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Division of Dockets Management (HFA-305)
Food and Drug Administration
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Docket No. FDA-2011-D-0360
Comments from the Lyme Disease Association, Inc. and Other Undersigned Parties on:
Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

These comments are submitted by the Lyme Disease Association, Inc. (LDA) and other parties as undersigned – who are involved across the country with Lyme and other tick-borne diseases (TBD). We provide these comments because of our commitment to and concern for Lyme and other TBD patients, health care providers who diagnose and/or treat patients who have or are suspected of having Lyme or other TBD, and laboratories whose professionals provide expert services to assist in diagnoses.

We are adamantly opposed to the FDA finalizing and implementing this Guidance for Lyme disease testing because it poses numerous threats to the ability of patients to obtain access to the highest quality diagnostics, in the soonest timeframe, and it will encroach on the physician's practice of medicine. Should the FDA, despite the many compelling objections that have been and will be raised, move forward and finalize this Guidance, we request that our comments be considered to lessen the harmful impacts of the Guidance on patients, physicians, and laboratories.

1. **The FDA has not been transparent in describing the specific failures of LDTs that compel such far-reaching changes, and, thus, also has not explained sufficiently how such failures would be remedied by the proposed Guidance.**

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?

Like many other parties, we do not doubt that the current systems for ensuring safety and effectiveness of LDTs can and should be improved. While we have been provided some talking points on why this Guidance is necessary, we have not been provided substantive data and analysis. FDA glosses over the need with general comments about a changed environment and complexity and refers to some problem areas, but again lacks in providing specifics and analysis.

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 that can be analyzed, so that intelligent judgments can be made as to the reasons for systemic testing failures and for circumstances that resulted in "tragedies" for some patients and families, the generalizability of those circumstances to the broad spectrum of diseases, the degree to which the FDA proposed Guidance would reduce vulnerabilities, and – critically important - whether alternative proposals and sets of

recommendations may be more responsive and efficacious.

FDA's proposed Guidance – and any other document we have seen- does not provide sufficient data and analysis of the problems to be able to evaluate possible solutions. Furthermore, FDA simply proposes itself as the solution. Unfortunately, there will be little opportunity to hear CMS' views on how CLIA could be strengthened because any issues of FDA vs. CMS are already a foregone political decision made at a higher level.

As the authors of CLIA and its amendments, Congress will not be living up to its responsibilities if it does not take steps to ensure that problems with the current system are appropriately identified and thoroughly analyzed and that alternative solutions are evaluated – taking into consideration the broad range of costs and benefits, including giving appropriate weight to issues such as impact on innovation and safeguarding the empowerment of physicians in the practice of medicine.

2. **The expert panel process which will be used to categorize tests and risks could be biased. This concern is based on the prior use of "experts" in Lyme disease.**

   There has been a long and clear practice of bias in communications and decision-making regarding Lyme disease. Individuals with vested interests in Lyme tests – but belonging to powerful medical societies - have been very vocal in lobbying agencies and in courting the press insisting that only FDA tests be allowed, even when many of those tests have poor sensitivity and specialty labs have made test improvements that can be a great benefit to physicians and to patients. Many peer-reviewed studies have found low sensitivity in existing Lyme tests, even while individuals in some federal agencies have defended the quality of the tests. Entrenched biases have to a significant extent overpowered science in relationship to Lyme disease, and FDA's proposal could exacerbate problems of inappropriate bias if the threat is not recognized and mitigated.

3. **There also is concern that "experts," who may or may not be involved with expert panels, may recommend that specialty lab tests be removed from the market pending FDA review or before review completion, citing safety reasons, which can be, e.g., too many positives.**

   Historically, there has been an obsessive focus by some individuals, both within and outside of government, on false positives, while minimizing patients' and treating physicians' concerns with the extremely serious health consequences of false negatives. False positives and false negatives are both important, and there should be a balanced assessment of their consequences. There potentially is even a catch-22 that a better performing test that had higher sensitivity and identified more cases of diseases could be considered high risk because it could lead to greater use of antibiotics.

   The threat of the development of antibiotic resistance also has been misused to argue against treatments for Lyme disease. Antibiotic resistance is of course a serious public health problem, but evidence does not support the use of antibiotics to treat Lyme as a significant contributor to the problem of resistance.

   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.

It is a simple reality that when it comes to a public face, HHS operating divisions project unity and provide one another a high level of professional courtesy by not critically judging the credibility and advisability of statements, opinions, policies, actions, etc. While this may be understandable from an organizational perspective – one Administration and one HHS – it raises valid concerns regarding stakeholder rights and protections when there are strong internal biases. What happens when FDA is pressured by an "expert" to target specialty labs that, for example, specialize in Lyme and other tick-borne diseases, or, more egregiously, to target a specific specialty lab?

4. **FDA clearance has not in itself resulted in quality and should not be presumed to be the solution for achieving quality.**

Government agencies have touted that all Lyme tests should be FDA approved, and through our analysis of FDA's process, we discovered that FDA cannot point to any "approved" Lyme tests; they are all "cleared" which means substantially equivalent to a predicate test–to what test exactly, no one knows, since FDA cannot point to any original predicate test for Lyme that was not itself also based on substantial equivalence.

Numerous studies have been conducted on the sensitivity of existing Lyme tests. Unfortunately, inappropriate biases also are apparent in numerous published articles regarding Lyme test sensitivity. For example, one study required a positive serologic test result for inclusion in the study, and then found that population to have 100% sensitivity. In drawing conclusions, the authors ignored the fact that pre-selecting patients with a positive test is quite different from evaluating infected individuals. Thus goes the world of Lyme disease. When standard commercial testing has been evaluated in clinical practice, sensitivity of the 2-tier system was 56% on average.

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 substantiated serious complaints about its regulated products, that system should remain in effect with perhaps 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."

5. **The process used for collecting adverse events (MAUDE) currently used by FDA for approved/cleared tests is already flawed– for Lyme, FDA cannot determine which test kits are being reported.**

Despite the inability of FDA to determine the specific test kits involved in complaints of FDA approved/cleared tests, under the proposed Guidance, the LDTs would be dumped into the same flawed MAUDE system. That action could put the newly cleared LDTs at a disadvantage, because the LDTs put into the MAUDE system potentially could receive greater scrutiny, since FDA would have the ability to more readily act upon the complaints.

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 who filed a complaint has had.

Although the current mechanism for evaluating adverse events from tests is flawed, 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.

6. **FDA should not insert itself into the practice of medicine.**

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.

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 well trained and certified lab professionals. It is misguided for FDA to assert that it can or that it should even attempt to proffer its own judgments to infringe on the collaborations of physicians, pathologists, chemists, microbiologists, geneticists, other credentialed laboratory professionals, and informed patients. 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.

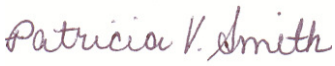
7. **Labeling and other publicly available resources should provide more information to patients and physicians to assist in decision-making.**

Information about Lyme disease testing is often conflicting, and a particular type of test used to test for Lyme may have a different interpretation than that same test used to test for another disease. Information on the nuances of tests in relationship to specific diseases or conditions is often difficult and time consuming to find, yet much of it greatly impacts patients' diagnosis. While labels are limited in the amount of information they can or should contain, certain types of information may be useful to physicians and to patients.

Many physicians and patients do not understand that certain Lyme testing protocols were developed for surveillance and not diagnosis. Additionally, many do not understand that certain tests, which may perform very well for other conditions, have relatively low sensitivity for Lyme disease and that an individual may have the disease despite a negative test. Consideration should be given to including in labeling and other test descriptions, where it is not already provided, clinically important information on purposes of tests (e.g. surveillance vs. diagnosis), sensitivity and specificity, and important warnings (e.g., a negative result does not rule out disease and further evaluation may be necessary).

Thank you for the opportunity to provide this input into the Guidance process. Do not hesitate to contact the Lyme Disease Association for further information or clarification.

Sincerely,



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