LYME DISEASE

Essential Background on Diagnostics

GOALS FOR THIS SESSION

- Ensure FDA has a complete understanding of the problem with Lyme disease diagnostics from 1995 forward.
- Open a dialogue with the FDA to rectify the problem with diagnostics currently on the market.
- Agree on a follow-up plan.

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EXECUTIVE SUMMARY

The Lyme disease diagnostic standard was manipulated at the behest of vaccine manufacturers and misrepresented to the FDA. Diagnostics manufacturers took advantage of FDA's relative inexperience with Lyme disease in the early 1990s, causing regulations to not be properly followed in the implementation of the revised standard.

As a result, the public has been continually harmed for 27 years by the lack of a valid diagnostic for all presentations of the disease.

THE PROBLEM

SmithKline Beecham and others manipulated the diagnostic standard for Lyme disease, excluding the known positive cases with low serum antibodies such that vaccines would look effective when they were not.

The LYMErix vaccine was withdrawn after three years on the market and many lawsuits for injury claims, but the manipulated diagnostic standard is perpetuated through the following:

- the CDC serum repository which screens samples using the manipulated diagnostic standard; samples are then used to validate diagnostic tests for FDA clearance
- the FDA 510(K) process, clearing based on the substantial equivalents.
- DNA patent interests of academics who license their products to test kit manufacturers

WHAT IS LYME DISEASE?

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QUICK FACTS

- Infection caused by spirochetal bacteria Borrelia burgdorferi--similar to the organism that causes syphilis
- Acquired primarily through the bite of a black legged tick; most people don’t notice the bite
- May also be passed from mother to fetus in utero
- No cure, no effective treatment
- Blood supply not being properly screened

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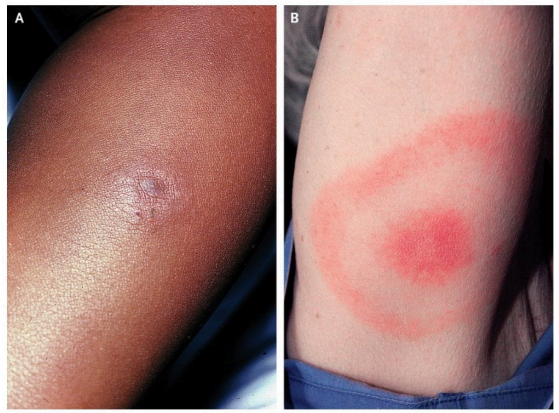
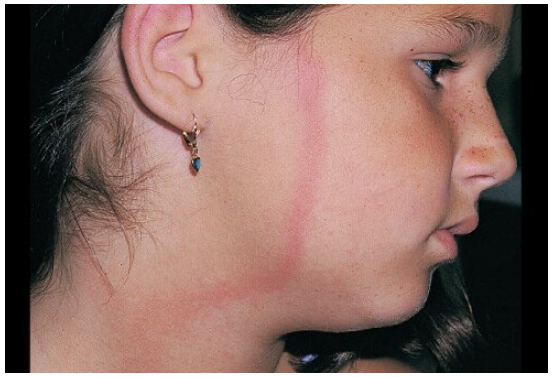
SIGNS & SYMPTOMS



Erythema Migrans on Skin of Different Colors.



- Widely varying (“protean”) symptoms.
- Bullseye rash (erythema migrans)—frequency disputed & appearance differs.
- Acute flu-like illness, meningitis, encephalopathy…
- Chronic symptoms: severe fatigue, pain, neurologic syndromes, “brain fog,” heart block, rashes, dysautonomia, increased susceptibility to infections.
- Long-term systemic effects can be disabling, including MS, ALS, cancers, etc.
- Chronic arthritis with no systemic symptoms in 20% or fewer cases—these are the cases the serology is designed to detect.

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EARLY HIV RESEARCHER GARY WORMSER: LYME IS A DISEASE OF IMMUNOSUPPRESSION

Gary Wormser of New York Medical College was an early HIV/AIDS researcher, so he is an expert in mechanisms of immunosuppression.

1) "The magnitude of modulation (immunosuppression) was directly dependent on the quantity of OspA." https://www.ncbi.nlm.nih.gov/pubmed/10865170

2) "…negative regulatory pathways intended to mitigate the severity and duration of the inflammation" (means post-septic shock response with long term immunosuppression afterwards). https://www.ncbi.nlm.nih.gov/pubmed/22246662

3) "This finding suggests that there is redundancy in the ability of the innate immune system to recognize B. burgdorferi and/or that these components can activate pathways that produce anti-inflammatory cytokines……the anti-inflammatory effects might be the more important function of TLR signaling." https://www.ncbi.nlm.nih.gov/pubmed/27976670

4) "Importantly, innate immune suppression increased with infection duration and depended on cooperative and synergistic interactions between DIO and B. burgdorferi infection." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5383418/

HISTORICAL CONTEXT

- HIV/AIDS emerged simultaneously.
- Lyme was spreading uncontrolled.
  - 1989: SmithKline lab in Philadelphia reported up to 2,500 tests performed *per day*. (Source available upon request.)
- Standard treatment for neurologic Lyme: intravenous antibiotics.
  - Insurance companies did not want to pay for treatment.
- Several acts passed into law making profiteering easy

SCALE OF THE PROBLEM

- Found in all 50 U.S. states & worldwide.
- Per CDC: Estimate potentially 476,000 new cases per year.
- Due to the manipulated diagnostic criteria, true number could be around 2 million.

"Now, in newly infested areas, we haven't been able to find any clean ticks. They're all infected."

-David Neitzel, Minnesota Department of Health vector-borne disease unit, 2018

Sources:
https://www.cdc.gov/lyme/datasurveillance/index.html
https://publicintegrity.org/environment/as-disease-bearing-ticks-head-north-weak-government-response-threatens-public-health/

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WHAT WAS KNOWN PRIOR TO LYME TEST MANIPULATION

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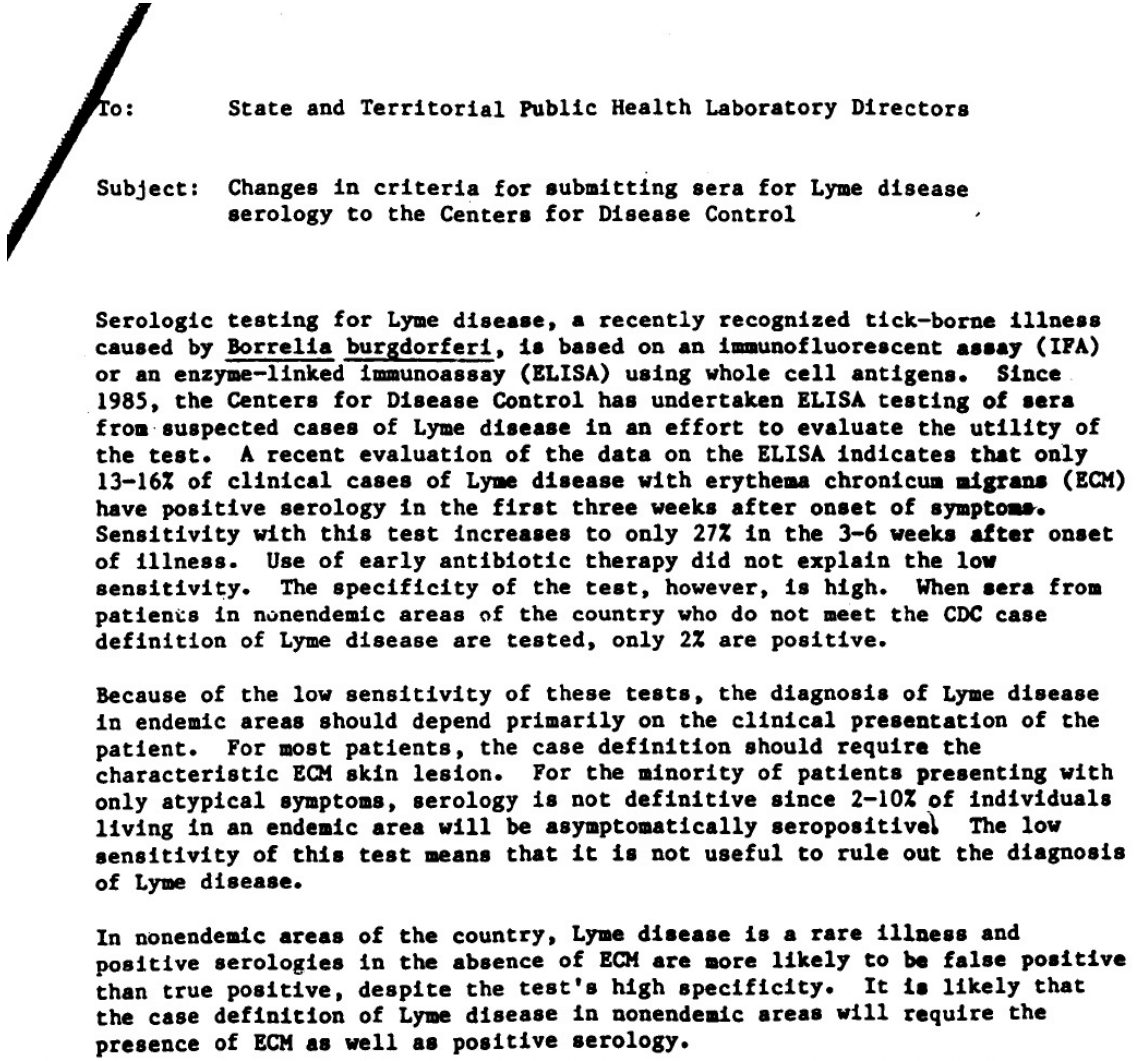
CDC REPORTS DISMAL SENSITIVITY OF ELISA

"A recent evaluation of the data on the ELISA indicates that only 13-16% of clinical cases of Lyme disease with erythema chronicum migrans (ECM) have positive serology in the first three weeks after onset of symptoms. Sensitivity with this test increases to only 27% in the 3-6 weeks after onset of illness."

The first Lyme tests were FDA cleared in 1987, presumably with similar sensitivity.



To: State and Territorial Public Health Laboratory Directors

Subject: Changes in criteria for submitting sera for Lyme disease serology to the Centers for Disease Control

Serologic testing for Lyme disease, a recently recognized tick-borne illness caused by Borrelia burgdorferi, is based on an immunofluorescent assay (IFA) or an enzyme-linked immunoassay (ELISA) using whole cell antigens. Since 1985, the Centers for Disease Control has undertaken ELISA testing of sera from suspected cases of Lyme disease in an effort to evaluate the utility of the test. A recent evaluation of the data on the ELISA indicates that only 13-16% of clinical cases of Lyme disease with erythema chronicum migrans (ECM) have positive serology in the first three weeks after onset of symptoms. Sensitivity with this test increases to only 27% in the 3-6 weeks after onset of illness. Use of early antibiotic therapy did not explain the low sensitivity. The specificity of the test, however, is high. When sera from patients in nonendemic areas of the country who do not meet the CDC case definition of Lyme disease are tested, only 2% are positive.

Because of the low sensitivity of these tests, the diagnosis of Lyme disease in endemic areas should depend primarily on the clinical presentation of the patient. For most patients, the case definition should require the characteristic ECM skin lesion. For the minority of patients presenting with only atypical symptoms, serology is not definitive since 2-10% of individuals living in an endemic area will be asymptomatically seropositive. The low sensitivity of this test means that it is not useful to rule out the diagnosis of Lyme disease.

In nonendemic areas of the country, Lyme disease is a rare illness and positive serologies in the absence of ECM are more likely to be false positive than true positive, despite the test's high specificity. It is likely that the case definition of Lyme disease in nonendemic areas will require the presence of ECM as well as positive serology.

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Source:
April 1988 letter from CDC to Oregon Public Health Laboratory

LOW OR NO IMMUNE RESPONSE

"We studied 17 patients who had presented with acute Lyme disease and received prompt treatment with oral antibiotics, but in whom chronic Lyme disease subsequently developed. Although these patients had clinically active disease, none had diagnostic levels of antibodies to B. burgdorferi on either a standard enzyme-linked immunosorbent assay or immunofluorescence assay. On Western blot analysis, the level of immunoglobulin reactivity against B. burgdorferi in serum from these patients was no greater than that in serum from normal controls."

"We conclude that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against B. burgdorferi and that a specific T-cell blastogenic response to B. burgdorferi is evidence of infection in sero-negative patients with clinical indications of chronic Lyme disease."

-Dattwyler, et al, "*Seronegative Lyme Disease*," New England Journal of Medicine, 1988

Source:
https://www.nejm.org/doi/full/10.1056/NEJM198812013192203

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LOW OR NO IMMUNE RESPONSE

"The ones that failed to mount a vigorous immune response tended to do worse, clinically. So, there was an inverse correlation between the degree of serologic response and the outcome. So, individuals with a poor immune response tend to have worse disease."

-Raymond Dattwyler, SUNY Stonybrook, at the June 1994 FDA Vaccines & Related Biologics Product Advisory Committee meeting

Source:
June 1994 FDA VRBPAC meeting transcript

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LOW OR NO IMMUNE RESPONSE

"Seronegativity is an unexplained feature and is a major obstacle to diagnosis when the hallmark, erythema (chronicum) migrans (ECM), is not observed, as happens in up to 50% of patients with Lyme disease. The main laboratory test for the disease, the detection of antibody to B burgdorferi, may also be negative in many instances."

Source:
Schutzer, et al, Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. *The Lancet*, 1990.

LOW OR NO IMMUNE RESPONSE

"What is the immune system if not a guard dog? Why has it stopped responding to the spirochetes in its midst?"

-Stephen Malawista, Yale researcher, quoted in his obituary in the New York Times, 2013

Source:
New York Times, September 18, 2013

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B CELL ABNORMALITIES

"Immature B cells can be seen in the spinal fluid. These cells can appear quite atypical—not unlike those of transformed or neoplastic lymphocytes."

"Not only are plasma cells plentiful in the spleen, lymph nodes and bone marrow, they are also represented by large and somewhat atypical-appearing precursor B cells as well."

-Allen Steere & Paul Duray, 1988

Source:
Clinical Pathologic Correlations of Lyme Disease by Stage

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FETAL TRANSMISSION

“We report the case of a woman who developed Lyme disease during the first trimester of pregnancy. She did not receive antibiotic therapy. Her infant, born at 35 weeks gestation, died of congenital heart disease during the first week of life. Histologic examination of autopsy material showed the Lyme disease spirochete in the spleen, kidneys, and bone marrow.”

-Steere, Duray, et al, 1985

Source:
Maternal-Fetal Transmission of the Lyme Disease Spirochete, Borrelia Burgdorferi

BORRELIA *CAUSE* IMMUNE SUPPRESSION

"...when lymphocytes are cultured in the presence of growing Bb there is a marked inhibition of NK activity on days 3, 5, and 7 when compared to lymphocytes cultured in BSKII media in the absence of spirochetes...The inhibition is directly attributable to the organism or its supernatants."

-Raymond Dattwyler, et al, SUNY Stonybrook, 1988

Source:
Modulation of Natural Killer Cell Activity by Borrelia Burgdorferi

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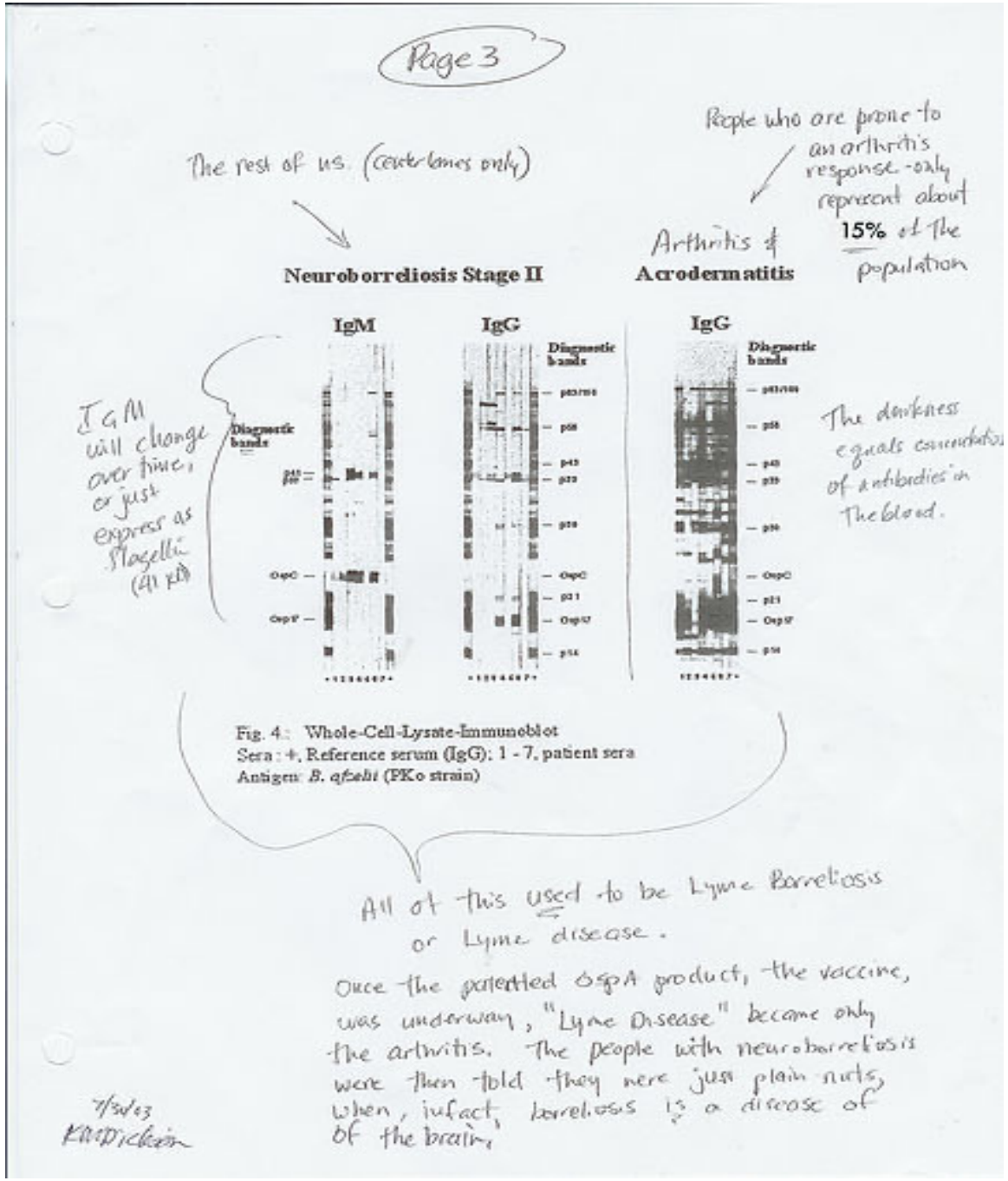
ARTHRITIS CASES HAVE HIGHEST IMMUNE RESPONSE

This image illustrates the difference between antibody responses of immune suppression cases (left two columns) and arthritis cases (right column).

Even though these were all known positive cases, the testing scheme from 1995 forward included only those with the highest serum antibodies.



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CDC: ARTHRITIS CASES HAVE HIGHEST IMMUNE RESPONSE

“When the overall proportion of positive tests was used as the outcome variable, donors who met the Lyme disease case definition were less likely to be seropositive than were donors who did not meet the case definition ($p = 0.01$, Table 1). When donors with erythema migrans were excluded, there was no association between the case definition and overall seropositivity (Table 2). Even when the analysis was limited to those serum specimens drawn at least 3 weeks after the onset of illness, there was no association between the case definition and seropositivity (Table 3). The logistic regression analysis confirmed the bivariate results. Regression analysis did, however, show an association between overall seropositivity and donors with arthritis when adjusted for the presence of erythema migrans and time from onset of illness to collection of serum sample (odds ratio = 1.014 per 1% increase in overall seropositivity, $p < 0.001$)."

- CDC, Lyme Disease Surveillance Summary, January 25, 1991

Source:
Lyme Disease Surveillance Summary

STEERE: ARTHRITIS CASES HAVE HIGH SERUM ANTIBODIES; CHRONIC NEURO LYME CASES ARE SERONEGATIVE

Allen Steere proved a *genetic association* of robust immune response with an arthritis outcome.

"When single serum samples from 80 patients with Lyme arthritis were tested, 57 (71%) showed antibody reactivity to recombinant Osp proteins; in contrast, none of 43 patients who had erythema migrans or Lyme meningitis ($P < 0.00001$) and 1 of 5 patients who had chronic neuroborreliosis but who never had arthritis ($P = 0.03$) showed antibody reactivity to these proteins."

-Allen Steere, et al, April 1993

Source:
Association of Treatment-Resistant Chronic Lyme Arthritis with HLA-DR4 and Antibody Reactivity to OspA and OspB of Borrelia burgdorferi

SCIENTIFIC KNOWLEDGE RECAP

By 1993 it was known that:

- Lyme disease causes immune suppression in most cases.
  - Those cases produce low serum antibodies.
  - Those cases are the sickest.
- Specific genetic markers in a minority of cases are associated with an arthritis outcome.
  - Those cases produce high serum antibodies.
  - Those cases have few symptoms aside from an arthritic knee.

Serology was **not** an effective way to diagnose the spectrum of presentations of Lyme disease, but Immunoblotting was marginally better than ELISA.

EVENTS LEADING TO ADOPTION OF MANIPULATED DIAGNOSTIC STANDARD

SEQUENCE OF EVENTS

1. Lyme disease vaccine manufacturers petitioned the FDA in June 1994 to change the Lyme disease diagnostic standard to facilitate phase III trials.
2. The standard was changed in October 1994 at the Second National Conference on Serodiagnosis of Lyme disease in Dearborn, Michigan.
3. Upon completion of Lyme vaccine trials, FDA issued guidance on interpretation of diagnostics (July 1997) and informed diagnostics manufacturers of required labeling changes (October 1997) which reflected the outcome of the Dearborn conference.

JUNE 1994

Manufacturers Petition the FDA Vaccines & Related Biologics Product Advisory Committee

- Primary purpose: gain FDA buy-in for plan to change case definition/testing standard on behalf of Lyme vaccine manufacturers
- Representatives of three Lyme vaccine manufacturers present
- Multiple conflicts with the manufacturers disclosed
- Meeting ended with a closed-door session with SmithKline, after the room was swept for recording devices

I would like to conclude my introduction with FDA's questions to the advisory committee. We ask that the committee consider these questions while they listen to the presentations this morning.

Number one. Is the CDC case definition for Lyme disease appropriate for a pivotal efficacy trial. Please comment on laboratory assays to support the diagnosis of the

Source: June 7, 1994 FDA VRBPAC meeting transcript

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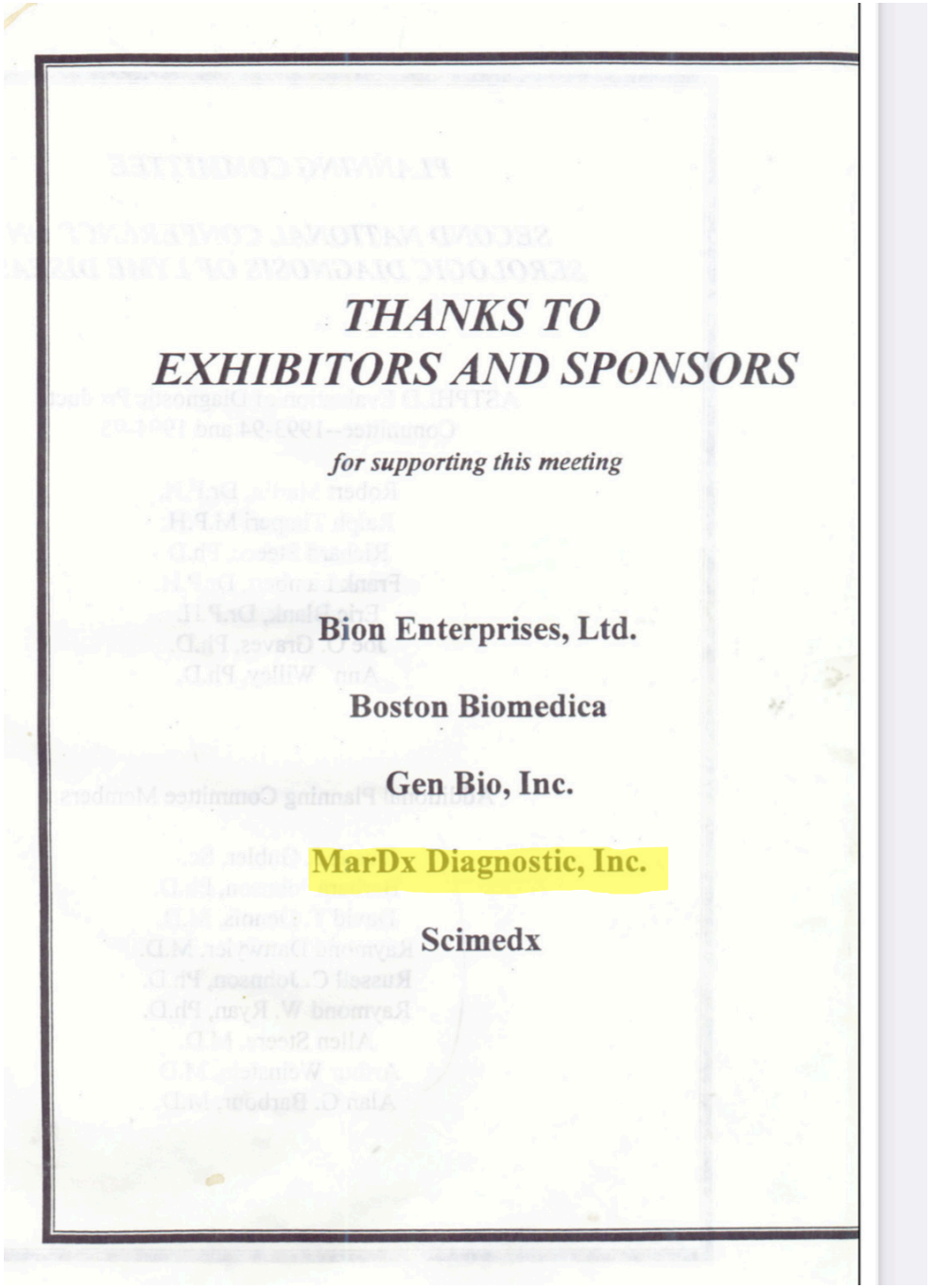
OCTOBER 1994

CDC Second National Conference on Serodiagnosis of Lyme Disease

- Co-organized by Association of State & Territorial Public Health Laboratory Directors (ASTPHLD, now known as Association of Public Health Laboratories—APHL) & sponsored by test kit manufacturers.
- Labs invited to give input reported widely varying accuracy of the proposed diagnostic methods.



THANKS TO
EXHIBITORS AND SPONSORS

for supporting this meeting

Bion Enterprises, Ltd.

Boston Biomedica

Gen Bio, Inc.

MarDx Diagnostic, Inc.

Scimedx

[October 1994 CDC Lyme conference transcript]

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LABS PRESENT AT DEARBORN

The various labs all performed different evaluations and had little agreement:

- Imugen: 9% met positivity criteria
- Lutheran Hosp., LaCrosse, WI: 34% IgM/22% IgG sensitivity
- IgeneX: 8% met the proposed criteria for positivity
- Wisconsin State Lab: 32% IgM/15% IgG sensitivity
- New York Medical College: 9/59 samples (15%) met positivity criteria for IgG
- Children's Hospital of Long Island Jewish Medical Center used arthritis samples only
- New York State DOH: evaluated by intensity of Western blot bands rather than lowest detectable analyte
- Johns Hopkins/CDC: used mouse sera
- Ontario Ministry of Health: found 66% of positive ELISA samples positive by WB, with unknown WB interpretation criteria
- IgeneX reported on their Lyme Urine Antigen Test (LUAT)
- MarDx used their own criteria and reported on various scenarios with the best result being 95% sensitivity/100% specificity. MarDx was contracted to provide test kits for LYMErix trials.

OCTOBER 1994

CDC Second National Conference on Serodiagnosis of Lyme Disease

- Outcome was a two-tier test method with first tier ELISA followed by a Western blot if positive or equivocal. Included interpretation of Western blots specifying certain IgM (2/3) and IgG (5/10) bands, plus timeframe of one month for acceptance of IgM positivity as “true positive.”

October 1994 CDC Lyme conference transcript

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OBJECTIONS

New York Department of Health:

> “If we followed a case confirmation scheme which incorporated the new two-test requirement for serologic confirmation on our 1995 cases, 1237 cases (81 %) of our non-EM cases would not have been confirmed. This represents 31 % of our total 1995 confirmed cases.”

April 15, 1996 letter from NYDOH to CDC

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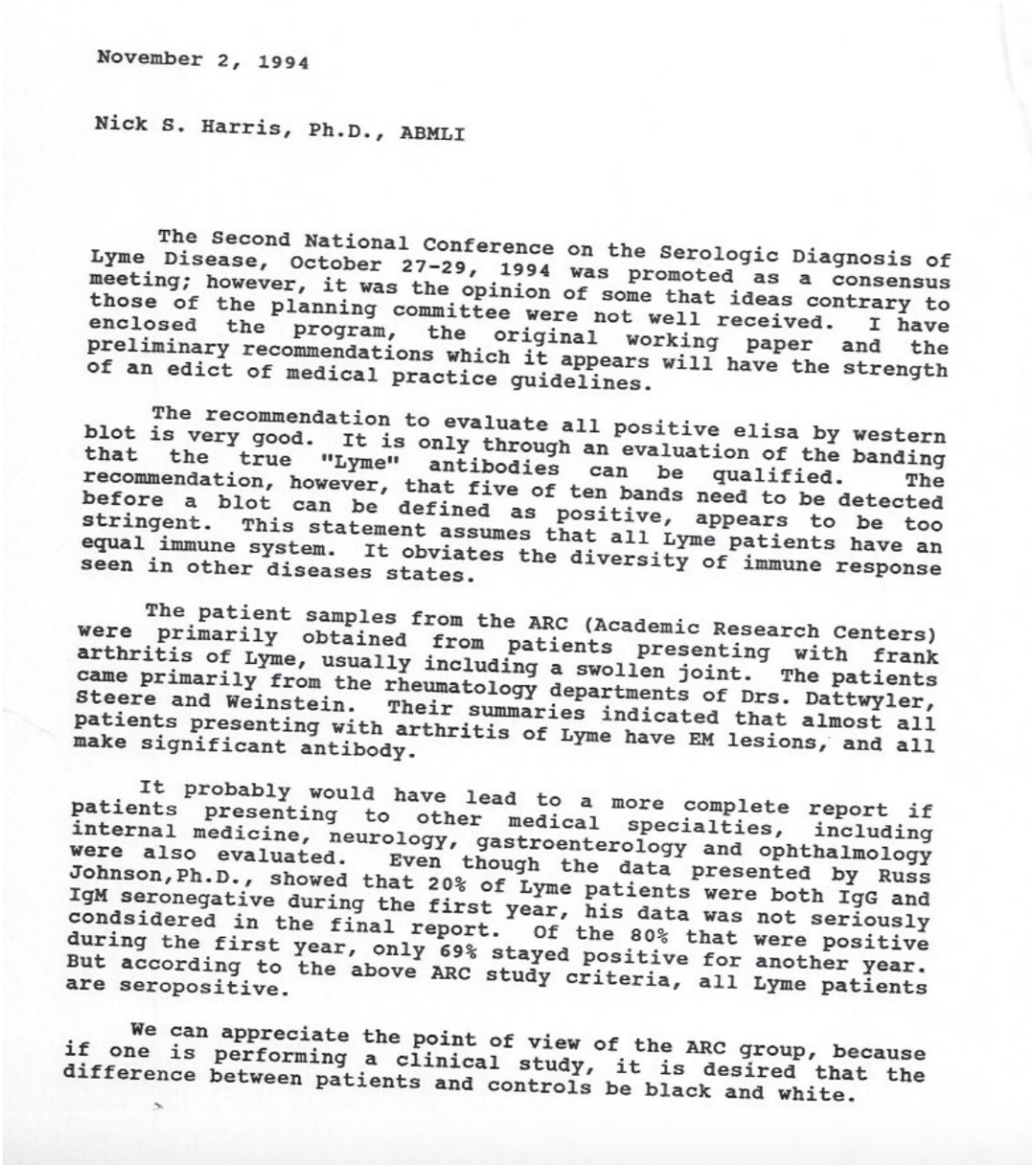
OBJECTIONS

Dr. Nick Harris, IgeneX:
"The patient samples from the ARC (Academic Research Centers) were primarily obtained from patients presenting with frank arthritis of Lyme, usually including a swollen joint. The patients came primarily from the rheumatology departments of Drs. **Dattwyler, Steere and Weinstein**. Their summaries indicated that almost all patients presenting with arthritis of Lyme have EM lesions, and all make significant antibody."



November 2, 1994

Nick S. Harris, Ph.D., ABMLI

The Second National Conference on the Serologic Diagnosis of Lyme Disease, October 27-29, 1994 was promoted as a consensus meeting; however, it was the opinion of some that ideas contrary to those of the planning committee were not well received. I have enclosed the program, the original working paper and the preliminary recommendations which it appears will have the strength of an edict of medical practice guidelines.

The recommendation to evaluate all positive elisa by western blot is very good. It is only through an evaluation of the banding that the true "Lyme" antibodies can be qualified. The recommendation, however, that five of ten bands need to be detected before a blot can be defined as positive, appears to be too stringent. This statement assumes that all Lyme patients have an equal immune system. It obviates the diversity of immune response seen in other diseases states.

The patient samples from the ARC (Academic Research Centers) were primarily obtained from patients presenting with frank arthritis of Lyme, usually including a swollen joint. The patients came primarily from the rheumatology departments of Drs. Dattwyler, Steere and Weinstein. Their summaries indicated that almost all patients presenting with arthritis of Lyme have EM lesions, and all make significant antibody.

It probably would have lead to a more complete report if patients presenting to other medical specialties, including internal medicine, neurology, gastroenterology and ophthalmology were also evaluated. Even though the data presented by Russ Johnson,Ph.D., showed that 20% of Lyme patients were both IgG and IgM seronegative during the first year, his data was not seriously condsidered in the final report. Of the 80% that were positive during the first year, only 69% stayed positive for another year. But according to the above ARC study criteria, all Lyme patients are seropositive.

We can appreciate the point of view of the ARC group, because if one is performing a clinical study, it is desired that the difference between patients and controls be black and white.

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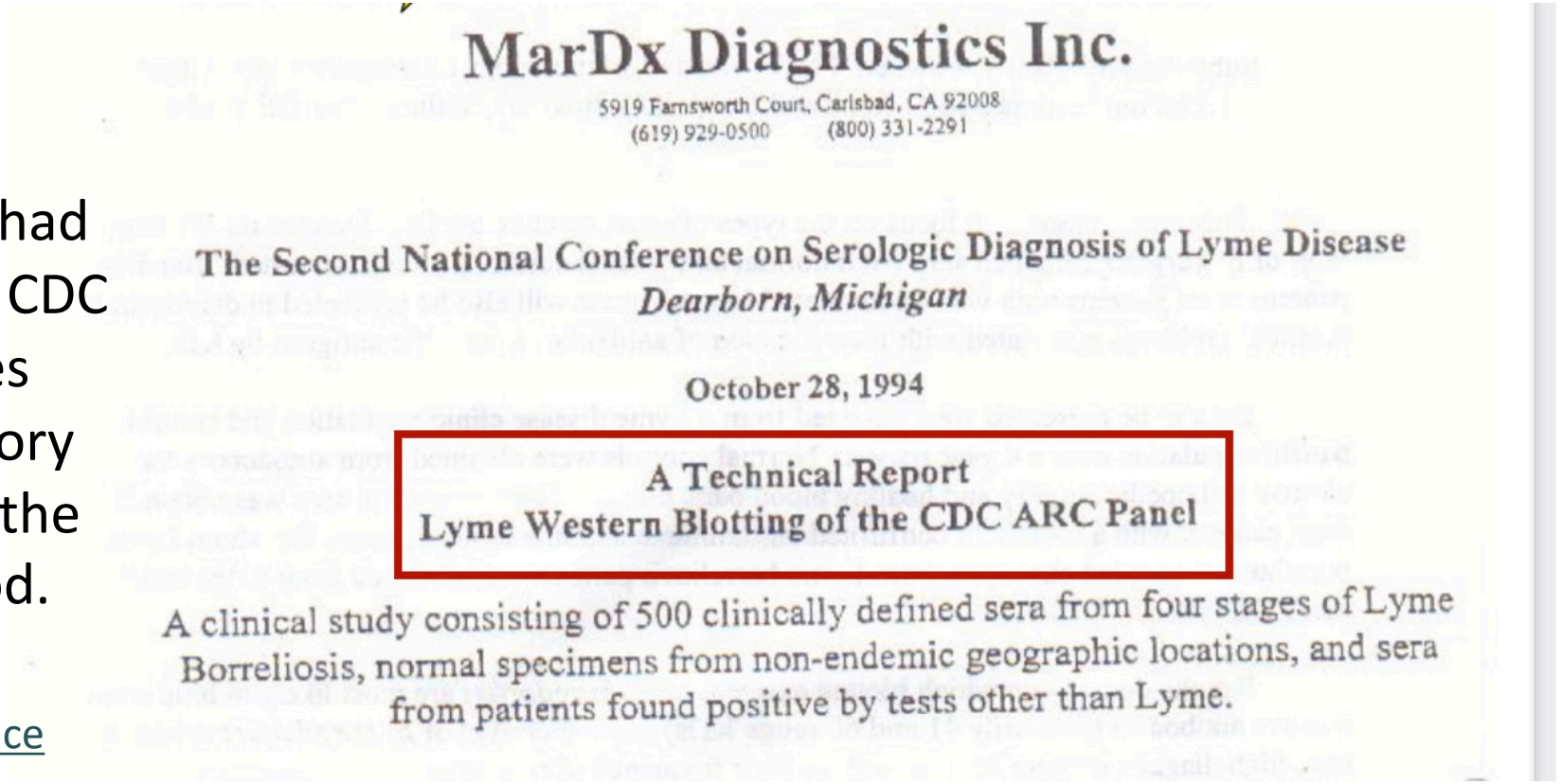
ARC PANEL ADOPTED BY CDC

MarDx Diagnostics

- Used the ARC Panel
- It appears the ARC Panel had already been adopted by CDC
- A recent CDC report states that Lyme Serum Repository samples are screened by the two-tier Dearborn method.

[October 1994 CDC Lyme conference transcript]



MarDx Diagnostics Inc.

5919 Farnsworth Court, Carlsbad, CA 92008
(619) 929-0500 (800) 331-2291

The Second National Conference on Serologic Diagnosis of Lyme Disease
Dearborn, Michigan

October 28, 1994

A Technical Report
Lyme Western Blotting of the CDC ARC Panel

A clinical study consisting of 500 clinically defined sera from four stages of Lyme Borreliosis, normal specimens from non-endemic geographic locations, and sera from patients found positive by tests other than Lyme.

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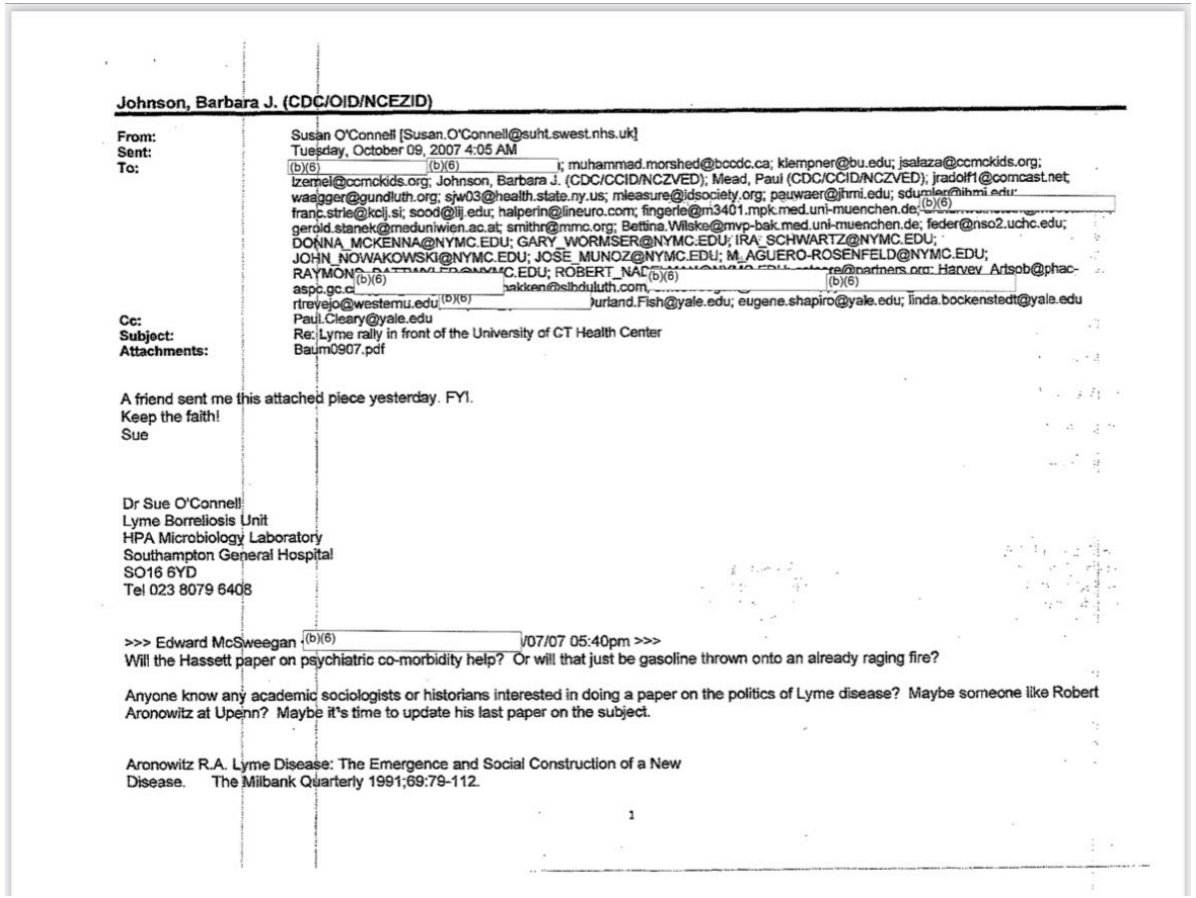
EMAIL AMONG DEARBORN PARTICIPANTS

"This battle cannot be won on a scientific front. We need to mount a socio-political offensive…We need reinforcements from outside our field."



Johnson, Barbara J. (CDC/OID/NCEZID)

From: Susan O'Connell [Susan.O'Connell@suht.swest.nhs.uk]
Sent: Tuesday, October 09, 2007 4:05 AM
To: (b)(6) (b)(6) i; muhammad.morshed@bccdc.ca; klempner@bu.edu; jsalaza@ccmckids.org; lzemel@ccmckids.org; Johnson, Barbara J. (CDC/CCID/NCZVED); Mead, Paul (CDC/CCID/NCZVED); jradolf1@comcast.net; waagger@gundluth.org; sjw03@health.state.ny.us; mleasure@idsociety.org; pauwaer@jhmi.edu; sdumler@jhmi.edu; franc.strle@kclj.si; sood@lij.edu; halperin@lineuro.com; fingerle@m3401.mpk.med.uni-muenchen.de; (b)(6) gerold.stanek@meduniwien.ac.at; smithr@mmc.org; Bettina.Wilske@mvp-bak.med.uni-muenchen.de; feder@nso2.uchc.edu; DONNA_MCKENNA@NYMC.EDU; GARY_WORMSER@NYMC.EDU; IRA_SCHWARTZ@NYMC.EDU; JOHN_NOWAKOWSKI@NYMC.EDU; JOSE_MUNOZ@NYMC.EDU; M_AGUERO-ROSENFELD@NYMC.EDU; RAYMON (b)(6) C.EDU; ROBERT_NA (b)(6) @partners.org; Harvey_Artsob@phac-aspc.gc.c (b)(6) hakken@slbduluth.com, (b)(6) rtrevejo@westernu.edu (b)(6) durland.Fish@yale.edu; eugene.shapiro@yale.edu; linda.bockenstedt@yale.edu
Cc: Paul.Cleary@yale.edu
Subject: Re: Lyme rally in front of the University of CT Health Center
Attachments: Baum0907.pdf

A friend sent me this attached piece yesterday. FYI.
Keep the faith!
Sue

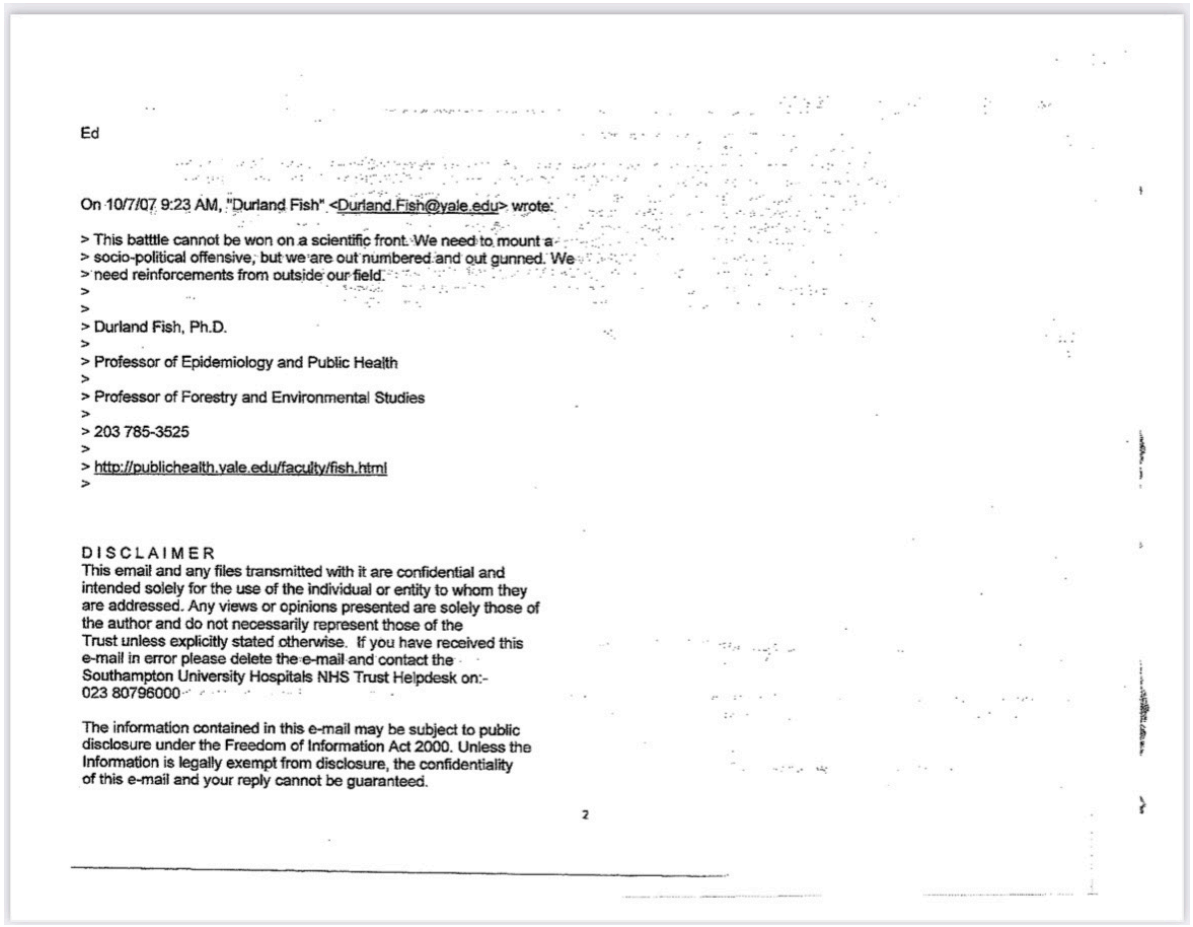
Dr Sue O'Connell
Lyme Borreliosis Unit
HPA Microbiology Laboratory
Southampton General Hospital
SO16 6YD
Tel 023 8079 6408

>>> Edward McSweegan (b)(6) /07/07 05:40pm >>>
Will the Hassett paper on psychiatric co-morbidity help? Or will that just be gasoline thrown onto an already raging fire?

Anyone know any academic sociologists or historians interested in doing a paper on the politics of Lyme disease? Maybe someone like Robert Aronowitz at Upenn? Maybe it's time to update his last paper on the subject.

Aronowitz R.A. Lyme Disease: The Emergence and Social Construction of a New Disease. The Milbank Quarterly 1991;69:79-112.

1



Ed

On 10/7/07 9:23 AM, "Durland Fish" <Durland.Fish@yale.edu> wrote:

> This batttle cannot be won on a scientific front. We need to mount a
> socio-political offensive, but we are out numbered and out gunned. We
> need reinforcements from outside our field.
>
>
> Durland Fish, Ph.D.
>
> Professor of Epidemiology and Public Health
>
> Professor of Forestry and Environmental Studies
>
> 203 785-3525
>
> http://publichealth.yale.edu/faculty/fish.html
>

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JULY 1997

FDA issues Public Health Advisory:

"The FDA microbiology panel has advised that package inserts of anti-Bb assays should promote the two-step testing algorithm recommended by the Second National Conference on Serologic Diagnosis of Lyme Disease which included representatives from the Centers for Disease Control and Prevention (CDC), the Association of State and Territorial Public Health Laboratory Directors, manufacturers of assays, academic researchers, and FDA."

We do not know what transpired to convince the FDA that they should make this recommendation.

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Home > Medical Devices > Medical Device Safety > Alerts and Notices (Medical Devices)

Medical Devices

FDA Public Health Advisory: Assays for Antibodies to Borrelia burgdorferi; Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease

July 7, 1997

To: Family practitioners, Internists, Infectious Disease Specialists, Clinical pathologists, General Practitioners, Pediatricians, Dermatologists

Purpose

FDA is advising you about the potential for misdiagnosis of Lyme disease. The results of commonly marketed assays for detecting antibody to *Borrelia burgdorferi* (anti-*Bb*), the organism that causes Lyme disease, may be easily misinterpreted. To reduce this risk of misdiagnosis we are providing guidance on the use and interpretation of these tests. It is important that clinicians understand the limitations of these tests. A positive result does not necessarily indicate current infection with *B. burgdorferi*, and patients with active Lyme disease may have a negative test result.[1-5]

Assays for anti-*Bb* should be used only to support a clinical diagnosis of Lyme disease. Physicians are advised to base diagnosis on history (including symptoms and exposure to the tick vector), physical findings, and laboratory data other than anti-*Bb* results. The most definitive diagnostic procedure, biopsy and isolation in culture, frequently yields organism when collection and culture procedures are optimal but often is not practical. Assays for anti-*Bb* can provide evidence of previous or current infection; however, to improve reliability, **results should be interpreted only in the context of a two-step testing algorithm (described below) and should not, by themselves, be used to establish a diagnosis of Lyme disease or to exclude *Bb* infection**. The two-step algorithm, as opposed to using a single test, increases the specificity of laboratory testing.

Although package inserts for some commercial assays describe their intended use "to aid in the diagnosis of Lyme disease," this statement does not fully reflect current knowledge about *Bb* infections and many such assays yield potentially misleading results. FDA is applying the following recommendations as it works with manufacturers to change package inserts and as it evaluates new assays for anti-*Bb*.

Recommendations for Two-Step Testing and Interpretation of Results

The FDA Microbiology Advisory Panel has advised that package inserts of anti-*Bb* assays should promote the two-step testing algorithm recommended by the Second National Conference on Serologic Diagnosis of Lyme Disease[1,2] which included representatives from the Centers for Disease Control and Prevention (CDC), the Association of State and Territorial Public Health Laboratory Directors, manufacturers of assays, academi researchers, and FDA.

- The first step is to perform an assay that detects either total or class-specific antibodies (IgM or IgG) by using enzyme-linked immunosorber technology ("ELISA" or "EIA") or indirect immunofluoresence microscopy ("IFA"). IgM levels usually peak 3-6 weeks after infection. IgG antibodies begin to be detectable several weeks after infection. The IgG response may continue to develop over the course of several month and generally persists for years.
- A negative result indicates that there was not serologic evidence of infection with *Bb* at the time the specimen was collected. A negative result should not be the basis for excluding *Bb* as the cause of illness, especially if blood was collected within 2 weeks of when symptoms began. If Lyme disease is strongly suspected, a second specimen should be collected 2 to 4 weeks after the first specimen and then tested.
- A positive or equivocal result is presumptive evidence of the presence of anti-*Bb*, should always be followed by second-step testing, and should not be reported until second-step testing is complete.
- The second step employs an assay that is more specific than that used for the first step. To date, Western-blot (immunoblot) assays have been used for second-step testing. This second test is more specific than ELISA or IFA because Western blot determines if serum contains antibodies (IgG or IgM) that react with appropriate *Bb* antigens separated by electrophoresis.
- A negative result indicates that no reliable serologic evidence of *Bb* infection was present at the time the specimen was collected. A negative result should not be the sole basis for excluding *Bb* as the cause of illness. If Lyme disease is strongly suspected, a second specimen collected 2 to 4 weeks after the first specimen should be tested.
- A positive result provides serologic evidence of past or current infection with *Bb*. Because the presence of even specific antibodies to *Bb* does not always indicate current infection, a positive result can support, but not establish, a clinical diagnosis of Lyme disease.

While this algorithm is a consensus approach for detecting serologic evidence of infection with *Bb*, the sensitivity and specificity of both steps are less than optimal. Physicians may be familiar with other two-step testing algorithms, such as that for antibodies to human immunodeficiency virus, in which a highly sensitive first-step assay is sometimes referred to as a "screening" test and a highly specific second-step assay, as "confirmatory." Because assays for anti-*Bb* should be used only for supporting a clinical diagnosis of Lyme disease and not for "screening" asymptomatic individuals "initial" is preferred for describing the first step. Second-step Western-blot assays are "supplemental" rather than "confirmatory" because of

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TECHNICAL ISSUES WITH LABELING CHANGES: MarDx CASE STUDY

This is from the K894224 file for MarDx.

- They were first to incorporate the Dearborn recommendations.
- These changes alone should have triggered an entirely new application.

CHECKLIST

Ref: Add to File/Consistency with Oct. 28, 1997 letter re assays for detection of antibo
Borrelia burgdorferi

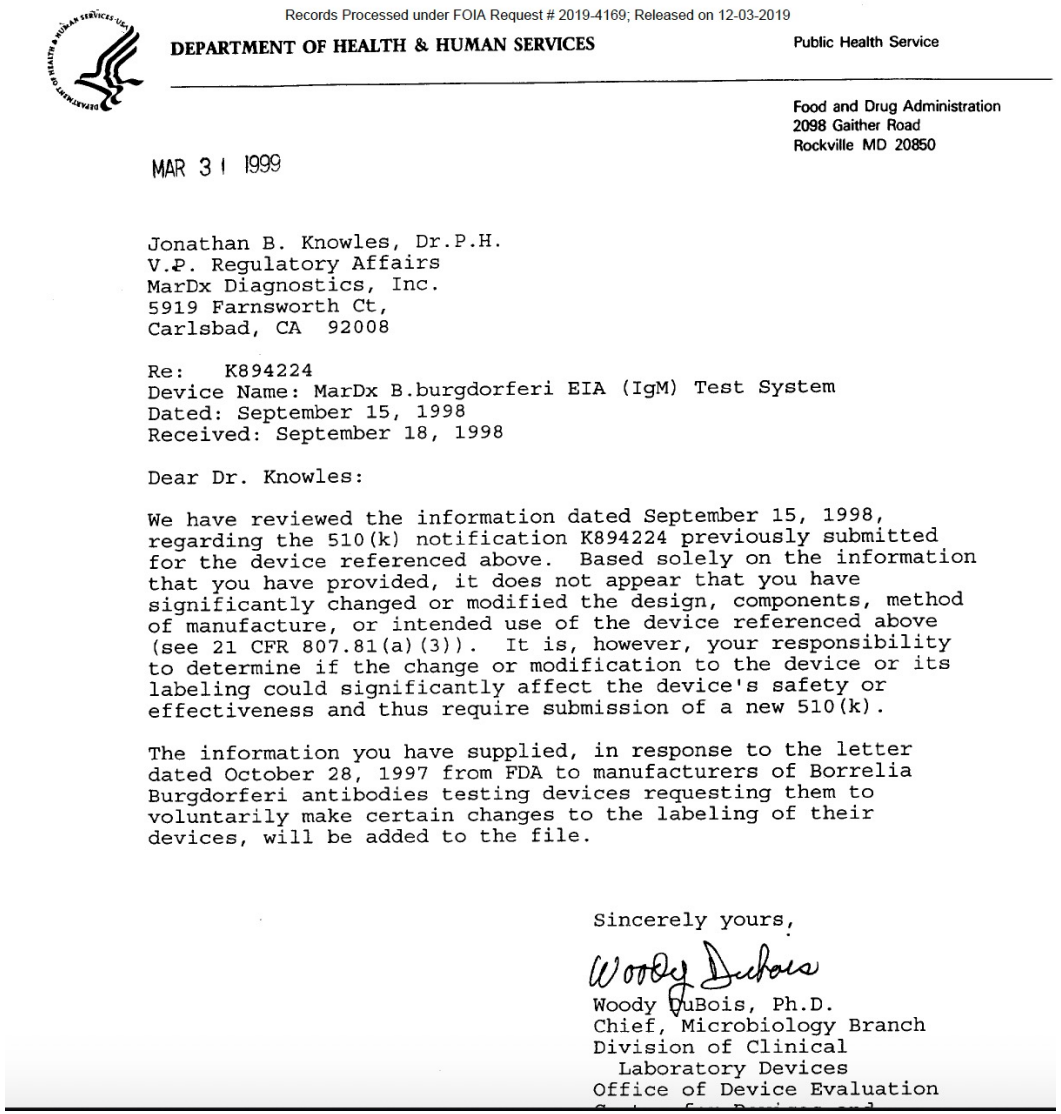
Sponsor: MarDx

Modifications:	**K894293** IgG	**K894224** IgM ✓	**K892206** IgG/IgM
INTENDED USE			
Qualitative	Y	Y	Y
Presumptive	Y	Y	Y
Sera from Bb symptomatic pts	Y	Y	Y
Supplement w 2nd step provide serological evidence of infection	Y	Y	Y
Negative results (1st or 2nd step) should NOT exclude infection	Y	Y	Y
SUMMARY			
Infection/current knowledge	Y	Y	Y
Development of AB response	Y	Y	Y
RESULTS	Y	Y	Y
Pos no results reported until 2nd step testing performed	Y	Y	Y
LIMITATIONS			
Low PPVw no history, symptoms or other findings	Y	Y	Y
PV in absence of 2nd test- may misdiagnose	Y	Y	Y
PERFORMANCE			
CDC Panel/other	Y	Y	Y
masked	Y	Y	Y
Stratified by time of collection after exposure & onset of symptoms	Y	Y	Y

OCTOBER 1997

FDA requests labeling changes:

"The information you have supplied, in response to the letter dated October 28, 1997 from FDA to manufacturers of Borrelia Burgdorferi antibodies testing devices requesting them to voluntarily make certain changes to the labeling of their devices, will be added to the file."



Records Processed under FOIA Request # 2019-4169; Released on 12-03-2019

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR 31 1999

Jonathan B. Knowles, Dr.P.H.
V.P. Regulatory Affairs
MarDx Diagnostics, Inc.
5919 Farnsworth Ct,
Carlsbad, CA 92008

Re: K894224
Device Name: MarDx B.burgdorferi EIA (IgM) Test System
Dated: September 15, 1998
Received: September 18, 1998

Dear Dr. Knowles:

We have reviewed the information dated September 15, 1998, regarding the 510(k) notification K894224 previously submitted for the device referenced above. Based solely on the information that you have provided, it does not appear that you have significantly changed or modified the design, components, method of manufacture, or intended use of the device referenced above (see 21 CFR 807.81(a)(3)). It is, however, your responsibility to determine if the change or modification to the device or its labeling could significantly affect the device's safety or effectiveness and thus require submission of a new 510(k).

The information you have supplied, in response to the letter dated October 28, 1997 from FDA to manufacturers of Borrelia Burgdorferi antibodies testing devices requesting them to voluntarily make certain changes to the labeling of their devices, will be added to the file.

Sincerely yours,

Woody DuBois

Woody DuBois, Ph.D.
Chief, Microbiology Branch
Division of Clinical
Laboratory Devices
Office of Device Evaluation

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TECHNICAL ISSUES WITH LABELING CHANGES: MarDx CASE STUDY

This is from the K894224 file for MarDx.

- Why was the highlighted item penciled in? Should require validation.

Add to File/Consistency with Oct. 28 letter re assays for detection of antibodies to Borrelia burgdorferi

Original K: 894224
ELISA/EIA/IFA IgM specific
Modifications: (see review)

Intended Use
- ✓ qualitative
- ✓ presumptive (first-step)
- ✓ sera from patients with history, signs or symptoms suggestive of infection with Bb
- ✓ supplement with second-step assay
- ✓ Positive 2nd step provide serological evidence of infection
- ✓ Negative results (either 1st or 2nd step) should not exclude infection

add within 1st month of suspected infection

Summary
- ✓ infection/current knowledge
- ✓ development of AB response

IgM useful during 1st month

Results ✓ Pos/eq -initial evidence with no results reported until 2nd step testing performed
Neg
- ✓ no detectable Abs specify IgM
- ✓ no R/O for infection

Limitations/Indications for use Tables/Summary
- * low NPV during early course of infection
- * low PPV in absence of 2nd step testing - likelihood of misdiagnosis and when testing patients with no history, symptoms or other clinical findings consistent with

Performance
- ✓ CDC panel/other
- ✓ masked
- ✓ stratified by time of collection after exposure/onset of symptoms

CHECKLIST

Ref: Add to File/Consistency with Oct. 28, 1997 letter re assays for detection of antibo
Borrelia burgdorferi

Sponsor: MarDx

Modifications:	K894293 IgG	K894224 IgM ✓	K892206 IgG/IgM
INTENDED USE			
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PERFORMANCE			
CDC Panel/other	Y	Y	Y
masked	Y	Y	Y
Stratified by time of collection after exposure & onset of symptoms	Y	Y	Y

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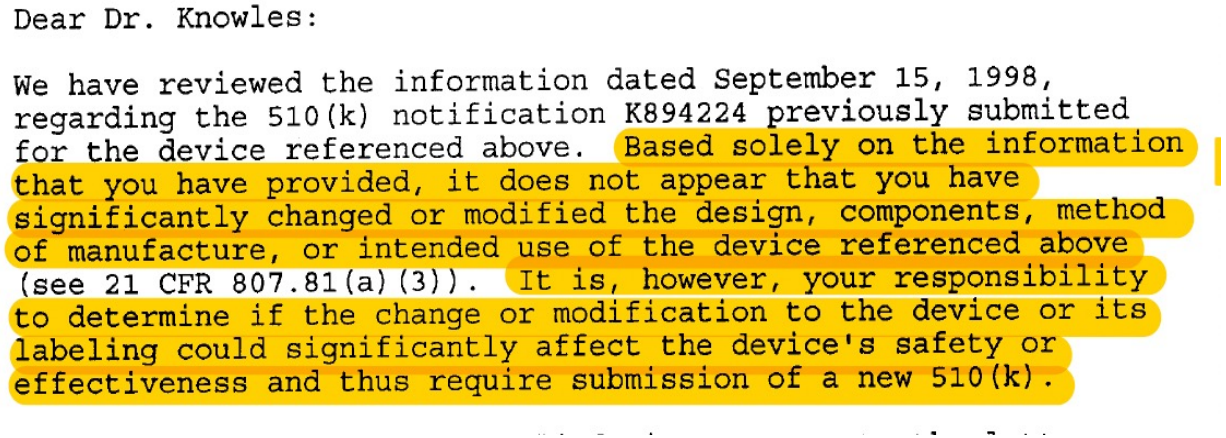
TECHNICAL ISSUES WITH LABELING CHANGES: MarDx CASE STUDY

This is from the K894224 file for MarDx.

- MarDx informed FDA of changes in addition to the Dearborn checklist.



Dear Dr. Knowles:

We have reviewed the information dated September 15, 1998, regarding the 510(k) notification K894224 previously submitted for the device referenced above. Based solely on the information that you have provided, it does not appear that you have significantly changed or modified the design, components, method of manufacture, or intended use of the device referenced above (see 21 CFR 807.81(a)(3)). It is, however, your responsibility to determine if the change or modification to the device or its labeling could significantly affect the device's safety or effectiveness and thus require submission of a new 510(k).

- Listed items DO modify the design of the device
- They changed the material for the conjugate and serum reagents
- they changed the calculations for cut off values
- they changed the wash procedure and stop times
- The changed from serial dilutions to a single dilution (may affect accuracy)

MARDX ADDITIONAL CHANGES

This is from the K894224 file for MarDx.

- They did change the performance specs (items 2, 4, 5, 6, 7, and 8)
- They admit they changed the specs to make it "simpler to use," which, today, would require validation.

There is no change in the intended use, no change in the indications for use, no change in the performance specifications and no change in the manufacturing and quality control specifications (except those relating to lyophilization).

All modifications were made following a design control process and have been determined not to have an adverse effect on the safety and effectiveness of the product. We feel that these changes will make the MarDx EIA Test System simpler to use for the laboratorian and eliminate some of the potential sources of user error.

Attached is the product insert that reflects the above modifications. If you have any questions please feel free to contact me directly.

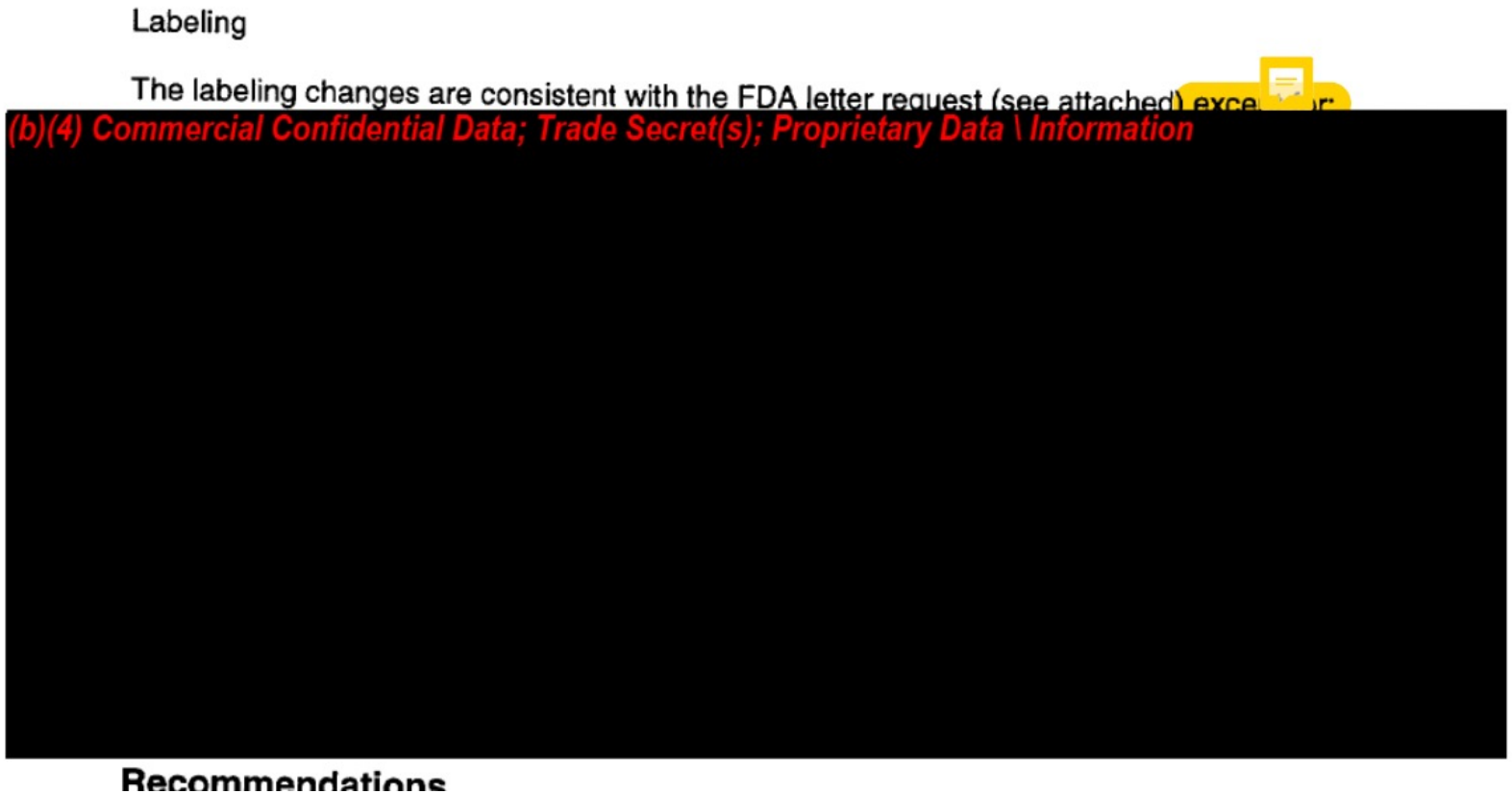
Sincerely,

Jonathan B. Knowles, Dr.P.H.
V.P. Regulatory Affairs
Phone: 800-331-2291
FAX: 760-929-0124
e-mail: jknow84243@sprynet.com

MARDX ADDITIONAL CHANGES

This is from the K894224 file for MarDx.

- What are the “exceptions” and why are they proprietary?



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MARDX ADDITIONAL CHANGES

This is from the K894224 file for MarDx.

- Design change

MarDx *B. burgdorferi* EIA (IgM) Test System.

Also, in accordance with the guidance document, "*Deciding When to Submit a 510(k) for a Change to an Existing Device*" (Jan 10, 1997, Flowchart D, p.32), MarDx wishes to inform the Office of Device Evaluation of changes made to the MarDx *B. burgdorferi* EIA IgM Test System which require documentation and addition to the file. Labeling changes have been made to reflect minor modifications that have been made in the test format as follows:

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MARDX ADDITIONAL CHANGES

This is from the K894224 file for MarDx.

- MarDx completed the checklist for Dearborn modifications and added these eight items.
- We believe item #5 refers to a change in cutoff value reported by Allen Steere in *Antibody responses to three genomic groups of Borrelia burgdorferi in European Lyme Borreliosis*, 1994, to exclude non-arthritis cases

Also, in accordance with the guidance document, "*Deciding When to Submit a 510(k) for a Change to an Existing Device*" (Jan 10, 1997, Flowchart D, p.32), MarDx wishes to inform the Office of Device Evaluation of changes made to the MarDx *B. burgdorferi* EIA IgM Test System which require documentation and addition to the file. Labeling changes have been made to reflect minor modifications that have been made in the test format as follows:

1. Lyophilized enzyme conjugate in this product will be supplied as liquid.
2. A static incubation step will replace the shaking incubation. There will be no change in temperature or timing of incubation.
3. Conjugate and serum reagents will be provided in plastic instead of glass vials.
4. Enzyme substrate provided as a one-part solution instead of two parts.
5. Calculations for mathematically determining the cut-off value have been refined to include index values and a correction factor. No change was made to the assay cut-off.
6. Assay wash procedure is simplified to 5 rinses without soaking from 3 rinses with soaking.
7. The maximum time between stopping the assay and spectrophotometric reading was reduced from 60 to 30 minutes.
8. The addition of goat anti-IgG (Marsorb G) to the controls and specimens, prior to testing, is performed in one dilution step instead of in two steps. The final concentration remains the same.

PERPETUATION OF THE MANIPULATED STANDARD

Twenty-seven years later:

- Nearly all subsequent FDA-cleared Lyme IVDs map back (“daisy chain”) to the MarDx diagnostics revised in 1998.
- The false diagnostic algorithm informs the standard of care authored by Infectious Diseases Society of America (IDSA).
- The same players authored the CLIA standards for Lyme testing, causing even deeper entrenchment in a faulty method.
- CDC Lyme Serum Repository (LSR) is screened using this method, therefore LSR samples cause the exclusion of non-arthritis cases from all research.

URGENCY TO RECTIFY INVALID LYME DIAGNOSTICS

This is history repeating.

- Lyme disease diagnostics are now even worse, as a “Modified Two-Tier Test” (MTTT) algorithm now is in place and likely will be used for efficacy trials of a new vaccine candidate from Valneva & Pfizer.
- The MTTT algorithm is more sensitive in the acute phase for HLA-linked Late Lyme Arthritis cases—not for the cases that have been excluded.
- We have contacted the FDA regarding these vaccine trials, which have been fast-tracked.
- The public continues to be harmed by the lack of a valid diagnostic.

HOW CAN THIS BE FIXED?

The problem is not that it is difficult to develop a properly validated test method that diagnoses arthritis and non-arthritis cases, but that the CDC serum repository has been reverse-engineered to reflect the artificially narrow case definition.

- We would like to continue to engage with the FDA as you investigate this matter
- Intra- and inter-agency cooperation is necessary
- We expect pushback from some insiders
- An acceptable replacement does not currently exist due to exclusion of non-arthritis cases by definition
- Prior to these events there were two flagellin-based tests developed (Yale, Abbott) that appeared sensitive/specific for ALL cases but those would need to be evaluated.

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HOW CAN THIS BE FIXED?

FDA must recognize the seriousness of this issue and take corrective action.

- Halt Valneva/Pfizer vaccine trials
- Investigate the events surrounding implementation of both the Standard Two-Tier Test method and the Modified Two-Tier Test method
  - Include all manufacturers that have cleared tests for this purpose (Zeus, Gold Standard Diagnostics, etc.
  - Issue recall-–no Lyme test is accurate

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ADDITIONAL DATA

This is not an exhaustive report, but merely an overview of the problem with diagnosing Lyme disease. We possess many documents in addition to those cited within this presentation and can share them as appropriate.

This report undoubtedly will raise more questions, and we are happy to address them as needed.

THANK YOU

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