January 29, 2015

VIA email

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Framework for Regulatory Oversight of Laboratory Developed Tests; Request for Comments
[Docket Nos. FDA-2011-D- 0360 and FDA- 2011 - D- 0357]

I am submitting this comment regarding the Regulatory Oversight of Laboratory Developed Tests on behalf of LymeDisease.org (LDo). We appreciate this opportunity to share our views.

LymeDisease.org is a national non-profit patient advocacy organization dedicated to research, education, and advocacy related to tick-borne diseases. We were founded in 1989 and have one of the broadest reaches of any organization serving patients with Lyme disease through our nationwide network of state groups, website presence, and print journal, *The Lyme Times*.

In addition to funding research and education outreach efforts, one of our central roles in the community is collecting, compiling, analyzing and disseminating information about Lyme disease. For example, we conduct large scale surveys—over 5,000 patients—to help characterize the disease and some of the burdens Lyme patients face in terms of quality of life and access to care. We have worked with Stanford University and Carnegie Mellon University to publish the results of these surveys in peer-reviewed journals. We believe the hope of the future in Lyme disease is "big data", which will enable more accurate and detailed analysis of tick-borne diseases, and we support the work of the National Patient-Centered Clinical Research Network (PCORnet). Our Chief Executive Officer sits on both the Steering and Executive Committees of PCORnet and heads their Patient Council.

Lyme disease is an emerging zoonotic disease spread by the bite of a tick. It is the most common vector-borne disease in the United States, with more than 300,000 new cases diagnosed each year according to the Centers for Disease Control and Prevention (CDC). A single tick bite can transmit more than one pathogen, and co-infections with multiple tick-borne pathogens are not uncommon. Over 14 other tick-borne pathogens have been identified to date. Hence, when we talk casually about patients with Lyme disease, we are frequently talking about a stew of infectious agents. A number of pathogens transmitted by ticks have no commercially available test and new pathogens are discovered regularly.

The diagnosis of Lyme disease is primarily a clinical one, based on exposure to ticks, history of a tick bite, the presence of a rash, physical examination and medical history as well as diagnostic tests. Few patients remember the tick bite and 30% or more never develop the characteristic rash. A good diagnostic test can accurately detect disease, help monitor treatment effectiveness, and determine when infection has been eliminated. Unfortunately, no such test exists for Lyme disease.

Current serological tests are based on 20-year old technology using indirect detection of antibodies and geared to high specificity (i.e., no false positives). Unlike the tests for HIV/AIDS, which have a sensitivity of greater than

99%, laboratory tests for Lyme disease have very low sensitivity and miss roughly half of Lyme cases (i.e., lots of false negatives). Although this is widely acknowledged during the first four weeks of disease before antibodies have developed, as the table below shows, it is also true of convalescent disease:

Sensitivity and Specificity of Commercial Two-Tier Tests for Convalescent/Late Stage Lyme disease

Study/Year	Sensitivity	Specificity
Schmitz (1993)	66%	100%
Engstrom(1995)	55%	96%
Ledue (1996)	44%	100%
Tilton (1997)	45%	100%
Trevejo (1999)	29%	100%
Bacon (2003)	67%	99%
Binnicker (2008)	49%	100%
Steere (2008)	18%	99%
TOTAL	46%	99%

References: (1-8)

Note, this is the state of FDA authorized tests. Some other tests that are not FDA authorized have far greater sensitivity and these are selected for use by knowledgeable physicians.(9) Indeed, the FDA issued a warning regarding Lyme tests, stating:

> The Food and Drug Administration (FDA) is concerned about the potential for misdiagnosis of Lyme disease based on the results of commonly marketed tests for detecting antibodies to Borrelia burgdorferi, the organism that causes Lyme disease. It is important that clinicians understand that a positive test result does not necessarily indicate current infection with B. burgdorferi, and a patient with active Lyme disease may have a negative test result.(10)

Lyme disease treatment can be highly successful but depends upon timely diagnosis. Misdiagnosis and delayed diagnosis are all too common. Most patients in our large-scale surveys of over 5,000 patients with chronic Lyme disease report that they were not diagnosed until more than two years after contracting the disease. By this time, the disease is much more difficult to treat.(11)

Treatment failures occur in both early and later Lyme disease, and, when they do, no laboratory test can determine whether infection requiring additional treatment persists. The lack of a biological marker for the disease also hampers clinical trials which depend upon an accurate end point to determine success.

A substantial proportion of patients diagnosed with Lyme disease develop debilitating symptoms that persist in the absence of initial treatment or following short-course antibiotic therapy.(12, 13) Chronic Lyme disease is associated with a worse quality of life than most other chronic illnesses, including congestive heart failure, diabetes, multiple sclerosis and arthritis.(11, 14, 15) Over forty percent of patients with chronic Lyme disease reported that they currently are unable to work because of Lyme disease and many patients report that they have received disability at some point in their illness.(11) For these patients, access to diagnosis and treatment are vital, because their current quality of life is unacceptable.

Although the FDA specifically points to the need for FDA regulation Lyme disease due to "exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease," the fact is that Lyme disease is treated with antibiotics that the FDA has approved and which are associated with low risk profiles. Although the politics of treating Lyme disease and associated rhetoric have heated up following an antitrust investigation into the Infectious Diseases Society of America (IDSA) regarding its Lyme disease guideline development process, the underlying safety profile has not changed.(16)

The FDA's own assessment of the use of even long term antibiotics underscores their favorable safety profile: "These antibiotics have an extensive history of use, and the lack of any serious adverse events as reported in these studies support their reputation as safe drugs."(17) Intravenous antibiotics are associated with the risks inherent with any intravenous delivery of drugs, but are no more risky.(18) A survey of over 3,000 patients with chronic Lyme disease found that roughly half of the patients were not being treated with antibiotics and, of those who were, only 7% were taking any form of parenteral antibiotics.(11) The decision of whether and what form of antibiotic might be appropriate treatment is subject to the same type of risk/benefit assessment that physicians and patients use when making such choices in other diseases.

Although Lyme disease is a clinical diagnosis, many physicians and insurers won't treat without a positive laboratory test, notwithstanding the poor quality of commercially available laboratory tests.(19) Hence, *testing is the gateway to diagnosis, treatment and insurance coverage for Lyme patients.* Patients select their physicians carefully for their expertise and physicians determine and interpret the results of laboratory tests. Patients view the right to select among diagnostic tests and to rely on the interpretation of those tests by their physicians as an access-to-healthcare issue.

Considering that what we commonly call Lyme disease is often a stew of pathogens, the ideal test would analyze the patient's blood to determine which of these pathogens are present. The clinician would then have a clear picture of the infectious agents involved to help inform treatment approaches for the individual patient. Although today's testing options fall far short of this ideal, DNA-based serology may unlock this potential in the near future if we encourage and foster innovation in test development.

Given all of this, it should not be surprising that Lyme patients are very concerned about the current poor quality of Lyme testing and the need for innovation. Better laboratory tests are crucial for diagnosis, to monitor treatment efficacy, and to run the clinical trials essential to establish effective treatment regimens to cure patients. Unfortunately, FDA involvement with Lyme tests has not improved their quality. Rather, it has given a false sense of quality assurance for substandard tests that harm patients.

We urge you to rescind your LDT guidance proposal and continue to permit laboratory testing services to be overseen by CLIA and CMS. The proposed guidance will harm patients by limiting access to necessary and innovative laboratory services essential for diagnosis and treatment of Lyme disease.

1. **Laboratory Diagnostic Tests Are But One Component of Clinical Judgment**

The state of Lyme disease testing is—at this point—rudimentary. The clinician needs all available information, imperfect though it is, in order to assess and diagnose patients. The role of the physician is integral in selecting the laboratory test and interpreting the results of the test. There is no direct-to-consumer marketing for Lyme laboratory tests. Laboratory tests are ordered by the doctor after examining the patient and determining that they have signs and symptoms consistent with Lyme disease.

Experienced physicians request tests that provide information regarding the specific antigens to which the patient is producing antibodies against, and to use this information to determine the likelihood that the patient has Lyme

disease. For example, antibody tests may be reported with different bands that have more or less significance in determining whether a patient has Lyme disease.

Clinicians use the laboratory test results together with tick exposure history, reported symptoms and physical findings to determine the likelihood that the patient has Lyme disease and make an initial diagnosis. If the test results are uncertain or if the test is known to have false negative and false positive results, these risks can be assessed by the physician. They can be explained to the patient in determining treatment options. Point-of-care determinations regarding whether a test is providing a false negative result in the face of the patient's clinical presentation is essential in diagnosis and treatment.

The central issue for patients and physicians is the probability that the test will aid in the diagnosis of the disease. In diagnosis, the test is one of many factors considered along with patient history, clinical presentation, physical findings, and response to treatment. The physician will then monitor the patient's progress and if the diagnosis and treatment assessment does not improve the patient's quality of life, the physician may re-assess and perhaps re-diagnose the patient. In this way, even false-positive results may be ruled out as the clinician monitors and adjusts course. This is the exercise of clinical judgment which is and should continue to be regulated under professional standards of care.

Hence, the risk of missed diagnosis and misdiagnosis can be mitigated through the exercise of clinical judgment. However, the effect of the new FDA guidance may be to preclude patients from having access to tests that they need to obtain appropriate diagnosis and treatment. *If a test is not on the market, there is no way to mitigate the risk of failure to diagnose an illness nor is there the flexibility to adjust course.*

The FDA cannot competently assess or mitigate the risks of misdiagnosis or failing to diagnose on a centralized basis for patients it does not see. The traditional medical device classification system is not appropriate to regulate testing. The existing CLIA and CMS systems and state and federal regulatory system provide the flexibility and oversight necessary for diagnostic testing. Because of this, LDT's should remain subject to the provisions of CLIA and the current regulatory scheme without further FDA intervention.

2. **Risk/Benefit Assessment with Laboratory Diagnostic Tests Should be Determined at the Patient/Physician Level**

Therapeutic medical devices pose risks different from those of diagnostic tests. Product safety in terms of manufacturing and design defects loom large with devices inserted into the body. In contrast, the risks associated with diagnostic tests are clinical in nature. They include the risk of misdiagnosing (and perhaps treating) a disease that is not present and the risk of failing to diagnose (and not treating) a disease that is present. Both of these risks are moderated by the exercise of clinical judgment of the treating physician. Key issues that physicians and patients need to weigh in this context are a) how acceptable is the patient's current quality of life (e.g. how severe is the condition?), b) how invasive is the test/treatment, c) how accurate is the test, and d) what are the consequences of "getting it wrong" (e.g. can the physician monitor, reassess and adjust diagnostic course?)

Where the treatment intervention is invasive (e.g. surgery), the clinician and patient will place a greater emphasis on safety, carefully assessing the potential that a test result may be a false negative. Perhaps additional testing will be done to develop a greater sense of certainty. When the patient is severely compromised by illness, there may be a greater willingness to bear the risk of a false positive if the treatment is not invasive and further corrections to the course of treatment may be made.

These types of assessments require weighing risks and benefits associated with false positives and false negatives in the context of the individual patient including that patient's tolerance for risk and the acceptability of the current quality of life for that patient. Physicians make this type of assessment in conjunction with patients as part of their exercise of clinical judgment, taking into account the values and preferences of the patient. This is part of the practice of medicine which the FDA should not regulate.

The risk/benefit assessment of Lyme tests is highly contextual and depends on the presentation and circumstances of the individual patient. These decisions should be made at the level of the physician and patient, who are best equipped to contextualize the assessment. CLIA and CMS are best suited to provide this flexibility.

3. **The FDA Device Regulatory Scheme is Not Suited for Diagnostic Test Regulation**

The underlying assumption of the proposed guidance is that FDA regulation of testing will improve the quality of laboratory tests by establishing their effectiveness and by monitoring adverse events associated with tests. Both processes are flawed when applied to diagnostic tests, however.

For example, in the case of Lyme disease, there are over 80 FDA authorized tests, but these tests were never demonstrated to be sensitive (see Table above). Instead, they were cleared as being equivalent to other cleared tests. Equivalency is not synonymous with quality when the reference test used is insensitive as is the case with Lyme disease. Hence, FDA clearance or approval does not indicate that tests are sensitive enough to accurately diagnose a disease. In our conversations with the FDA, the problem of a poor reference or predicate test establishing a low "equivalency" bar was acknowledged, but it was clear that these poor tests would remain on the market without having to establish efficacy. This misleads patients and consumers who may believe that FDA authorized tests meet a high quality level.

Equally alarming, the FDA system of determining adverse events does not work for Lyme disease laboratory tests (and presumably many other diseases). It requires that patients or their physicians know the manufacturer of the test that generates an adverse event, often in this case a missed diagnosis of Lyme disease. However, the laboratory service middlemen like Quest Diagnostics, LabCorp Diagnostics, and others who draw and process patient blood do not use their own tests. They use test kits manufactured by others. One physician spent two weeks without success trying to track down the manufacturer of a test used by a laboratory service provider. The end result is that the FDA has a number of "worthless" complaints filed against "unknown" test manufacturers. This broken adverse-event reporting system therefore fails to identify poor quality Lyme laboratory tests, and their developers cannot be tracked, reported or held accountable.

FDA authorization does not assure effectiveness or safety of laboratory tests and is ill suited to regulatory oversight of laboratory tests, which should remain under the authority of CLIA and CMS.

4. **The Use of Expert Panels in Lyme Disease is Not an Impartial or Disinterested Process.**

The FDA is proposing to use expert panels to help with the review of new technology. Expert panels have come under increased scrutiny because of commercial conflicts of interest. Beyond simple financial ties, expert panels may also have organizational loyalties that lead to researcher cronyism that favors products on the market (and the interests of their close peers who may have commercial ties) over newer tests that pose a competitive threat to those products.

Panel members on the Lyme disease treatment guidelines of the Infectious Diseases Society of America (IDSA) were found to have commercial ties to laboratory test manufacturers.(16) The guidelines require positive serology for diagnosis even though the sensitivity of existing lab tests is quite low (see Table above). These guidelines have created significant access-to-care barriers for patients.

As the Institute of Medicine has noted, Lyme disease is one of the most contentious diseases.(20) Unfortunately, a deeply polemic schism exists between certain research experts who are members of the IDSA on the one hand and community physicians and patients on the other hand. The controversy is fueled not only by commercial and industry ties held by IDSA researchers, but also by intellectual conflicts of interest and organizational loyalty affiliations. The result is that peer review in grant funding applications and medical publications is largely a bully pulpit for the enfranchised. The use of experts in assessing innovative new tests entering the market may essentially allow experts with such ties or peer affiliated ties to sit in judgment of newer technologies developed by competitors.

Systems relying on expert panels or FDA accredited third party reviews in Lyme disease have a high risk of bias, and outcomes do not reflect or promote patient interests. The use of expert panels in Lyme disease by the FDA does not assure process integrity.

5. The Need for Innovation in Lyme Disease is High

Lyme disease is not a rare illness. However, it was not until 2013 that the CDC increased its estimates of the incidence of the disease from 30,000 to more than 300,000 new cases each year. Before the CDC revision, Lyme disease met the definition of a rare disease and certainly has been an orphan disease in the sense that it is a research-disadvantaged disease. For example, while it is six times more prevalent than HIV/AIDS, it receives less than one percent of the amount of NIH funding allotted to HIV/AIDS. A similar lack of interest is seen with pharmaceutical companies on the treatment side, as traditional treatments for Lyme disease are generic antibiotics. Only three NIH-funded treatment trials have been published and these involved samples of less than 78 patients. A good diagnostic test is necessary not only for the diagnosis of Lyme disease, but also to determine the clinical beginning and ends points in treatment trials to establish cures. Also, like rare diseases, patients are generally very well educated about the disease. *Hence, it is critical that any and all fast track options be available to research-disadvantaged diseases like Lyme disease.*

Research-disadvantaged diseases face substantial challenges in obtaining funding and attracting investment interest from commercial organizations. Barriers to innovation imposed by regulatory environments can suppress innovation for years and require financial investments that smaller companies likely to lead the charge in innovation cannot meet. Innovation in testing depends upon a level competitive playing field that permits smaller companies to enter the market in a timely fashion without economic barriers. In Lyme disease, most laboratory tests are based on technology that is over 20 years old. New diagnostic tests should not be held to a higher standard of sensitivity or specificity than those of the currently FDA-approved or cleared Lyme tests. (Innovation should not be placed at a competitive disadvantage compared to tests currently on the market.)

Requiring FDA approval would place a barrier to market entry on new diagnostic tests and would dis-incentivize innovation by those on the market who would not feel the heat of competitive pressure.

6. Patients Are Concerned About False Negative Tests and the Need for Innovation

LymeDisease.org conducts large scale surveys of patients in the Lyme community to characterize their condition and concerns. On October 21, 2014, we launched a survey regarding the proposed FDA guidance and we have received over 7,500 responses to date. The survey covered issues regarding innovation, the importance of testing to diagnosis, treatment and insurance coverage, and the risk of over- and under-diagnosis. The results make it clear that the risk of not being diagnosed and treated for Lyme disease because of a false-negative is one of the greatest concerns of patients and that the development of new innovative tests is viewed as a critical need.

More than 50% of Lyme patients report having been denied a diagnosis due to negative serology. Over 75% stated that a positive laboratory test was important or very important for diagnosis and treatment, while 60% said it was important for insurance coverage. Approximately 80% reported that their clinically diagnosis was based on supporting laboratory tests, apparently after repeat testing necessitated by the poor state of Lyme tests. These results underscore the fact that testing is the gateway to diagnosis, treatment and insurance coverage for Lyme patients.

The FDA assumes that the greatest risk to patients are the risks associated with false positive test results leading to misdiagnosis and treatment for a condition that the patient does not have. However, patients whose quality of life is poor—those who are unable to work or who are on disability as many Lyme patients are—know that the risk of failing to diagnose and treat is the greater risk. Over 50% of Lyme patients reported having been diagnosed with another condition (e.g. fibromyalgia, chronic fatigue syndrome, depression, or neurodegenerative disease) that later turned out to be caused by Lyme disease. When asked which was the greatest risk to patients, 98% pointed to the risk of not being diagnosed and treated when you have Lyme disease.

When asked to weigh the importance of innovation in Lyme testing against the importance of making sure tests were rigorously evaluated, 89% viewed innovation as more important.

The current state of laboratory testing in Lyme disease is poor. The hope for the future lies in the development of innovative tests based on emerging technology. We need to favor innovation over tests developed in the past. We believe that providing FDA oversight of LDTs for Lyme disease is a mistake because it will diminish both the availability and accuracy of innovative laboratory test and harm patients by denying them access to diagnostic tests necessary to obtain treatment and improve their quality of life.

Very truly yours,

Lorraine Johnson, JD, MBA, Executive Director
LymeDisease.org, formerly CALDA
Empowering patients through advocacy, education and research

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