The Coalition for 21st centurymedicine

**January 5, 2015**

**VIA Electronic Mail to: cures@mail.house.gov**

Honorable Fred Upton, Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

**RE: 21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

Dear Chairman Upton:

On behalf of the Coalition for 21st Century Medicine (the "Coalition"), I am pleased to respond to your request for responses to the questions you posed to stakeholders regarding the regulation of innovative diagnostic tests.

The Coalition for 21st Century Medicine 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. Given the Coalition's mission, we have a keen interest in the extent to which the U.S. Food and Drug Administration ("FDA") intends to regulate LDTs as medical devices[1] as well as in the regulation of *in vitro* diagnostics more broadly.

Below, please find our response to the questions you raised in the above-captioned announcement. (For ease of reference, the Committee's language is provided in bold text.)

[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 seq.) to regulate LDTs as medical devices, including those that it sought to define for discussion in draft FDA guidance as *In Vitro Multivariate Index Assays* ("IVDMIAs"). The Coalition does not address this question in this response. Consistent with the approach that the Coalition has taken throughout the FDA's consideration of this issue, 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)).

1. **Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?**

We agree there should be clear lines separating the development and manufacturing of a diagnostic test, the actual conduct of a diagnostic test, and the practice of medicine.

- The "development" of a diagnostic test refers to the steps taken by a manufacturer (in the case of an IVD test kit) or laboratory (in the case of an LDT) with respect to the conception and design of the test.
- The "manufacturing" of a diagnostic test refers to the process through which the physical materials required to perform a diagnostic test (e.g., reagents, supplies, equipment) are produced.
- The "actual conduct of a diagnostic test" refers to the procedures that a laboratory follows to collect, prepare and examine specimens taken from the human body, and analyze and report the result(s) of such tests.
- The "practice of medicine" refers to a medical professional's interpretation and use of the information provided by a diagnostic test in the diagnosis of disease or other conditions, determination of prognosis, prediction of treatment outcome, and/or treatment selection. The practice of medicine may also include the actual conduct of a diagnostic test by a certified and licensed clinical laboratory as directed by a medical professional.

2. **In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device", but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation by the FDA?**

With respect to both distributed test kits and LDTs, the "device" should be the collection of physical materials required to run the test (e.g., reagents, supplies, equipment—but not the patient sample itself) together with the directions for use. The "development" and "manufacturing" of these materials may be appropriate for regulation by the FDA.

The "actual conduct of a diagnostic test" and "practice of medicine" are already subject to regulation under CLIA, state laboratory licensure, and healing arts laws and should not fall under regulation by the FDA.

3. **FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?**

In assessing the risk associated with an *in vitro* diagnostic product, the FDA should consider the seriousness of the disease to which a result relates and the materiality of the result to a medical professional's diagnostic, prognostic or therapeutic decision. Diagnostics intended for use in patients with serious conditions and/or that direct a physician to make a particular diagnosis or offer a particular treatment should be considered higher risk than diagnostics intended for use in patients with less serious conditions and/or that provide information that is not by itself determinative with respect to patient management. Of particular importance are the risks associated with any management change indicated by the diagnostic test results and the impact when the results are inaccurate—i.e., the impact of a false negative or a false positive result on patient outcomes.

The risks posed by an *in vitro* diagnostic test differ from those posed by a therapeutic device. While a therapeutic medical device has a direct impact on the structure or function of the body, an *in vitro* diagnostic test's impact is indirect – i.e., it only affects the structure or function of the body insofar as a medical professional uses the result of the test in patient management (unless the test requires an invasive procedure to obtain the specimen that would not otherwise be performed).

The risks associated with LDTs are similar to the risks associated with distributed tests.

Although the traditional medical device classification system is risk-based, it is not appropriate for diagnostic products because of the different risks posed by diagnostic tests (see above). A classification framework for *in vitro* diagnostic tests should focus specifically on the characteristics that are most relevant to the performance and use of an *in vitro* diagnostic test (e.g., analytical and clinical validity).

4. **The current pre-market review standards that apply to *in vitro* diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?**

The concepts of "safety" and "effectiveness" do not speak to the critical elements of diagnostic test performance. Rather, in assessing whether an *in vitro* diagnostic test (whether a test kit or and LDT) functions as claimed, the FDA should consider whether the test is analytically valid (i.e., accurate, reliable, and reproducible) and clinically valid (i.e., that the result reported by the test accurately diagnoses diseases, determines prognosis, or predicts clinical outcomes).

5. **Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?**

Yes, because of the inherent difficulties of evaluating use of laboratory tests in a clinical setting, we believe in many instances shifting reliance toward post-market processes could improve patient access without significantly compromising health or safety.

Outcomes trials regarding the use of an *in vitro* diagnostic test are difficult to run because they require researchers to link (a) the result of a test to a patient management decision, and (b) the patient management decision to a health outcome. It can be prohibitively expensive to run such

tests – particularly where the outcome of interest is not immediately apparent (e.g., cancer recurrence) – because it may take several years for subjects to reach an endpoint of interest. Researchers may need to enroll large numbers of subjects to ensure the trial has adequate statistical power to account for intervening factors between the diagnostic test and the outcome of interest. Moreover, variability in therapeutic interventions may confound the effect of the diagnostic test on patient outcomes.

Therefore, the FDA should reconsider the balance between the amount and type of clinical data that reasonably can be obtained on a pre-market basis versus through post-market controls. We believe greater emphasis on post-market studies could be particularly important for diagnostic tests that represent substantial improvements over existing diagnostic tests and/or meet significant unmet needs. Further, we encourage the FDA to increase its reliance on published, peer-reviewed articles that are not reports of randomized, controlled trials (e.g., reports from quasi- or non-experimental designs, clinical practice guidelines, nationally or internationally-accepted standards) when assessing a diagnostic test.

FDA should also consider the technical and economic feasibility of pre-market as well as post-market trials and the studies that the Agency requires or recommends that a sponsor conduct. As above, with diagnostic tests for certain diseases or conditions (e.g., early stage breast cancer, prediabetes or prehypertension), studies assessing long-term endpoints would require many years to complete and large numbers of subjects to control for confounding factors. It would not be feasible economically for most diagnostic test sponsors to conduct studies assessing long-term endpoints in these conditions. Even if a sponsor were able to raise the resources to conduct such a study, it is likely that the analytical methodology or bioinformatics would advance substantially over the course of the study such that the results would no longer be relevant once the study is completed.

6. **A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?**

A supplemental application should only be required if a change has a clinically meaningful impact on a test's performance (i.e., the change would reasonably be expected to lead to a change in patient diagnosis, patient prognosis, or prediction of outcome to treatment compared with the expected result using the original test).

Testing methodologies are constantly evolving—especially in molecular testing (e.g., those made possible by dramatic advances in sequencing) as new findings about the relationship of specific gene markers and clinical conditions are reported every day. However, a change in test methodology or the addition of a new marker to a diagnostic test panel will not necessarily change a test's performance. For example, one may have analytically validated a test for reporting specific variants of a particular gene. Insofar as new information is widely available in the published literature about the biological role of specific variants, reference to this information in laboratory test reports should not require pre-market review and clearance/approval by the FDA.

In general, the requirement for submission of a supplemental clearance or approval should not differ between LDTs and distributed test kits.

7. **We have heard a lot of about the practice of medicine and its relationship with medical product "labeling". What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?**

Consistent with other regulated products, the "labeling" for a diagnostic test may include the packaging and any other written, printed, or graphic material that is included with the packaging for or that otherwise accompanies the physical materials that are used in performing the diagnostic test. However, standards for dissemination of scientific information regarding diagnostic tests should differ from the standards applicable to "traditional" medical devices.

The performance of a laboratory test is a medical service. In recognition of this fact, CLIA regulations require laboratories to provide clinical consultation to clients, assist clients in ensuring that appropriate tests are ordered to meet clinical expectations, ensure that reports of test results include patient information required for patient specific interpretation, and ensure that consultation is available and communicated to patients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions. Labeling requirements for diagnostic tests should not stand in the way of fulfilling these requirements. Regardless whether information is furnished by a laboratory or a manufacturer of a distributed kit, information that is truthful and non-misleading should be lawful to disseminate. The standards for dissemination of scientific information for diagnostic tests should recognize that for many tests the manufacturer and the provider of the test are the same entity.

8. **The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?**

There is considerable overlap between the requirements outlined in the draft LDT guidance documents and those promulgated under CLIA. For example, FDA and CLIA have similar – but not identical – quality systems requirements with respect to management responsibility, quality audits, personnel requirements, document controls, purchasing controls, identification and traceability, production and process controls, inspection, measuring and test equipment, general recordkeeping, servicing, and statistical techniques. (We have attached a summary table that compares the FDA and CLIA quality systems requirements--*see* Appendix.)

Establishing a single, consolidated set of requirements would enhance provider understanding of the requirements that may apply to their activities.

**9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g., rare cancers or blood disorders, Ebola)?**

An expedited regulatory pathway should be made available to manufacturers and laboratories that develop diagnostic tests used for rare diseases and diagnostic tests needed for emergency or unmet needs.

In defining what constitutes a "rare" disease, the FDA should consider its criteria for designating orphan conditions (e.g., that the disease or condition affects fewer than 200,000 people in the United States [total prevalent population]). Although the FDA has a device-specific exemption for rare conditions (the humanitarian device exemption (HDE)), this exemption is available only for devices intended to treat or diagnose a disease that affects fewer than 4,000 people in the United States per year. Because *in vitro* diagnostics are often used for purposes of treatment selection – i.e., to identify a subset of patients with a condition in whom a treatment may be appropriate – it would be appropriate to make "rare" status available to conditions consistent with those used to designate orphan drugs.

Customized diagnostic tests – i.e., tests developed by an individual provider for use with an individual patient – should not be subject to regulation by the FDA. (The development and performance of such tests should be considered as part of the practice of medicine.)

**10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be "grandfathered" into the marketplace? What transition process should be used for new product introductions?**

Insofar as a novel regulatory scheme is developed for diagnostic tests,

- Existing distributed test kits – i.e., tests that are currently regulated as medical devices by the FDA – should be allowed, for a period of time after the implementation of the new framework, to comply with the requirements for medical devices under the FFDCA or the requirements of a new diagnostics-specific framework. After a period of time, a previous approval or clearance under the FFDCA should be deemed an approval under the new framework, and distributed test kits should be required to comply with the regulatory requirements established under the new scheme.
- Existing LDTs should continue to be under enforcement discretion for a period of time after the implementation of the new framework. Eventually, however, an LDT should be required to obtain an approval from the FDA to the extent such approval is required under the new framework. In deciding which LDTs should be subject to the regulatory scheme first, the FDA should prioritize the LDTs that pose the greatest risk to patient health based on a risk scheme that has been proposed, vetted by the public, and adopted through regulation prior to implementation so that providers have sufficient notice and time to adapt to the new regulatory process.
- New distributed test kits should, for a period of time after the implementation of the new framework, be permitted to submit a marketing application as either a medical device

under FFDCA or under the new framework applicable to diagnostics. Insofar as a new distributed kit is approved or cleared under the FFDCA, such approval or clearance should be deemed an approval under the new framework at the same time such deeming occurs for existing distributed tests.

- New LDTs should be required to comply with the new regulatory framework from the date of implementation of the statute. This may involve notification and adverse event reporting when requirements for such notification and adverse event reporting under the new framework are implemented. With respect to pre-market submission, this should follow the same prioritization as for existing LDTs, above, considering which LDTs pose the greatest risk to patient health.

**11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?**

The development of new, more accurate, or more efficient diagnostic tests may be encouraged by (a) the provision of a priority review voucher to the sponsor of an innovative diagnostic test and/or (b) the establishment of a Medicare reimbursement premium for laboratories that perform an innovative diagnostic test.

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We hope that you have found these comments helpful. If you have any questions about our comments, please contact Mitch Nelles, Ph.D., at 415.287.2374 or via e-mail mnelles@CareDxInc.com.

Sincerely yours,

/s/

Coalition for 21st Century Medicine

**Appendix – Comparison of FDA and CLIA Quality Systems Requirements**

| Requirement | Applies to Manufacturers (of test kits)? | Applies to Laboratories (performing LDTs)? |
|---|---|---|
| **Quality systems requirements** | | |
| **Management responsibility (for implementing quality system)** | √ | √ |
| **Quality audits** | √ | √ |
| **Personnel requirements** | √ | √ |
| **Design controls** | | |
| **Design controls** | √ | Not required |
| **Document controls** | | |
| **Document controls*** | √ | √ |
| **Purchasing controls** | | |
| **Purchasing controls** | √ | √ |
| **Identification and traceability** | | |
| **Identification** | √ | √ |
| **Production and process controls** | | |
| **Production and process controls (e.g., environmental, buildings)** | √ | √ |
| **Inspection, measuring and test equipment** | √ | √ |
| **Acceptance activities** | | |
| **Receiving, in-process, and finished device acceptance** | √ | Not required |
| **Acceptance status** | √ | Not required |
| **Nonconforming product** | | |
| **Nonconforming product** | √ | Not required |
| **Corrective and preventive action** | | |
| **Corrective and preventive action** | √ | √ |
| **Labeling and packaging control** | | |
| **Device labeling** | √ | Not required |

| Requirement | Applies to Manufacturers (of test kits)? | Applies to Laboratories (performing LDTs)? |
|---|---|---|
| **Device packaging** | √ | Not required |
| **Handling, storage, distribution, and installation** | | |
| **Handling** | √ | Not required |
| **Storage** | √ | Not required |
| **Distribution** | √ | Not required |
| **Installation** | √ | Not required |
| **Records** | | |
| **General requirements (recordkeeping)** | √ | √ |
| **Device master record** | √ | Not required |
| **Device history record** | √ | Not required |
| **Quality system record** | √ | Not required |
| **Complaint files** | √ | √ |
| **Servicing** | | |
| **Servicing** | √ | √ |
| **Statistical techniques** | | |
| **Statistical techniques (for establishing, controlling and/or verifying acceptability of process capability and product characteristics)** | √ | √ |