept Paper* at 1-2.

Paper. Most recently, FDA has changed the label for Vectibix and Erbitux (post-approval) to include information on variations in the KRAS gene that may impact patient response to the treatment.¹⁰

Another important example is one in which a diagnostic is developed that may be useful to inform treatment decisions about specific therapies, but where the particular use may not be included in the FDA-approved package labeling. For example, 5-fluorouracil is approved by the FDA for the treatment of Stage III colon cancer. It is not specifically approved for adjuvant use in patients with Stage II colon cancer.¹¹ However, adjuvant use in patients with Stage II colon cancer is a setting where there is substantial medical need for new diagnostics to help identify those who are more versus less likely to benefit from adjuvant treatment. While diagnostics may be developed to assess treatment benefit for a range of combinations of chemotherapeutic agents across different stages of specific cancers in which the drugs/biologicals are actually used, it is unlikely that all of the clinical combinations used in practice will have been included in the FDA-approved package labeling for the drugs/biologicals. FDA should consider how it will handle regulatory clearance/approval of such broad-based diagnostics as well as labeling changes for the associated therapeutic products.

Second, the Concept Paper uses multiple terms to refer to the diagnostic tests that would be subject to the regulatory pathway described by the Concept Paper (“diagnostic test kit,” “diagnostic test,” “device”). Consistent use of terminology is essential when not all terms are interchangeable or defined clearly in statutes or regulation. The Concept Paper should clarify the regulatory treatment for both IVDs and LDTs with respect to co-developed and companion diagnostics.

Presently, FDA reviews most novel IVDs prior to marketing and has stated that all diagnostic tests (IVDs and LDTs) are medical devices, but that it continues to exercise enforcement discretion with regard to LDTs. Therefore, FDA needs to provide more specific clarity on how these two types of tests differ in regulatory oversight and approval requirements, if at all, with respect to companion diagnostics. Regulations and guidance must address any differences in regulatory requirements with LDTs, including the application of CLIA and the treatment of laboratory services. For example, labeling is provided with IVDs to explain to the laboratory how to run the test as well as to identify intended use claims that have been established by the kit manufacturer and cleared or approved by the FDA. With LDTs, the laboratory does not need labeling to tell it how to run the test. Further, under CLIA, the laboratory must interact directly with the treating physician and provide the physician certain information about the test whether it is labeled or not. This is consistent with the practice of medicine, in that FDA-regulated products may

¹⁰ Class Labeling Changes to anti-EGFR monoclonal antibodies, cetuximab (Erbitux) and panitumumab (Vectibix): KRAS Mutations. On July 17, 2009, changes were made to the product labels of cetuximab (Erbitux, ImClone Systems, Branchburg, NJ) and panitumumab (Vectibix, Amgen, Thousand Oaks, CA). Retrospective subset analyses of trials in patients with colorectal cancers having KRAS mutations noted a lack of benefit associated with these monoclonal antibodies...Labeling changes have been implemented in the INDICATIONS AND USAGE, CLINICAL PHARMACOLOGY, and CLINICAL STUDIES sections of both cetuximab and panitumumab product labels. www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm

¹¹ “FDA approval of drugs to treat colon cancer (CC) dates back to the 1962 approval of fluorouracil (5FU) for the palliative treatment of CC (an approval which also included the palliative treatment of rectal, breast, gastric, and pancreatic cancers). In the initial era of cancer drug approval, the few existing cancer drugs were approved based on modest antitumor activity. Because the patent on 5FU expired many years ago and because generic versions of 5FU are available, drug companies have not submitted data to update the 5FU drug label for additional CC indications, such as adjuvant treatment of CC. 5FU use is, however, described in the labels of other drugs for adjuvant, first-line and subsequent therapies for colorectal cancer, in combination with leucovorin, levamisole, camptosar or oxaliplatin.” *FDA Background for Colon Cancer Endpoints Workshop*, November 2003. www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm120847.pdf

be lawfully used in a manner other than the FDA approved use in the treatment of patients by a physician. FDA should also clarify for enforcement purposes which elements of an LDT, if any, it considers to be outside of the elements/processes considered to be the practice of laboratory medicine regulated under state licensure, as well as CLIA laboratory quality standards. FDA should first define and undertake a more transparent approach to addressing these issues through rulemaking that would create a more forward-thinking paradigm. Such a pathway should be risk-based.

Third, the Agency must more clearly address the level of evidence necessary to validate diagnostic tests for purposes of referencing or requiring such tests within the therapeutic labeling. To the extent that different levels of evidence may be necessary for referencing a test for non-mandatory use or potentially for mandatory use, those differences should be clarified. A revised Concept Paper or proposed draft guidance should address the different scenarios for the timing of the diagnostic relative to the therapeutic and consider the associated labeling scenarios and how labeling impacts clinical use. The Agency needs to provide more specific guidance on review and approval of labeling changes to an approved therapeutic based on a new or modified diagnostic; approval of labeling/marketing practices for a existing diagnostic based on a new indication for the therapeutic; and how those scenarios fit into the co-development paradigm.

Personalized medicine is intended to address unfulfilled needs for patient-specific medical information. A new paradigm for oversight should be developed, working together with a broad range of stakeholders, that includes specific regulatory proposals that promote transparency and truthfulness of claims made and assure the accuracy, reliability and timeliness of testing, while maintaining incentives for continuous innovation in this emerging field of medicine. Therapeutic labeling has included in the indications section both a requirement to use genetic testing¹² as well as less specific references to genetic based LDTs, which were indicated because, for example, “retrospective subset analyses of trials in patients with colorectal cancers having *KRAS* mutations noted a lack of benefit associated with these monoclonal antibodies.”¹³

FDA should clarify its process for adding companion diagnostics to drug labeling, in particular LDTs such as warfarin pharmacogenetic testing (2C9 and VKor), HLA-B*5701 for abacavir hypersensitivity, HLA-B*1502 for carbamazepine toxicity, and HIV tropism testing for Selzentry. Moreover, FDA should propose clear and consistent terminology for the label (test name) and further explain what information about a diagnostic assay must be provided in the product label when several marketed diagnostic assays are available in addition to the one used in the clinical trial (such as with Vectabix and Erbitux) and explain the Agency’s objectives and expectations with respect to how clinicians should interpret any differences (or no differences) in the labeling of a drug product under these scenarios.

¹² Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy. These include HercepTest™ and Pathway® HER-2/neu (IHC assays) and PathVysion® and HER2 FISH pharmDx™ (FISH assays)...Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown.

¹³ See Footnote 8.

SPECIFIC COMMENTS ON THE CONCEPT PAPER:

1. Introduction, Background and Scope:

Specific Recommendations:

- Expand the scope of the Concept Paper. As currently drafted it is too limited and not likely to accommodate most practical diagnostic development strategies.
- Identify, describe and/or distinguish specifically the diagnostic assays that have been developed as companions to drugs already approved for clinical use as well as those that have been developed for use with a particular drug before FDA has approved the drug as safe and effective for clinical use. In addition, FDA should describe how the Agency will treat these varying scenarios as compared to the “ideal” co-development pathway envisioned by the Concept Paper, in particular with respect to acceptable methods of validation.
- Identify the requirements for assay validation throughout the lifecycle of drug development, specifically the more common scenarios of biomarker discovery late in the drug approval process or after the drug has been approved for commercialization, including markers developed for uses or combinations of therapies that are common in clinical practice but not included in FDA-approved labeling for the therapeutic product. Provide more examples of recent parallel development of drug and diagnostic as companion products. For example, FDA has recently mentioned the following drugs where a prospective analysis of a diagnostic was included pre-approval, such as imatinib and KIT + GIST and Selzentry and CCR5 + tropic HIV-1.
- Clarify the regulatory process for other diagnostic development scenarios, such as proposals to rely on clinical studies of the diagnostic involving use of archival samples that are conducted prior to the approval of the therapeutic. These include erlotinib and EGFR for lung cancer as well as nilotinib and UGT hyperbilirubin.
- Address implications for a single diagnostic test used for multiple drugs (e.g. CYP2D6 alleles), or multiple tests used for one drug (e.g. HER2 FISH and IHC for Herceptin).
- Modify Figure 1, which reflects the ideal pathway, to include a set of examples of what may happen at different stages of the development process (e.g. if the biomarker is not discovered until later in the development process, then the qualification and validation of the biomarker will not happen until a time later than indicated in Figure 1). The Figure should illustrate a “sliding scale” of assay development into the phase II of clinical development and beyond. Alternatively, different versions of Figure 1 could be constructed that reflect a companion diagnostic joining the drug development process at different stages.
- Clarify the definition and use of “marker assay validation.” Does the FDA mean the drug target or a new biomarker? What is meant by validation in this instance and how will such marker validation relate to the end product (i.e. assay for drug?), especially when at certain stages in the development process the “marker” may not be qualified?

2. Review Procedures Issues:

Specific Recommendations:

- Describe more specifically the process for working across FDA centers, divisions and offices by clarifying which FDA Center/Division/Office will lead joint meetings for co-developed diagnostics, how meetings will proceed and be managed throughout the co-development process, and the level of involvement of the Office of Combination Products (OCP).¹⁴
- Update Figure 2 to describe flexibility in the approval process, for instance where:
 - a biomarker not developed at the time of product approval, for which studies involving use of archival samples may be the only feasible approach to develop the marker within a reasonable time frame and development cost, or
 - the test already exists and no new test is required at this time, or
 - the test is available but for a different indication.
- Describe the proposed process to reflect commencement of biomarker development at the phase II or phase III trial stage.
- Describe more clearly, both in text and graphically in the figures, how FDA will accommodate necessary flexibility in the diagnostic review process with respect to new clinical and research findings discovered prior to filing a New Drug Application (NDA) or Biologic License Agreement (BLA) for the associated therapy, as well as discovery subsequent to the approval of an NDA or BLA.
- Provide guidelines for minimum data required for target and/or marker validation for any given test or specifically reference existing documents that might provide this information (e.g. guidance documents¹⁵ or Clinical Laboratory Standards Institute (CLSI) requirements for test validation).¹⁶
- Provide more specific guidance on: (a) requirements for (1) approval of labeling changes to an approved therapeutic based on a new or modified diagnostic and (2) approval of labeling for a cleared or approved diagnostic based on a new indication for the therapeutic; and (b) how those scenarios fit into the co-development paradigm.
- Define more clearly the circumstances/parameters under which drug manufacturers and/or diagnostics manufacturers should follow the proposed co-development process as opposed to the traditional two-track process.

¹⁴ Intercenter Agreement between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health outlines the working relationships that exist between CBER and CDRH for certain categories of medical devices or specified medical devices.
www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm

¹⁵ See e.g. FDA Guidance “Pharmacogenetic Tests and Genetic Tests for Heritable Markers” June 19, 2007.

¹⁶ See e.g. CLSI “Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition” (C28-A3) *November 2008* Provides guidance for determining reference values and reference intervals for quantitative clinical laboratory tests.

- Identify requirements for inclusion of a diagnostic test in the label of a particular drug product/therapy and the process for doing so for both the therapeutic manufacturer and the diagnostic developer.¹⁷
- Clarify the investigational device exemption (“IDE”) process and requirements with respect to co-developed and companion diagnostics. Currently LDTs are subject to different requirements under CLIA.¹⁸
- Specifically address the challenges related to diagnostic approval timelines vs. drug approval timelines. Drug approval times can be very lengthy and during that time a diagnostic may change substantially (e.g., there may be technological improvements in the assay platform or there may be updates to algorithms used to assess outcomes) as new data are incorporated into the test process. FDA should address how it proposes to deal with this challenge if the diagnostic developer is not the drug developer, which more closely reflects the present state of the industry.

3. Analytical Test Validation:

Specific Recommendations:

- Provide more information related to the assessments (e.g. marker validation) that should be completed before committing to the analytical validation. Analytical requirements should begin by listing the sample acquisition requirements, including numbers of samples. If the required numbers of samples depends on the level of concordance between clinical trial test and commercial test, provide an algorithm to calculate the required sample numbers.
- Provide specific guidance on FDA requirements (study design, statistical analysis plan, and numbers of samples). As recognized in recent FDA discussions on this topic, such as those related to KRAS mutation and impact of clinical studies using archival samples from a prospective study,¹⁹ it is not realistic to assume that 100% of samples from a given clinical trial can be retested with the final commercial assay.
- Develop proposed guidelines specific to the co-development process or reference existing FDA guidelines or other guidance documents (e.g. CLSI)²⁰ that define the appropriate requirements for sample collection and handling. Sample collection and handling is one of the most critical requirements for assay validation and is of particular importance for assays that are measured in blood or other tissue products (e.g. serum, plasma, peripheral blood mononuclear cells (PBMCs, etc.) which require standardized methods of collection. Additionally, these guidelines should comprehend that informed consent requirements may make it prohibitive to reach >95% collection rates, such as in the case of cancer patients.

¹⁷ See e.g. . “FDA Final Rule - Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices.”

¹⁸ See Footnote 8.

¹⁹ See Footnote 8.

²⁰ See e.g. CLSI Document MM13-A – *Collection, Transport, Preparation and Storage of Specimens for Molecular Methods* ISBN 1-56238-591-7.

- Reference standards adopted by CLSI, and/or other recognized governing bodies, when appropriate, as guidelines for analyte concentration specifications and standards for conducting and validating clinical assays.²¹ In many instances such guidelines may provide sufficient requirements for assay performance as well (e.g. when a test already exists for the biomarker).
- Address more fully issues related to progressive/ongoing technology and platform development related to software and instrumentation that could impact the development process. Describe how the typical lifecycle of the assay/platform will impact companion diagnostics analytical validation.

4. **Preclinical Pilot Feasibility Studies:**

Specific Recommendations:

- Identify more specifically parameters for acceptable cut-offs and ranges for the specific assays and provide clear examples, such as categories that depend on the sample type and the assay type.
- Substantially expand the guidance on prespecifications of assay cutoffs or draft separate detailed guidance for industry on methods to define cutoffs and establish estimates of performance. The Concept Paper notes, “Estimates of performance can be severely biased when test cut-offs are chosen post-hoc to optimize test performance.” However, the Concept Paper fails to further explain that assay cut-offs used in the clinical utility phase may not be defined until after the clinical validation testing is completed. Therefore, the clinical validation study must be sufficiently powered to account for this possibility and contemplate further refinement of the cut-off continuing into the prospective study that defines clinical utility for the biomarker and assay. In addition, with respect to multidimensional examination of setting the cutoff, FDA guidance should comprehend various analytical approaches to obtaining a result, such as a combination of percent cells stained with intensity using an algorithm or score (e.g., Allred score for ER and PR staining), whether or not internal tissue control elements are present and stained appropriately. The guidance should also allow for application of a continuous variable or defining a cut-off using a pre-specified algorithm if image analysis is used.
- Identify examples where Receiver-Operating Characteristic (ROC) curve is useful in defining the cut-off for semi-quantitative and quantitative assays, including clinical validation of semi-quantitative or quantitative immunoassays and quantitative polymerase chain reaction (qPCR) assays.
- Address more specifically the importance of [and acceptable methods for] ensuring the assay used to re-evaluate patients who fall into an “indeterminate” category for clinical utility is well validated and sufficiently different to provide the necessary clinical result for the patient.

²¹ NCCLS (now CLSI) EP17-A: **Protocols for Determination of Limits of Detection and Limits of Quantitation, Approved Guideline** ISBN-56238-551-8; See also **Biomarkers for pharmacogenetic and pharmacogenomic studies: Locking down analytical performance** Elizabeth Mansfield, Zivana Tezak, Sousan Altaie , Kathleen Simon and Steven Gutman (December 2007).

5. General Approaches to Define Clinical Test Validations:

Specific Recommendations:

- Specifically address the appropriateness and potential application of adaptive trial design within the guidance on clinical test validation and clinical utility of the companion diagnostics, such as expanded cohort in a First Time in Human (FTIH) study of patients selected for marker vs. patients who are not selected.

6. Clinical Utility²²:

Specific Recommendations:

- Address more specifically the types of study design and extent of clinical trial data required to validate a companion diagnostic. Clarify that randomized controlled trials, although the “Gold Standard,” may not be necessary or appropriate in many cases. This section in particular implies that the diagnostic and the drug are either manufactured by the same company, or by two companies with common interests. This is often not the case, and given the different timelines associated with the development of drugs vs. diagnostics, requiring that clinical utility be demonstrated for both drug and diagnostic products could add significantly to the time required for their release. Requiring developers of companion diagnostics to provide right of reference to existing data may mitigate this risk, if the trial design allows the utility of both products to be adequately demonstrated.
- Provide more guidance on evidence requirements, especially spiked or manipulated specimens that occur infrequently.
- Discuss the limitation in selecting study populations, insofar as for some serious or life-threatening conditions (e.g. cancer), risk-benefit considerations may limit the populations eligible for a study of the therapeutic agent and therefore limit determination of rates of false positive and false negative test results. For example, it may not be ethical to randomize patients to a treatment arm if prior evidence with the diagnostic suggests that the patient is unlikely to respond or would likely experience a toxic effect from the treatment. Under the study design illustrated in Figure 4, special monitoring may be required for patients in the Test Negative subgroup if prior evidence suggests that the new drug is likely to be ineffective in this subgroup. Appropriate use of interim analyses, with pre-specified stopping rules for lack of efficacy in this subgroup, may minimize the risk of unnecessarily exposing patients to ineffective therapy. Under such circumstances, the trial could continue enrolling Test Positive patients. Analysis of such trial design results could be subject to limitations similar to those described for the trial design shown in Figure 5 in Section 6.5.

²² “Clinical utility” is a concept that needs further clarification. It is not explicitly mentioned in the FDCA nor FDA regulations. FDA should work with stakeholders to define “clinical utility” in a clear and consistent manner. We suggest incorporation of a glossary term for the SACGHS approved definition (from ***U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services***): “Clinical utility refers to the usefulness of the test and the value of information to the person being tested. If a test has utility, it means that the results-positive or negative- provide information that is of value to the person being tested because he or she can use that information to seek an effective treatment or preventative strategy. Even if no interventions are available to treat or prevent disease, there may be benefits associated with knowledge of a result.”

- Discuss specifically the implications of the FDA Oncologic Drugs Advisory Committee (ODAC) recommendations from the December 16, 2008 meeting for use of archival samples from a prospective trial to validate a test with regard to global informed consent without obtaining new consent for the validation study of the diagnostic test.
- Provide additional guidance on bridging studies for tests where the final version may not be available for phase III drug trials.
- Elaborate further on drug efficacy and safety study designs and identify potential situations in which excluding patients who do not express the respective biomarker is necessary. FDA has identified this study design as a viable option, but in other FDA communications to industry inclusion of a “negative” subgroup is still strongly recommended.
- Address more specifically, with respect to clinical utility, the dichotomy between diagnostics intended to correspond with a single drug, and diagnostics that do not correspond to a specific drug or pharmacological class of drugs.

In conclusion, the foundation of personalized medicine, as discussed in these comments, is advanced diagnostic testing intended to improve a physician’s ability to assess whether an individual patient is or is not likely to benefit from treatments for his or her disease or condition, then targeting therapies to individual patients to maximize their effective, safe, and efficient use. Innovative diagnostic testing is becoming the standard of care for many diseases, so it is essential to ensure accurate, reliable, and timely diagnostics are available to reduce harm to patients and better utilize scarce resources.

For these reasons, it is critical that regulatory oversight of advanced diagnostic and related therapeutics innovations (and innovators) strike the right balance between assuring patient safety and embracing policies that encourage the incorporation of rapidly advancing scientific methods and knowledge.

These objectives are unachievable without a clear, transparent regulatory framework that includes clear statements of all relevant oversight policies and which has been publicly vetted prior to implementation. PMC looks forward to continuing our dialogue with the Agency on drug-diagnostic co-development issues, including the comments and recommendations outlined in this submission on the Concept Paper, and other matters related to personalized medicine.

If you have any questions about our comments and recommendations, please contact Amy M. Miller, Ph.D., at 202-589-1770. Thank you for your consideration of these comments and the attached suggestions on proposed topics for FDA public workshop and/or white paper series.

Sincerely,

Amy M. Miller, Ph.D.
Public Policy Director
Personalized Medicine Coalition

ADDENDUM

Personalized Medicine Coalition (PMC) Drug-Diagnostic Co-Development FDA Workshop / White Paper Series Suggestions

At FDA's request, PMC is providing the following suggested topics for FDA public workshops and/or white papers to better inform FDA and relevant stakeholders of issues related to updating the FDA April 2005 Drug-Diagnostic Co-Development Concept Paper:

1. **Analysis of Regulatory Precedent for Companion Diagnostics.** A comprehensive description of the current regulatory processes for approval and label updates for companion diagnostics that would specifically address:
 - a. the basis for the approval or update
 - b. the regulatory path to the approval or update
 - c. suggestions for improving the regulatory pathway to approval and/or label update
 - d. discussion of differences, if any, in the FDA processes and decision making had the approvals/label updates been subject to the guidelines suggested in the Concept Paper and/or in light of the current environment.
2. **Review and Analysis of Evidence Requirements.** Address questions such as:
 - a. What type of evidence is/should be required?
 - b. What is the proper use of archival sample studies?
 - c. What kinds of populations must be evaluated?

For example, enriched samples make scientific sense but sometimes FDA officials require "negative" subgroups in trials, or a subgroup that does not have the biomarker under investigation. In such cases outcomes data using prospectively planned analysis of archived samples from completed prospective trials may be more appropriate.

3. **Issues Beyond the Stated Scope of the Concept Paper.** For example,
 - a. pharmacogenomic testing for the purposes of dosing determinations and drug monitoring
 - b. the use of one test with multiple drugs or several tests for serial or parallel use with a single drug
 - c. tests that are not intended for further development or those that do not affect the results of clinical trial.
4. **Pre-clinical Pilot Feasibility Studies.** Specifically, a comprehensive discussion of setting cutoffs including, open ROC curves and bootstrapping.
5. **Adaptive Trial Design.** Explore best practices in clinical trials designed to be adaptive to the data as it is processed, thus allowing for flexibility to utilize continuously emerging knowledge generated as the trial progresses.
6. **FDA Intra-Agency Coordination and Leadership.** Discuss the importance of, and identify specific proposals for, more effective and efficient interaction among CDRH, CDER, CBER, and OCP and clarify the role of the Critical Path Initiative.