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

Ranking Member Frank Pallone
235 237 Cannon HOB
Washington, DC 20515
By email to: cures@mail.house.gov

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

Dear Chairman Upton and Ranking Member Pallone:

The following comments are submitted from the national non-profit Lyme disease Association, Inc., (LDA), a volunteer-run organization which was started almost 24 years ago and consists of patients and families of patients. The LDA provides public and physician education and has presented 15 Continuing Medical Education (CME) conferences for physicians, most in conjunction with Columbia University in New York. LDA has provided 97 research grants which have led to 35 peer reviewed publications in journals such as *JAMA*, *Genetics*, *Infection & Immunity*, and *Emerging Infectious Diseases*. LDA has a program for families without insurance for Lyme disease diagnosis and treatment, LymeAid 4 Kids, created in conjunction with internationally acclaimed author Amy Tan, which has provided a quarter of a million dollars to help children get diagnosed or receive treatment. The LDA and an affiliate organization endowed the Columbia University Lyme and Tick-Borne Diseases Research Center in New York.

LDA's responses are made based on the areas which it feels are most relevant to patient stakeholders.

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?

The answer to the question depends on from what or whose perspective you are looking at the processes. From a regulatory perspective, there should be strong lines of separation, and FDA would be well served by embracing its historical perspective that it does not insert itself into the practice of medicine. Absolutely, clinical validity is a critical test attribute which regulatory bodies should seek to ensure; however, in its guidance, FDA does not articulate or describe an appropriate role or process of how that might be achieved. Unfortunately, FDA seems to be intent on embracing regulatory overreach and inappropriately inserting itself into the interpretive component of tests and into clinical decision making.

However, looking at the lines between the practice of medicine, the conduct of test, and the development/manufacturing of tests from an operational perspective, there needs to be – and often is – a close working relationship and collaboration with physicians in the practice of medicine and laboratories in the

utilization and interpretation of diagnostic tests. The interpretive process is becoming more complex, but laboratory professionals are quickly adjusting and providing a higher, more complex level of service. Similarly, the details of risk evaluations, including cost-benefit analyses, should remain the purview of the physician and his/her collaborators – such as lab professionals. It will be extremely damaging for FDA to attempt to reduce the complex, professional service of the interpretive process into a test component subject to regulation.

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?

As noted above, the professional service of the interpretive process and clinical decision making, such as evaluations of costs and benefits, should not be subject to regulatory judgments or processes of the FDA. However, more fundamentally than formulating various definitions - since the FDA is bringing all laboratory tests under its domain with respect to this proposed guidance, we need to ask what are the reasons for the changeover of LDTs and are the reasons logical and valid?

The FDA has indicated it has problems with certain LDTs and safety, yet various entities have asked for examples of those safety concerns, and FDA has not provided detailed data, which can be analyzed so that intelligent judgments can be made as to the reasons for testing “tragedies,” the generalizability of those circumstances to the broad spectrum of diseases, the degree to which the FDA proposed guidance would reduce vulnerabilities, and whether alternative recommendations may be more responsive and efficacious.

For example, FDA cites the fact that there is no mechanism for adverse events in LDTs under CLIA so it will move LDTs under its authority, which has the MAUDE system for adverse events. Examining that system finds it is flawed at best. For example, the FDA indicated to the LDA and others that it had no complaints on FDA approved/cleared Lyme tests. Examination of the system showed in actuality there were complaints filed; however, they were not acted upon by FDA. The reason for non-action turns out to be that the system does not permit distinction between different Lyme tests, and further examination uncovers the fact that it is virtually impossible to obtain from a laboratory (one with tests approved/cleared by FDA) which test a particular patient had who filed the complaint has had. CONCLUSION: The mechanism for evaluating adverse events from tests is flawed, but rather than fixing that system and then working with CLIA to require adverse events reporting on the tests it approves, FDA is dumping an untold number of tests into the flawed system, and illogically using the presence of that flawed system as a reason for such an action.

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?

Implicit in the fact that a medical device is generally a physical object which is used upon the body or inserted into the body, often for long periods of time, there is generally a higher level of risk involved with devices and different kinds of risks, such as device failure, and infection related to the device implant and the complications of those risks. The risks involved with tests are mainly those which occur from whether the test is successful in picking up the disease and what are the rates of false negative and false positives from the tests. These risks must be evaluated in the context of how those factors come into play in the treatment process. If a test has too many false negatives, those individuals will not be diagnosed, or not diagnosed in a timely fashion. With Lyme disease, for example, often the existent Lyme tests are not sensitive enough to pick up Lyme disease. This factor may be related to the strain variations related to infection, which are becoming increasingly common in Lyme and other tick-borne diseases, and is one reason specialty labs are beginning to add more than one strain to their LDTs.

In the case of an ELISA which depends upon antibody detection, the Lyme test can only test for free antibody, and often the antibody and antigen complex in Lyme patients, and thus the test might produce a negative result when the person has Lyme. Existing protocols call for a 2 step test, an ELISA, and if positive or equivocal,

followed by a Western Blot which must show particular bands that CDC decided upon in 1994 and apparently has not reevaluated despite the increased prevalence, expanding area, and changing face of Lyme. There is ample peer review which shows that the existing 2 step is not adequate and misses a high percent of patients. Those patients may go on to develop chronic symptoms from Lyme or other TBDs if left untreated while the patient pursues a diagnosis. At least one lab developing LDTs has kept up with the testing failures and tried to be innovative, instead of only a strict positive or negative result, they also report out the actual bands which show up. Looking at those bands, doctors familiar with the disease are able to use the information it contains to affirm a diagnosis in difficult cases. We asked another lab to do that for their FDA cleared Lyme tests and were told they could not as it was approved by FDA with certain labeling requirements preventing that from happening.

If the tests are false positive, pertaining to Lyme and other tick-borne bacterial diseases, the consequent to the patient is that perhaps they get a course of antibiotics which may not be effective for whatever they have. If treatment does not appear to be working, the doctor continues to search for other diagnoses. It is a risk but one which patients themselves need to be able to discuss with the physician and evaluate the risk in the context of the consequences of going undiagnosed and thus untreated while a spirochete is allowed to reproduce and begin an attack which could affect every system in the body, muscles, brain, heart, eyes, etc.

In the case of Lyme disease, the FDA cannot really speak about the FDA approved/cleared tests. The reason for this situation is because all FDA tests for Lyme right now say they are “substantially equivalent” to some other gold standard test (a predicate test) and are not listed as FDA approved. FDA definition: A predicate device is a device that (i) was legally marketed prior to May 28, 1976 (preamendments device), for which a premarket approval application (PMA) is not required; or (ii) has been classified or reclassified into Class I or II;4 or (iii) has been found SE through the 510(k) process. See 21 CFR 807.92(a)(3). However, after being questioned on the issue, the FDA has not been able to come up with what that first predicate test is or answer where it came from. So how can anyone judge the risks involved with FDA cleared tests for Lyme?

CONCLUSIONS: Currently, CLIA regulates and has regulated the LDTs in a process which appears to be defined specifically for testing. The process may need an additional component, such as an adverse events reporting system, but if it does, such an addition could be worked upon simultaneously by both FDA and CLIA, since it would be mutually beneficial to have one standard system that not only functions but also is a system in which complaints can be and actually are acted upon.

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?

Since the risk factors for tests and devices are not necessarily the same, as discussed, if the LDTs are to be placed under the Guidance, new standards need to be developed, and those need to be developed prior to accepting any new guidance.

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

Unfortunately, the manner in which FDA approval is now designed and carried out, there does not seem to be an effective way for patients to have access to cutting edge diagnostic tests under FDA approval/clearance. Technology and regulations governing technology are never and will never be on equal footing in the same timeframe, which is why in the case of CLIA approved tests, when you have a system which is generally effective and has few if any substantiated serious complaints about its regulated products, that system should remain in effect with perhaps minor modifications to address any shortcomings, not “perceived” shortcomings but “substantiated” shortcomings. It would be a mistake to “throw out the baby with the bath water.”

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?

Since there are serious concerns about the increased regulations of LDTs under the Guidance— how that will stifle innovation and prevent patients from receiving the latest tests, especially in areas where controversy exists about the efficacy of existent tests — such as in Lyme disease—a difference in process for LDTs would most likely be a benefit, not only bringing new technology where it is quickly needed in a controlled way, but also permitting patients access to it.

We must not forget we live in a global economy now. The world is a smaller place, and where health care is concerned, people in the US are no longer allowing their health care to be dictated by unwieldy, unnecessary government regulations. Aided by the Internet and social media and more positive economics, people are travelling around the world to countries which used to be considered substandard for health care practices, to get cutting edge treatments and health care in general.

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?

Information about Lyme disease testing is often conflicting, and a particular test used to test for Lyme may behave differently than that same test used to test for another disease. Information such as this is difficult and time consuming to find, yet much of it greatly impacts patients’ diagnosis. Obviously, labels cannot contain a large volume of information but should contain the sensitivity and specificity of that particular test. In the case of the Lyme ELISA, perhaps labeling could also include the information that one can test negative and still have the disease.

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?

We are not sure that assessing the FDA’s quality systems compared with CLIA is a productive exercise. FDA approval of Lyme tests does not equate with quality. In fact, to obtain FDA clearance, the requirements of a lab test need only to meet the low bar set by other previously FDA approved/cleared tests. A review of the FDA listed Lyme tests shows all as “substantially equivalent,” and thus “cleared,” and not “approved.” There is no obvious predicate, nor can FDA cite one. We have previously explained how the adverse events system for FDA tests cannot work as it lacks a mechanism for determining which particular test kit is being used by the complainant. So how is anyone able to ascertain how well FDA regulation is working with respect to Lyme disease? That means if a company can afford to go through the FDA “approval” process, it can introduce more poorly-performing tests on the market. That does not help patients, who should be the primary focus.

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)?

Lyme is not a rare disease, however, it has often been treated as one, with citations in journals saying Lyme is hard to catch and easy to cure. In 2013, CDC finally came out with numbers of 300,000 cases of Lyme annually, 10 times more than reported cases. Even this may be under reporting. Part of the reason for underreporting lies in the failure of testing to pick up the cases. Even when doctors diagnose based on symptoms, history, exposure, ruling out other illnesses, they may not get positive tests due to some of the items mentioned in above questions,

and thus those cases are not always counted as “Lyme.” Any system that regulates testing in the area of Lyme disease needs to delineate that the criteria to be positive for tests such as those criteria used by CDC for surveillance purposes are not to be used as diagnostic criteria. Unfortunately, the lines become blurred and doctors have been using tests to diagnose according to CDC surveillance criteria, NOT diagnostic criteria. Any system needs to be mindful of that distinction. If the tests results are only based on a negative, which is predicated upon a surveillance definition, that needs to be indicated in labeling.

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?

In the area of Lyme disease, one of the primary problems is that FDA-approved tests for Lyme are notoriously insensitive and have been shown to miss more than 50% of Lyme disease cases. Currently, the FDA has approved 83 Lyme tests, which are produced by 28 companies. Approximately 90% of these are ELISA tests, the first test required under the CDC two-tiered lab test recommendations for Lyme disease—recommendations that have become requirements. Studies by the American College of Pathologists concluded that the currently available ELISA tests for Lyme do not have adequate sensitivity to meet the two-tiered approach recommended by the CDC. The Council of State and Territorial Epidemiologists even recognized the inadequacy of the ELISA as a screening tool, and revised the CDC surveillance system to permit standalone Western blots, which also have challenges.

CONCLUSION: All current FDA approved/cleared diagnostic tests should not be grandfathered in, as they are not necessarily reliable, and their adverse events reports have not been followed up on due to the inadequacy of the reporting system as mentioned in other questions. However, if grandfathering is approved under the Guidance for all FDA/cleared/approved tests, then LDTs should also be grandfathered in as they have also been government regulated and approved and should be brought into the process as all current tests.

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

Generally it is a known fact that more government regulation leads to less innovation. In this case, however, tests should be removed from the FDA purview entirely and left/placed under CLIA. Scrutiny can be given to CLIA regulations, similar to what is being done to some extent by government in this Guidance process to provide a climate more conducive to development and marketing of new technologies. Since tests are different than devices, that necessitates making the regulatory process specific to them, so it only addresses test concerns, not device concerns with potentially higher levels of risk. Also, the government needs to use experts who are forward looking in regard to testing technology. While old technologies are still sometimes safe and effective, there is so much more out there now with DNA testing, culturing, even the use of nanotechnology to aid in diagnosis. Just as new gene therapies are being successfully used to treat formerly fatal diseases, new tools are available to maximize diagnostics by more quickly and successfully bringing the patient to the point of being able to use the new treatments. Private industry is going in that direction and government needs to look at the strides they are making and encourage development with funds and with friendly policies.

Thank you for the opportunity to comment on this important issue.

Sincerely,

Patricia V. Smith

Patricia V. Smith,
President