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Division of Dockets Management (HFA– 305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2011-D-0215
Draft Guidance for Industry and FDA Staff on In Vitro Companion Diagnostic Devices

On behalf of The Coalition for 21st Century Medicine (the "Coalition"), we are pleased to submit comments to the Docket in response to the Food and Drug Administration's (the "FDA") request for comments regarding issues related to the draft guidance entitled, "Draft Guidance for Industry and FDA Staff on In Vitro Companion Diagnostic Devices" ("Draft Guidance").

The Coalition comprises some of the world's most innovative diagnostic technology companies, clinical laboratories, venture capital companies, and patient groups working to support appropriate regulatory oversight and fair reimbursement policies to promote innovation in the development and use of advanced personalized diagnostic testing. Coalition members develop and perform clinical diagnostic testing, so-called laboratory developed tests ("LDTs"), invest in such companies, and also represent patient groups whose members obtain such tests. Some of these LDTs may be offered, now or in the future, as a companion test service to guide treatment selection and dosing. In addition, Coalition members may now or in the future partner with therapeutics developers to develop and perform new companion or co-developed clinical diagnostic testing services. As such, the Coalition members would be directly affected by the implementation of this Draft Guidance.

While the Coalition applauds FDA's efforts to establish a more transparent and efficient process for review and clearance of concurrently developed companion diagnostics and

therapeutic products, we respectfully submit for FDA's consideration a number of important concerns that the Coalition believes could hinder continued accelerated innovation in pharmacogenomics.

Principally, the Coalition is concerned about (1) the limitations of the proposed labeling provisions with respect to sufficiently identifying the approved companion diagnostic test for both providers and payers, (2) the treatment of clinical diagnostic tests services that may be developed before or after a therapeutic product receives marketing approval, (3) the lack of proposed pathway for companion testing services that are necessary for the safe and effective off-label uses of approved therapeutic products, where such off-label use has become the recognized standard of clinical care among physicians and there is little or no incentive for therapeutics manufacturers to invest in new trials for such uses, and (4) the overall fragmented and "non-binding 'guidance'" approach to policymaking in areas related to FDA oversight of clinical laboratory test services.

1. **Companion Diagnostics should be identified in the labeling of the novel therapeutic by its proprietary name or at least sufficiently to clearly identify the particular test service intended. Additionally, the Agency should clarify how it intends to identify the "test" and what will constitute the diagnostic test "label" if the companion diagnostic is a clinical laboratory test service.**

The Draft Guidance calls for the identification of the "type" of diagnostic test in the therapeutic label by non-proprietary description of the intended use rather than the proprietary test name. The two recent companion diagnostic/therapeutic approvals are instructive in how FDA intends to identify the diagnostic product in the therapeutic labeling—i.e., (1) by specifying in the Indications for Use section of the labeling for the therapeutic that its indicated use is tied to findings from an FDA approved or cleared diagnostic test (without specifying any specific brand) and (2) by describing the specific test(s) used in the clinical studies supporting product approval. The Coalition questions whether this labeling policy will achieve the FDA's desired effect of facilitating the development of more than one FDA approved or cleared companion diagnostic, as stated in the Draft Guidance. This labeling policy does not indicate what is meant by "an FDA approved test." Would any other test cleared or approved by FDA for the same marker count or is the intent for this to be limited to another test approved by FDA specifically for use with the same therapeutic? Moreover, it is unclear if an FDA cleared or approved test that may be modified by a clinical laboratory, as is well established under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"), would continue to be considered "an FDA approved diagnostic test" consistent with the therapeutic labeling identifying such test. For example, if the approved companion test was distributed by the IVD manufacturer to a clinical laboratory and that test were modified by the clinical laboratory performing the test, how would such modifications affect the ability of the laboratory to offer the test as the "approved" companion diagnostic identified in the therapeutic label? This is currently permissible under CLIA and FDA's enforcement discretion policy for LDTs. These are important issues for FDA to consider under its nonproprietary labeling policy.

In addition, this labeling policy does not provide guidance on the appropriate use of the therapeutic with laboratory-developed tests that may be in widespread use at the time the therapeutic is approved. Given the widespread confidence in LDTs by providers and broad coverage by payers, the non-proprietary labeling policy would create a lack of clarity for both providers, who are free to order any diagnostic test they choose as part of the practice of medicine, as well as payers. This effect of this policy more likely would be a corresponding lack of incentive for clinical laboratories or IVD manufacturers to seek FDA approval for a companion diagnostic indication.

In an established marketplace where oversight for LDTs has long been provided by CMS at the federal level as well as by state regulatory bodies, and FDA clearance or approval has never been required, there is little evidence that FDA approval conveys a marketing advantage to laboratory services, regardless of how much a laboratory or manufacturer may advertise that it is "FDA approved." Distributed test kits are assumed to be FDA approved if lawfully marketed and in the absence of a new policy to require such FDA premarket review of laboratory services by FDA, there is no expectation that lack of FDA approval represents anything other that the norm to ordering physicians and pathologists in the practice of clinical and laboratory medicine. Additionally, since it remains unclear whether the FDA "seal of approval" will be a significant determining factor for third party payer coverage and payment determinations, there seems to be a greater benefit to public health and to incentivizing the voluntary submission of additional tests to FDA by a policy of identifying the proprietary name of the diagnostic in the therapeutic labeling.

2. The Draft Guidance does not sufficiently clarify how FDA intends to treat currently marketed clinical laboratory services that may be later discovered by a drug manufacturer to have a companion diagnostic indication, as defined by the Draft Guidance, during the clinical trials for a novel therapeutic. Additionally, there is insufficient clarity in the Draft Guidance with respect to how FDA views qualified biomarker identification in a novel drug trial as compared to a companion diagnostic that must be cleared by FDA for use with the novel drug, when the laboratory test service used in the drug trial would be the same proprietary test offered as the companion diagnostic with the drug.

In the absence of a comprehensive policy with respect to how FDA will treat laboratory developed test services, there is neither an incentive nor a reasonably transparent and predictable regulatory pathway for a laboratory with either a new or a currently marketed LDT to seek FDA clearance or approval for a companion indication as defined in the Draft Guidance. At the same time, once a therapeutic company (who holds the clinical data necessary to support a premarket application) achieves marketing approval for its novel drug, there appears to be little incentive to partner with additional diagnostics developers to invest in the FDA clearance or approval of additional diagnostic tests under the Draft Guidance.

Insofar as a pre-market approval application would be required for a subsequent diagnostic to obtain comparable labeling with respect to the therapeutic, it would be prohibitively

expensive and time consuming for the developer of a follow on diagnostic to conduct such studies once the therapeutic has been approved, if the same types of studies are required and the test is not reclassified. Unlike the circumstances when the innovator diagnostic is developed, it would be unlikely that the therapeutic sponsor—or anyone else—would be conducting a controlled trial of the therapeutic in which the follow on diagnostic could be studies. If a follow on diagnostic may be cleared under a 510(k) determination of substantial equivalence to the innovator diagnostic that obtained approval with the therapeutic, presuming such tests would be reclassified, this would render meaningless the marketing benefit the innovator deserves for the investment it made in the pre-market approval it obtained through co-development with the therapeutic. This would create a substantial disincentive to diagnostic manufacturers to participate in co-development projects. It would be more efficient for them to wait until someone else obtains initial approval coincident with the therapeutic, and then the diagnostic manufacturer can bring its test to market with much lower investment and shorter time to market.

Merely stating that the therapeutic is approved for use only with an "FDA cleared or approved" diagnostic test fails to recognize the reality of the practice of clinical and laboratory medicine in the marketplace and will disincentivize investment in more innovative companion diagnostics.

3. The lack of proposed pathway for the broad spectrum of "companion diagnostics," including those that are developed using prospective analysis of archived samples to provide essential information for the safe and effective use of a long- approved drug product, particularly where that use may be off-label but also the long established standard of clinical care, will continue to limit the advancement of pharmacogenomics.

The Draft Guidance is limited in its focus to companion diagnostics that are "co-developed" with a novel drug product, and leaves many open questions regarding policies for companion diagnostic products that are not developed simultaneously with a new drug product (more commonly known as "companion diagnostics"). For example, it does not identify a reasonable regulatory pathway for companion diagnostics that provide information essential for the safe and effective use of long-marketed drug, in particular where such use is for an indication that is not on the approved drug label, but for which such "off-label" use has become the recognized standard of clinical care among physicians, particularly in oncology. While off-label use of FDA approved products constitute the practice of medicine, the lack of clear policies with respect to the broad spectrum of "companion diagnostics" fails to recognizes the opportunity for better health outcomes from incredible advances in diagnostic testing. The Coalition urges FDA to develop appropriate, predictable and transparent policies that address the broad spectrum of "companion diagnostics," not just those that are developed concurrent with a new drug product. We note that this issue was raised to the Agency at least 3 years ago yet it does not appear that any new thinking or proposals are forthcoming from the Agency to address this issue.

4. Impact of the fragmented approach to policymaking related to oversight of clinical diagnostic tests through multiple non-binding guidance documents.

Finally, the fragmented approach to policymaking related to oversight of clinical diagnostic tests through multiple non-binding guidance documents, like that described in this Draft Guidance, creates questions and further uncertainty that will result in increasing reluctance to invest in advanced innovative diagnostics. This is especially true when FDA has already announced its intention to create a separate regulatory process to address FDA premarket oversight of LDTs more generally and has published two other regulatory processes to address FDA requirements for reagents used in LDTs (the ASR final guidance and the draft RUO guidance.

Molecular diagnostics are the foundation of the rapidly emerging field of personalized medicine and advanced diagnostics are critical to ensuring appropriate utilization of therapeutics as well as to identifying early, molecular signals of disease to allow preventive interventions. As such, it is critical that FDA consider a carefully balanced and appropriately tailored risk-based approach to establishing and enforcing a policy that would, for the first time, require pre-market review and clearance of certain laboratory developed tests under the medical device regulatory framework.[1]

As we have previously stated, the Coalition supports an FDA-centered regulatory framework for advanced diagnostics that is risk-based, transparent, and promotes public health by facilitating timely introduction of accurate and reliable advanced diagnostic tests and by providing clinically useful information to patients and healthcare providers. It is critically important that if the FDA is going to narrow the longstanding policy of enforcement discretion with respect to any indications for use for LDTs, the Agency should move forward with a regulatory oversight framework that is clear, predictable, and coordinated.

While the FDA has stated in this Draft Guidance that "clinical laboratory tests intended to provide information that is useful to the physician regarding use of the therapeutic product, but that are not a determining factor in the safe and effective use of the therapeutic product" are excluded from the definition of "companion diagnostic device," the Draft Guidance apparently would include in such definition clinical laboratory services that are such a determining factor.

Absent a change in the FDA's longstanding enforcement discretion policy with respect to all laboratory developed tests, the Draft Guidance appears to include certain LDTs without

[1] The Coalition acknowledges that some groups have questioned whether FDA has the authority under the Federal Food, Drug and Cosmetic Act (21 U.S.C . § 301 et s~.) to regulate laboratory-developed tests, including those that it sought to define for discussion in draft agency guidance as *In Vitro Multivariate Index Assays* ("IVDMIAs"), as medical devices. The Coalition does not address this question. These comments include references to the Coalition's recommendations as to how FDA should proceed if it makes a final policy determination to regulate these laboratory services and their components as medical devices. The Coalition's comments supportive of certain approaches to regulation should not be considered an acknowledgement by the Coalition or any of its members that FDA has the authority to regulate laboratory services as medical devices. In addition, these comments do not represent an admission by the Coalition or any of its members that any particular laboratory service is a "device" as that term is defined under Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C . § 321(h)).

addressing critical questions raised by the Coalition and other stakeholders, including patients for whom these tests are ordered by their treating physicians, with respect to appropriate and least burdensome oversight of laboratory services. Ultimately, the most critical aspect of the need for oversight of any test is impact on patient treatment and care decisions, but avoiding a piecemeal approach to policymaking for LDTs also supports the FDA's recently stated regulatory science objectives to support innovation and minimize regulatory burden on industry[2], which promotes patient access to potentially life saving diagnostics test information.

Given the uncertainly this Draft Guidance creates with respect to clinical laboratory services that could be considered, pursuant to the definitions established in this Draft Guidance, "companion diagnostics", we encourage FDA to abandon this piecemeal approach to diagnostics oversight policy generally. We urge FDA instead to propose new, better-suited regulations for notice and comment that would establish appropriate regulatory policies related to the broad spectrum of companion diagnostics, whether offered as a laboratory service or a distributed diagnostic test kit, in concert with more comprehensive policies and regulations that can reasonably accommodate the unique aspects of laboratory services while at the same time minimize overly burdensome and potentially duplicative regulation on such laboratories services. FDA regulation through Draft Guidance will continue to inhibit the establishment of a more practical, rational and least burdensome approach to ensuring the accuracy and reliability of all forms of in vitro diagnostics.

CONCLUSION:

The Coalition supports FDA's goal of working to assure that patients have access to timely, accurate and reliable testing that can improve patient outcomes and reduce healthcare resource utilization, while at the same time supporting innovation and investment in increasingly targeted diagnostics and related therapeutic products. We look forward to working with FDA to establish a flexible and balanced approach to addressing advanced diagnostics products that recognizes the appropriate role of CLIA and provides regulatory clarity to both clinical laboratories, distributed diagnostic kit manufacturers, treating physicians and patients. At the same time, we express concerns about the Agency continued piecemeal approach to regulation through draft guidance documents, which have a chilling effect on the investment necessary to advance greater identification and effective utilization of more targeted therapies.

We appreciate your consideration of our comments and we look forward to continuing our mutually constructive dialogue with the Agency on these issues specifically, and more generally on issues related to the oversight of laboratory developed tests. If you have any questions about our comments, please contact on behalf of the Coalition for 21st Century

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[2] *I am determined to make sure FDA's role contributes to the development of new therapies and does not serve as a barrier*.--Peggy Hamburg, FDA Commissioner (BioCentury, September 2011*)*

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