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Conflicts of Interest in Lyme Disease: Laboratory Testing, Vaccination, and Treatment Guidelines

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Conflicts of Interest in Lyme Disease: Treatment, Laboratory Testing, and Vaccination

Lyme Disease Association, Inc.

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EXECUTIVE SUMMARY

For more than a decade, Lyme disease has been the object of debate. On one side are academicians, pharmaceutical companies, and government agencies, who claim the disease is usually mild and virtually always easily cured. On the other side are chronic Lyme disease patients and their doctors, who say that infection may survive the standard four weeks of antibiotic treatment, and that its impact may be debilitating and difficult to treat.

This report adds another dimension to the debate by focusing on Lyme disease as a business model. An examination of patents, marketing agreements, and revenue streams reveals the potential for the appearance of conflict of interest for many of the individuals setting Lyme disease policy. These policies, created in part to enable the analysis of data required for product approval, have also served to disenfranchise large numbers of infected patients no longer meeting the official standard for diagnosis with the disease. Untreated by physicians and uncovered by insurance companies, these patients have become increasingly ill. In the pages that follow we will detail the straightforward path of revenue and its relationship to multinational pharmaceutical companies, venture-backed biotechnology firms, government agencies, and academicians.

LDA hopes that Congress and other officials will study the information presented in this report as a springboard for their own review. Such review is of the utmost urgency because Lyme disease is the most rapidly spreading vector-borne infection in the United

States, prevalent not just in the Northeast, but in California, Wisconsin, Minnesota, and across the continental US. As long as the status quo is allowed to stand, large numbers of people exposed to this rapidly emerging infection will continue to go undiagnosed and untreated for Lyme disease, and will be placed at severe risk for lifelong health problems, including arthritis, neurological impairment, psychiatric illness, cardiac illness, gastrointestinal disease, and more.

Section I

Symptoms and Scope of Lyme Disease

Lyme disease is a multisystemic infection caused by a spiral-shaped bacterium, or spirochete, called *Borrelia burgdorferi*. It is most commonly transmitted to humans through the bite of an infected *Ixodes scapularis* or *Ixodes pacificus* tick in its ecosystem of choice--the shaded, woody areas of the suburban United States.

Though most people still associate Lyme with the single infection caused by the Bb spirochete, recent studies show it can be far more complex. Ticks that carry *Borrelia burgdorferi* may also carry co-infections such as *Ehrlichia* and *Babesia*, leading to a broader definition of Lyme disease in recent years.

“To me, Lyme disease is not simply an infection with *Borrelia burgdorferi*, but a complex illness potentially consisting of multiple tick-derived co-infections,” says Joseph J.

Burrascano Jr., M.D., whose *Diagnostic Hints and Treatment Guidelines for Lyme and Other Tick Borne Illnesses* now form a standard of care for many physicians in the field.

“In later stages, it also includes collateral conditions that result from being ill with multiple pathogens, each of which can have profound impact on the person's overall health. Together, damage to virtually all bodily systems can result.”

Geographic Penetration and Rate of Spread

Still most common in Northeast states like New York, New Jersey, Connecticut, and Massachusetts, Lyme disease is nonetheless spreading rapidly nationwide; it is already entrenched in a wide range of states from California and Wisconsin to Texas, Minnesota, and Florida, and has established footholds in the rest. Lyme disease is prevalent across the United States. Ticks do not know geographic boundaries. A patient's county of residence does not accurately reflect their total Lyme disease risk, since people travel, pets travel, and ticks travel. This creates a dynamic situation with many opportunities for exposure for each individual. Almost 15,000 new cases a year are reported in the United States, but those numbers are deceptively low, according to estimates from Yale University and elsewhere that some 90% of the cases meeting CDC research criteria are not reported, bringing the number of reportable cases to more than 1, 500,000 since 1980 and more than 130,000 in 1999 alone.

The Numbers at a Glance

Lyme Disease Cases Reported by State, 1995 – 1999^{i[1]}

	1995	1996	1997	1998	1999
Alabama	12	9	11	24	19
Alaska	0	0	2	1	0
Arizona	1	0	4	1	2
Arkansas	11	27	25	8	7
California	84	64	147	135	141
Colorado	0	0	0	0	0
Connecticut	1,548	3,104	2,205	3,434	2,302
Delaware	56	173	109	77	64
District of Columbia	3	3	10	8	6
Florida	17	55	56	71	57

Georgia	14	1	7	5	0
Guam	0	0	0	1	0
Hawaii	0	1	0	0	0
Idaho	0	2	4	7	5
Illinois	18	10	13	14	12
Indiana	19	32	33	39	21
Iowa	16	19	8	27	20
Kansas	23	36	4	13	12
Kentucky	16	26	18	27	19
Louisiana	9	9	6	15	11
Maine	45	63	12	78	41
Maryland	454	447	482	659	826
Massachusetts	189	321	290	699	999
Michigan	5	28	27	17	1
Minnesota	208	251	195	261	253
Mississippi	17	24	21	17	13
Missouri	53	52	28	12	28
Nebraska	6	5	2	4	11
Nevada	6	2	2	6	2
New Hampshire	28	47	37	45	26
New Jersey	1,703	2,190	1,933	1,911	966
New Mexico	1	1	1	4	1
New York	4,438	5,301	3,326	4,640	4,091
North Carolina	84	66	34	63	74
North Dakota	0	2	0	0	1
Ohio	30	32	40	47	78
Oklahoma	63	42	35	13	8
Oregon	20	19	20	21	14
Pennsylvania	1,562	2,814	2,062	2,760	2,312
Rhode Island	345	534	409	789	464
South Carolina	17	9	3	8	7
South Dakota	0	0	1	0	0
Tennessee	28	24	44	47	57
Texas	77	97	50	32	35
Utah	1	1	1	0	5
Vermont	9	26	8	11	24
Virginia	55	57	63	73	119
Washington	10	18	10	7	11
West Virginia	26	12	10	13	19
Wisconsin	369	396	478	657	117
Wyoming	4	3	3	1	3
	1995	1996	1997	1998	1999

Totals by Year	11,700	16,455	12,289	16,802	13,306
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*Montana will not accept reports until the *B. burgdorferi* spirochete has been isolated from two stages of infective tick.

According to Dr. Robert Schoen, clinical professor at Yale University School of Medicine, “the significant increase of cases of Lyme disease ... beginning in the early 1980s”^{ii[2]} represents the spread of Lyme disease from longtime endemic areas to adjacent geographical regions. “For example, in Connecticut in a 12-town region around Lyme, which is highly endemic for the disease, the number of cases over the past five years or so has been fairly stable. But throughout the rest of the state, we see many more cases in other counties, such as Fairfield County, Litchfield County, and New Haven County. And it is this geographic spread of the disease,” says Schoen, “which seems to result in these additional cases.”

“Several lines of evidence suggest that Lyme disease is very much underreported,” Yale University’s Robert Schoen told an FDA panel in 1998.^{iii[3]} “Data from Maryland as well as ... from Connecticut all point to the fact that perhaps only about 10 percent of cases ... are actually reported by physicians In a study done by Matthew Carter and associates at the Connecticut Department of Health, you can see that through an active surveillance, they identified about 1,000 cases among 400 physicians who maintain an active Lyme disease surveillance. With almost 11,000 practicing physicians in Connecticut, the number of cases reported was only about 10 percent of the expected reporting.”

Misdiagnosis

In addition to the 90% of Lyme cases Yale’s Dr. Schoen says are diagnosed but never reported to the CDC, there are those that simply go unrecognized. Many, including

frontline medical professionals, consider the patient report of a tick bite and a definitive “bull’s eye” rash as prerequisite for diagnosis. But fewer than 50% of patients with Lyme disease recall a tick bite. In some studies this number is as low as 15% in culture-proven Lyme borreliosis infection. Likewise, fewer than 50% of patients with Lyme disease recall citation any rash; and although the bull's eye presentation is considered classic, it is not the most common dermatological manifestation of early-localized Lyme infection. Atypical forms of this rash, taking on a large variety of forms, are seen far more commonly. It can last a few hours or up to several weeks. The rash can be very small or very large (up to twelve inches across), and can imitate such skin problems as hives, eczema, sunburn, poison ivy, fleabites, and so on. The rash can itch or feel hot or may not be felt at all. The rash can disappear and return several weeks later. For those with dark skin the rash may look like a bruise.

But most practitioners, even those in endemic areas, simply are unaware of the complexity and diverse presentation. Addressing a recent FDA hearing on antimicrobials for early Lyme disease,^{iv[4]} SUNY Stony Brook rheumatologist Raymond Dattwyler noted that in the heavily endemic area of Long Island where he himself works, practitioners, including pediatric infectious disease experts, regularly fail to recognize the EM. “One guy at our hospital was teaching the house staff that erythema migrans was always a flat lesion,” Dattwyler told the FDA, and “that if there was any edema in the lesion that it couldn't be erythema migrans.” Dattwyler pulled out some culture-positive lesions to show his SUNY Stony Brook colleague that, indeed, the EM rash could be raised as well, hopefully preventing any more young physicians in his charge from mastering the wrong set of facts.

Often, Dattwyler added, patients remain ill because physicians fail to recognize or diagnose “other tick-borne infectious diseases that are in these endemic areas.

Certainly, Babesia and Ehrlichia (HGE) are becoming more common. HGE and Babesia carriage rates in our ticks are quite high in the Northeast, so that it is not uncommon that 20 to 30 percent of the ticks that are infected with Borrelia have another pathogen, as well." If the co-infections are untreated, patients treated for Lyme alone may not get well.

The Great Imitator

When, due to these diagnostic errors, patients are treated insufficiently or not at all, they become extremely ill. Since the Lyme spirochete can infect virtually any organ in the body, it can mimic many other diseases. Called "The Great Imitator," it has been misdiagnosed as multiple sclerosis, Parkinson's disease, lupus, Alzheimer's, arthritis, amyotrophic lateral sclerosis (Lou Gehrig's disease), fibromyalgia, Guillain-Barré, and chronic fatigue syndrome, among others.

Several days or weeks after a bite from an infected tick, a patient usually experiences flu-like symptoms such as aches and pains in muscles and joints, low-grade fever, and/or fatigue. But no organ is spared. Other possible symptoms include:

- Jaw -- pain, difficulty chewing
- Bladder -- frequent or painful urination, repeated "urinary tract infection"
- Lung -- respiratory infection, cough, asthma, pneumonia
- Ear -- pain, hearing loss, ringing, sensitivity to noise
- Eyes -- pain due to inflammation, sensitivity to light, sclerotic drooping of eyelid, conjunctivitis, blurring or double vision
- Throat -- sore throat, swollen glands, cough, hoarseness, difficulty swallowing
- Neurological -- headaches, facial paralysis, seizures, meningitis, stiff neck, burning, tingling, or prickling sensations, loss of reflexes, loss of coordination,

MS-like syndrome

- Stomach -- pain, diarrhea, nausea, vomiting, abdominal cramps, anorexia
- Heart -- weakness, dizziness, irregular heartbeat, myocarditis, pericarditis, palpitations, heart blockage, enlarged heart, fainting, inflammation of muscle or membrane, shortness of breath, chest pain
- Joint -- arthralgias or arthritis, muscle inflammation and pain
- Other Organs -- liver infection, elevated liver enzymes, enlarged spleen, swollen testicles, irregular or ceased menses
- Neuropsychiatric -- mood swings, irritability, poor concentration, cognitive loss, memory loss, loss of appetite, mental deterioration, depression, disorientation, sleep disturbance
- Pregnancy -- miscarriage, premature birth, birth defects, stillbirth
- Skin -- single or multiple rash, hives

The symptoms may occur in any combination, in any sequence, and over any time frame.

Neuroborreliosis

Over the years doctors have discovered that Lyme disease, if not treated early or sufficiently, can trigger a host of neuropsychiatric symptoms as the spirochete disseminates throughout the central nervous system and the brain. Dr. Brian Fallon,^{v[5]} an associate professor of clinical psychiatry at Columbia University and director of the Lyme Disease Research Program at the New York State Psychiatric Institute, explained that the spirochete is quite efficient and can spread to the brain even before the "bull's eye" rash appears (if it does at all.)

Along with physical manifestations such as facial paralysis, shooting pains, numbness and tingling, the spirochete can cause cognitive problems (marked memory loss, confusion, and difficulty with concentration) and behavioral changes including mood

swings, extremely low frustration tolerance, and inability to deal with multiple stimuli like excessive noise or light.

"In rarer cases, patients may develop a full-blown manic episode where they become psychotic or they may have such severe memory problems that they appear to be demented," said Fallon. "The gamut of psychiatric problems most commonly consists of disturbances of mood accompanied by disturbances of sleep but also can be associated with fear that approaches paranoia and in rare cases, psychotic episodes."

Fallon recently completed a study which indicated that neuropsychiatric manifestations of Lyme in children produce symptoms similar to attention deficit disorder and may also be mistaken for laziness and behavioral problems because of the fatigue and personality disturbances associated with Lyme. "If Lyme disease isn't recognized, these kids may just appear to be bad kids when in fact they're not bad kids, they're just kids who are sick." According to Fallon, once Lyme infiltrates the brain cells, the infection becomes far more difficult to treat.

Section II The Scientific Debates

Knowledgeable professionals agree that when treated extremely early in the life cycle of their disease, most Lyme patients will get well. Professionals also agree that Lyme disease patients who have gone undiagnosed and now suffer later stage disease may continue to experience debilitating symptoms following a month-long course of antibiotics. All agree that these symptoms--arthritic, neurological, and multisystemic--can last for months, years, or throughout life.

Knowledgeable professionals across a wide range of disciplines also agree with the CDC position that Lyme disease must be initially diagnosed clinically, since no blood, urine, or

cell culture test is free of false negatives and false positives. While some contend Lyme is underdiagnosed and others that it is overdiagnosed, most recognized authorities believe that initial diagnosis of Lyme disease can be based on blood tests alone.

Common Misconceptions on the Part of Physicians

Even in the face of this consensus, misunderstandings abound. Particularly notable is the belief among many primary care physicians (even those in endemic areas) that, in the absence of a recollected tick bite and classic bull's eye rash, positive blood tests are required for diagnosis. This notion, widely held and practiced by local doctors, is contrary to guidelines established by the CDC, the NIH, and the Practice Guidelines for the Treatment of Lyme Disease from the Infectious Diseases Society of America.

The First Scientific Controversy: Persistence of Infection

Much of the medical mainstream, including the Yale-based physicians who originally studied Lyme disease, contend most cases can be successfully treated with 30 to 60 days of antibiotics, which they contend kills the Lyme spirochete. If symptoms continue, say these physicians, they are probably caused by something other than the Lyme bacteria. The condition they frequently cite is an ill-defined "post-Lyme" syndrome, resulting, theoretically, when Lyme disease inflicts permanent damage to the body's organs and immune system. Alternatively, they suggest, illnesses unresponsive to a month or two of antibiotic treatment are caused by an unrelated problem, like chronic fatigue syndrome, psychiatric illness, lupus, multiple sclerosis, or fibromyalgia. Moreover, these same physicians question long regimens of expensive antibiotics, labeling them as unnecessary and sometimes dangerous. The treatment protocols embraced by this group have been clarified in "The Practice Guidelines for the Treatment of Lyme Disease," produced by the Infectious Diseases Society of America (IDSA.) The Society is a medical and professional organization based in Alexandria, Virginia.

The very sickest patients, who almost universally continue to decline under such treatment protocols, have found their way to a group of clinicians and researchers whose studies and experience stand in powerful opposition to the findings and opinions at Yale. These doctors, including such experts as psychiatrist Brian Fallon of Columbia Presbyterian and Dr. Willy Burgdorfer, the National Institutes of Health scientist who discovered the Lyme spirochete, *Borrelia burgdorferi*, say that an audit of the peer-reviewed literature reveals no evidence that infection cannot survive the standard 4 weeks of antibiotic treatment. Instead, these clinicians and researchers contend, patients with continuing symptoms are usually ill because the *Borrelia burgdorferi* spirochete has never been eradicated from the body. Their views are best expressed by the International Lyme and Associated Diseases Society (ILADS,) a professional medical and research organization whose members include physicians with international reputations for treating chronic Lyme disease and related complications, including the co-infections. ILADS is based in Andover, Maine.

Evidence for Persistence

Mainstream, IDSA physicians support *only* short-term antibiotic protocols because, they point out, controlled, double-blind studies have not yet demonstrated any clearcut advantage to longer-term treatment in people who are chronically ill. One recent NIH study on long-term antibiotic treatment was halted, for instance, because on a planned break of the “blind” to check progress, auditors found no difference between test subjects and controls. Another NIH-funded study of long-term antibiotic treatment is still ongoing at Columbia University. While the results are not yet in, it may be that all such studies are problematic to one degree or another based on the range of co-infections,

known and unknown, and hundreds of borrelia sub-strains, each responding differently to the variety of antibiotics in the arsenal available today.

IDSA physicians resist this idea, pointing, instead, to studies suggesting that persistent symptoms may be due to autoimmune problems that continue even after the microbe has been killed. “Preliminary evidence suggests that relapsing symptoms in adequately treated patients with documented Lyme disease are more likely the result of tissue damage due to a possible autoimmune condition induced by the original infection,” according to the American Lyme Disease Foundation, the umbrella support group with many IDSA physicians on its board.^{vi[6]}

ILADS physicians, unique among practitioners for experience in wielding the range of different antibiotics, have found that trial and error is often the key to remission of symptoms; the medicines they use are not necessarily those but as is often the case in medicine, bending such flexibility to double-blind studies may be difficult, indeed.

Indeed, While double-blind studies of simple antibiotic protocols have been inconclusive, dozens of peer reviewed studies in microbiology and cell biology journals nonetheless indicate that active, ongoing spirochetal infection is the cause of the persistent symptoms in chronic Lyme disease. In fact, notes ILADS, there has never in the history of this illness been one study that proves even in the simplest way that 30 days of antibiotic treatment cures Lyme disease. However there is now an abundance of research from around the world showing that the Lyme disease spirochete can persevere.^{vii[7]} Much of it comes from scientists at institutions like Yale and Tufts.

In 1990, for instance, Tom Schwan and a team that included, among others, researchers from the Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases (NIAID,) part of NIH, found that “active cases of Lyme disease may show clinical relapse following antibiotic therapy. The latency and relapse phenomena suggest that the Lyme disease spirochete is capable of survival in the host for prolonged periods of time,” the report said. To determine this, they studied 63 patients with erythema migrans, the signature skin lesion of Lyme disease, removing the active edge of the rash for biopsy and examining growth in test tube cultures. “Sixteen biopsies yielded spirochetes after prolonged incubations of up to 10.5 months,” the team reported, “suggesting that *Borrelia burgdorferi* may be very slow to divide in certain situations.” Their conclusion: “Some patients with Lyme borreliosis may require more than the currently recommended two to three week course of antibiotic therapy to eradicate strains of the spirochete which grow slowly.”^{viii[8]}

In that same year, Allen Steere and team reported this finding: “Six months after a two-week course of intravenous ceftriaxone (2 g daily), 17 patients (63 percent) had improvement, 6 (22 percent) had improvement but then relapsed, and 4 (15 percent) had no change in their condition.” The interpretation? “These chronic neurologic abnormalities began months to years after the onset of infection, sometimes after long periods of latency, as in neurosyphilis,” the team reported in the prestigious *New England Journal of Medicine*. “The typical response of our patients to antibiotic therapy supports the role of spirochetal infection in the pathogenesis of each of the syndromes described here...The likely reason for relapse is failure to eradicate the spirochete...This is reminiscent of far advanced neurosyphilis... This last article is one of many studies that show continuing symptoms are most likely due to persistence of the spirochete.”^{ix[9]}

More evidence came in 1993, when V. Preac-Mursic of the University of Munich in Germany cultivated *Borrelia burgdorferi* from biopsies of the iris and skin as well as samples of cerebrospinal fluid after antibiotic therapy for Lyme borreliosis. Although the patients in this study, by and large, tested negative by Western blot--although they lacked diagnostic antibody titers—they still had subclinical or clinical disease. Concludes Preac-Mursic: “Persistence of *B. burgdorferi* cannot be excluded when the serum is negative for antibodies against it.”^{x[10]}

Also in that year, Mark Klempner of Tufts showed that *Borrelia burgdorferi* could settle within the fibroblasts of cells. Those same spirochetes, grown in fibroblasts cultured in a test tube and then treated with antibiotics, survived as well. Reported Klempner: “The observation of viable spirochetes within fibroblasts coupled to protection of *B. burgdorferi* from extracellular microbicidal antibiotics by fibroblasts suggests that *B. burgdorferi* may be among the small number of bacteria that can cause chronic infection by localizing within host cells where they remain sequestered from some antimicrobial agents and the host humoral immune response.”^{xi[11]}

In the past year, even more data has emerged. Cornell University scientist Rheinhard Staubinger, for instance, infected 16 dogs with *Borrelia burgdorferi* by tick bite. Four months (120 days) after tick exposure, 12 dogs were treated with antibiotics for 30 days while 4 control dogs were not treated at all. “At euthanasia, single tissues of the antibiotic-treated dogs and multiple tissues of all control dogs were *Borrelia*-positive by polymerase chain reaction,” Staubinger reports. “From this study and our previous

investigations, it appears likely that *B. burgdorferi* maintains a persistent infection with live organisms albeit at a very low level. ^{xiii[12]}

And Yale rheumatologist Stephen Malawista, a longtime collaborator with Allen Steere, has concluded that Lyme arthritis can virtually always be traced to either persistent infection or the antigenic waste left behind. “My thesis here is that patients will be free of Lyme arthritis, prolonged or not, when the last Bb has shown itself to the immune system

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and been killed, and its antigens have been biodegraded,” he writes. “Although it may prove to be wrong, I believe that this formulation best fits the clinical facts of Lyme disease, and may possibly direct our thinking along useful lines.”^{xiii[13]}

Persistence of Lyme disease following antibiotic treatment makes even more sense in light of recent findings from the fields of infectious disease, molecular evolution, genomics, and cellular biology:

1. 1. There are some 300 different strains of *Borrelia burgdorferi*. In experiments performed both in vivo and in vitro and presented in the peer-reviewed literature, it has been shown that different strains respond differently or not at all to the host of antibiotics used to treat Lyme disease. It therefore makes sense that patients--especially those with late-stage disseminated disease--may need rounds of more than a single antibiotic for a single month to get well. ^{xiv[14]}
1. 1. About 30% of the ticks carrying the *Borrelia burgdorferi* spirochete also transmit other microbial diseases, including *Ehrlichia*, *Bartonella*, *Rickettsia*, and *Babesia*.

Although some medications may be useful for treating *Borrelia burgdorferi* alone, they may be ineffective against the co-infections. For instance, amoxicillin will be ineffective against *Ehrlichia* (which requires doxycycline or another antibiotic in the tetracycline family) as well as *Babesia* (often treated with Mepron.) Because an untreated co-infection can persist and produce severe symptoms even if *Borrelia burgdorferi* is eradicated, and because multiple infections coexisting infections may interact, co-infections can complicate the clinical picture. Given these facts, say the clinicians, it is easy to see why a month of low-dose doxycycline or amoxicillin might fail to do the trick when tick-borne disease has been undiagnosed and untreated in an individual for years. This commonsense approach is borne out in practice, as physicians utilize longer-term treatments in a variety of combinations before seeing results.^{xv[15]}

1. 1. Microbiologists say that *Borrelia burgdorferi* has the genetic capacity to express an elaborate, variable, and rapidly-changing complement of “lipoproteins.” Structured like lipid-protein sandwiches, lipoproteins present in abundance confer microorganisms with the ability to change form and function depending upon the environment. As the environment changes from deer to tick to human, from blood to muscle to brain, *Borrelia burgdorferi* can produce a cascade of lipoproteins (or antigens) best suited to its current niche and survival.^{xvi[16]}
1. 1. According to one theory still under investigation, *Bb* spirochetes under environmental stress lose their cell walls, becoming resistant to conventional antibiotics. One line of research suggests that when under pressure from its

environment, the Lyme disease spirochete loses its cell wall. In doing so, it becomes resistant to the majority of antibiotics, which are engineered to work by attaching to bacterial cell walls. Scientists who have observed this process in test tubes report that cell-wall-deficient Bb spirochetes exist as tiny “L” forms able to hide within cells, and also collect en masse to form spirochete generators known as “cysts.” The L-forms and cyst forms are said to generate more cell-wall-deficient spirochetes that continue to disseminate throughout the body’s tissues and hide inside cells. When a given environmental stressor --including antibiotic therapy is halted, the spirochetes may come out of hiding and revert to conventional, cell-walled forms. Clinicians say they can treat the cell-wall-deficient forms of the Lyme disease spirochete with Flagyl, an antibiotic that causes them to convert to cell-wall forms, which are vulnerable to conventional antibiotics. The L-cyst phenomenon, when and if proven in vivo, will help explain the etiology of chronic Lyme disease.^{xvii[17]}, ^{xviii[18]}

1. 1. *Borrelia burgdorferi* is undergoing a period of rapid evolution, according to molecular biologists at the University of Utah Medical School, the London School of Hygiene and Tropical Medicine, and The Institute for Genomic Research in Rockville, Maryland. Numerous recent arrangements of DNA have left many genes in a state of “serious mutational decay,” the researchers have reported, making *Borrelia burgdorferi* one of the most volatile and unpredictable pathogens in our midst.^{xix[19]}

How to put all this in perspective? Dr. Kenneth B. Liegner, a nationally noted Lyme disease expert in Armonk, New York, says these findings “reveal the deficiencies of the existing paradigm for Lyme disease, have been very hard for the medical community to

reconcile, and presage a revolution in our conceptualization of this disease. These observations lead one to the conclusion that certain subsets of patients with Lyme disease may require prolonged antibiotic treatment and that presently available chemotherapeutic modalities may be suppressing but not eradicating the infection. Thus, individuals who have demonstrated relapses following aggressive treatment may require an open-ended antibiotic approach provided that they are deriving clinical benefit and not experiencing any adverse effects and that they wish to be treated.” xx[20]

The Second Scientific Controversy: Underdiagnosis or Overdiagnosis

The second controversy involves the question of diagnosis: Those working in academia and conducting clinical trials for pharmaceutical companies and government tend to
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assert that Lyme disease is overdiagnosed, while hands-on Lyme clinicians say it is underdiagnosed.

The issue is critical. If a doctor sees Lyme disease as underdiagnosed and thus treats all comers, the actual diagnosis might remain unrecognized and untreated while unnecessary use of antibiotics might lead to antibiotic-resistant infections in the human blood reservoir at large. On the other hand, if a doctor sees Lyme disease as overdiagnosed and thus hesitates to treat, patients will go on to develop late stage, disseminated Lyme disease. Tens of thousands of Americans are tragic testimony to option number two. By the time such individuals are finally diagnosed, they are often simply too sick to respond to a single month of antibiotics. Either they must accept the guidelines of IDSA and Yale physicians that they now have the incurable and debilitating autoimmune disorder known as “Post-Lyme Syndrome,” or they must find a physician who believes that longer-term

antibiotic treatment at a higher dose may eradicate the spirochete that conventional therapy could not.

The overdiagnosis-underdiagnosis debate and the issue of chronicity are key to the quagmire of Lyme disease politics and the conflicts of interest that result. The reason is this: Redefinition in these areas was a prerequisite for launch of Lyme disease products, including vaccines and diagnostic tests. Because the issues resulting in ethical conflicts are complex, we'd like to walk you through them chronologically, with a brief history of Lyme disease itself.

Section III

The History of Lyme Disease: A Story of Medicine and Politics

Physicians in Europe identified Lyme disease more than a hundred years ago. But for most of the past 30 years, the center of mainstream Lyme research has been Yale University, home to the US doctor who identified "Lyme arthritis" in 39 children and 12 adults following notable reports from two Connecticut mothers. That physician, Dr. Allen Steere, went on to make the disease the hallmark of his career. Working with Yale associates like Dr. Stephen Malawista, Dr. Robert Schoen, and Dr. Eugene Shapiro, Steere proved the Connecticut syndrome--named for its epicenter in the town of Lyme--was caused by the bite of an Ixodes tick. Years later, government scientist Willie Burgdorfer of the Rocky Mountain Laboratories discovered that the tick transmitted Lyme disease through a spirochetal bacterium, *Borrelia burgdorferi*, named after its discoverer.

Lyme Disease and Diagnosis

But though the critical microbe had been found, the effort to diagnose Lyme remained a challenge, in large part due to the absence of a gold standard laboratory test--one that could culture *Bb* spirochetes from the blood. Sparse in number and generally found in tissue instead of the blood, *Bb*, it turned out, could be detected only indirectly, through the immune response as measured by tests like ELISA (an acronym for enzyme-linked immunoabsorbent assay) or Western blot.

As indirect tests, both the ELISA and the Western blot measure the immune system's response to an infectious agent rather than looking for components of the agent itself. In a Lyme disease ELISA, antigens (proteins that evoke an immune response in humans) from *Borrelia burgdorferi* are fixed to a solid-phase medium and incubated with diluted preparations of the patient's serum. If antibodies to the organism are present in the patient's blood, they will bind to the antigen. These bound antibodies can then be detected when a second solution, which contains antibodies to human antibodies, is added to the preparation. Linked to these second antibodies is an enzyme, which changes color when a certain chemical is added to the mix.

Although the methodology is somewhat complicated, the basic principle is simple: the test looks for antibodies in the patient's serum that react to the antigens present in *Borrelia burgdorferi*. If such antibodies exist in the patient's blood, this finding is an indication that the patient has been previously exposed to *B. burgdorferi*.

However, many different species of bacteria can share common proteins. Most Lyme disease ELISAs use sonicated whole *Borrelia burgdorferi*--*B. burgdorferi*

cells broken down with high frequency sound waves--as the antigen in the test. It is possible that a given patient's serum can react with the *B. burgdorferi* preparation even if the patient hasn't been exposed to Bb, perhaps because Bb shares proteins with another infectious agent that the patient's immune system has encountered. For example, some patients with periodontal disease, which is sometimes associated with an oral spirochete, might test positive on a Lyme ELISA, because their sera will react to components of Bb (like the flagellar protein, which is shared by many spirochetes) even though they themselves have never been infected with Bb.

Therefore, some positive Lyme disease ELISA results can be "false" positives.

To distinguish the false positives from the true positives, the Western blot (also known as an immunoblot) is used. In this test, the laboratory looks for antibodies directed against a wide range of Bb proteins. This is done by first disrupting Bb cells with an electrical current and then "blotting" the separated proteins onto nitrocellulose, nylon, or other synthetic membranes. The current causes the proteins to separate according to their mass, measured in kilodaltons (kDa). From here on, the procedure is similar to the ELISA--the various Bb antigens are exposed to the patient's serum, and reactivity is measured the same way (by linking an enzyme to a second antibody that reacts to the human antibodies). If the patient has antibodies to a specific Bb protein, a "band" will form at a specific place on the immunoblot. For example, if a patient has antibodies directed against Outer Surface Protein A (OspA) of Bb, there will be a WB band at 31 kDa. By looking at the band pattern of patient's WB results, the lab can determine if the patient's immune response is specific for Bb.

A layer of complexity is added to analysis because the Western blot report usually contains two parts: IgM and IgG. These are immunoglobulins (antibody proteins) produced by the immune system to fight infection. IgM is produced fairly early in the course of an infection, while IgG response comes later. Some patients might

already have an IgM response at the time of the EM rash, although that is uncommon. The IgG response, according to the traditional model, tends to start several weeks after infection and peak months or even years later. In some patients, the IgM response can remain elevated; in others it might decline, regardless of whether treatment is successful. Similarly, IgG response can remain strong or decline with time, again regardless of treatment. Most WB results report separate IgM and IgG band patterns and the criteria for a positive result are different for the two immunoglobulins.

In establishing a nationwide standard for a positive WB, one must make several assumptions--that all 300 strains of Bb will provoke similar immune responses in all patients, that all patients will mount a measurable immune response when exposed to Bb, and that the IgG immune response will persist in an infected patient. Assuming normal amounts of variation found in nature, it is a given that unusual banding patterns will occur.

Raising the Bar

Back in what now seems like the prehistory of Lyme disease testing, the year 1991, these unavoidable variables were magnified by a system mired in chaos. There was, at the time, no agreed-upon standard for what constituted a positive Western blot. Different laboratories used different antigen preparations made from different strains of the Bb spirochete to run the test. Thereafter, they also interpreted the results differently. Some required a certain number of bands to constitute a positive result, while others required more bands or less. Some felt that certain bands should be given a higher priority than others.

Into the void in 1993 stepped rheumatologist Allen Steere, by then a professor at Tufts University in Boston. In a study^{xxi[21]} published in February of that year with Frank Dressler and colleagues from Germany, he performed immunoblots on several dozen patients with well-characterized Lyme disease and a strong antibody response. By looking at the resulting blot patterns and doing some fairly involved statistical analysis, the team determined which bands showed up most often and which best distinguished Lyme disease patients from control subjects who did not have Lyme disease.

They found that by requiring 2 of the 8 most common IgM bands in early disease and 5 of the 10 most common IgG bands after the first weeks of infection, they could make the results the most specific, in their view, without sacrificing too much sensitivity.

("Sensitivity" means the ability of the test to detect patients who have the disease; "specificity" means the ability of the test to exclude those who don't. Usually, an increase in one of these measures means a decrease in the other.)

Steere later tested the theory in a group of 237 patients seen in a diagnostic Lyme disease clinic and in 74 patients with erythema migrans or summer flu-like illnesses. He reported that the IgM blot had a sensitivity of 32% and a specificity of 100% in early disease; after the first weeks of infection, the IgG blot had a sensitivity of 83% and a specificity of 95%.

The study also suggested using Western blot to check ELISA. Among patients with indeterminate IgG responses by ELISA, Steere found, 6 of 9 with active Lyme disease had positive blots compared with 2 of 34 patients with other illnesses. On the surface, the study seemed to bring order to chaos. But to the community of Lyme physicians treating late-stage patients, Steere's report was problematic.

For one thing, according to ILADS experts,^{xxii[22]} he gave equal weight to each band included, whether the band was specific to Lyme disease or not. This flew in the face of a

general consensus that different bands on a Western blot have different relative importance. Many Lyme patients, for instance, show reactive bands at 60 and/or 66 kDa. But these bands correspond to common proteins in many bacteria, not just *Borrelia burgdorferi*, and so are of limited diagnostic usefulness, especially in the absence of other, more species-specific bands. The band at 41 kDa corresponds to Bb's flagella, the whiplike organelles used for locomotion, and is one of the earliest to show up on the Western blots of Lyme disease patients. But it is also the most commonly appearing band in control subjects, probably because people are exposed to a variety of spirochetes throughout life and so their sera might cross-react with this protein.

Yet in the Steere/Dressler study, these bands were weighted on a par with species-specific bands at 83, 94, and even 23-25 kDa (the highly expressed OspC.) ILADS scientists and many other doctors believe that any patient whose IgM or IgG Western blot exhibits bands at, say, any three (or even two) of these locations most likely has been infected with *B. burgdorferi*, regardless of whether any other bands are present. They feel that these bands on a Lyme Western blot are simply more meaningful than other, less specific ones and that a rational interpretation of a WB result should take this into account.^{xxiii[23]}

Another issue was the type of patient Steere had used to generate results. As a rheumatologist, it was only natural that his patients present with a frank arthritis of Lyme, often with a swollen joint. His subset of rheumatology patients seemed to fit a specific profile in that virtually all had EM lesions and made significant antibody. But the study did not include patients from other disciplines, including those who might show up at the office of a gastroenterologist, neurologist, or ophthalmologist. Indeed, since Lyme is multisystemic, it can manifest its symptoms in any one of these areas, and it has long

been noted that the profile—including the immunological profile—differs to some extent based on the set of presenting symptoms.

Even more puzzling was the omission from consideration of bands at 31 and 34 kDa, corresponding to OspA and OspB, among the most species-specific proteins of the organism. Often absent in early disease, Osps A and B tended to come into prominence as patients become increasingly ill. Although the absence of either of these bands from a patient's immunoblot did not rule out Lyme disease, their presence was hardly meaningless.

Finally, a couple of months thereafter Steere published a paper^{xxiv[24]xxv[25]xxvi[26]} on overdiagnosis of Lyme disease in the *Journal of the American Medical Association*. Of the 788 patients seen at his clinic, Steere wrote, 180 (23%) had active Lyme disease, usually arthritis, encephalopathy, or polyneuropathy. One hundred fifty-six patients (20%) had previous Lyme disease and another current illness, most commonly chronic fatigue syndrome or fibromyalgia. And the remaining 452 patients (57%) did not have Lyme disease at all. “Of the patients who did not have Lyme disease, 45% had had positive serological test results for Lyme disease in other laboratories,” Steere wrote, “but all were seronegative in our laboratory. Prior to referral, 409 of the 788 patients had been treated with antibiotic therapy. In 322 (79%) of these patients, the reason for lack of response was incorrect diagnosis.” His conclusion: “Only a minority of the patients referred to the clinic met diagnostic criteria for Lyme disease. The most common reason for lack of response to antibiotic therapy was misdiagnosis.”

This paper has been critiqued formally on a number of fronts. Especially notable are complaints from numerous ILADS physicians as well as the chemist Carl Brenner, one of two patients sitting on the National Institute of Allergy and Infectious Diseases (NIAID)

Advisory Committee for Clinical Studies on Chronic Lyme. Problems most frequently cited follow, below:

1. 1. **Claims to Superior Serology not Proven:** Steere reported that 98% of the patients (176 out of 180) found to have active Lyme disease, but none of the patients (0 out of 452) who had never had Lyme disease but who were evaluated for suspected Lyme at his clinic were seropositive by enzyme-linked immunosorbent assay (ELISA) and/or Western blot *in his lab alone*. If so, it would mean he had developed a test far beyond the state of the art for 1993, not to mention today. Indeed, he claimed that of 452 patients in the study who were determined to have never had Lyme disease, 203 (45%) had obtained "false" positive results from *another* laboratory. It is difficult to accept uncritically his claim that the antibody testing protocols he uses are so far and away superior to any other without the same independent testing other labs are subjected to. The reasoning is circular: The presumption is that his tests are superior because they render the highest correlation between seropositivity and actual Lyme disease, but the definition of "actual Lyme disease" in the study is derived almost exclusively from the test results generated at his lab.
2. 2. **Nearly exclusive reliance on serologies for diagnosis.** Although false negative serologies are widely recognized as common in early Lyme disease, it is often claimed that they are extremely rare phenomena later in the course of the illness. The many cases of seronegative, culture-positive "late" Lyme disease that have been identified and reported, however, make this claim untenable. ^{xxvii[27]} ^{xxviii[28]}
^{xxix[29]} ^{xxx[30]}
3. 3. **A history of exposure in an area where *B. burgdorferi* has been recovered from ticks required for a diagnosis.** This approach systematically excludes all patients from areas that have not been investigated for *B. burgdorferi*

infestation. In light of the fact that thousands of clear-cut cases of Lyme disease, complete with physician-verified erythema migrans, and/or clinical findings and positive serologies, have been reported from "nonendemic" and unstudied areas, such a restriction is inappropriate.

4. 4. **Response to treatment required for diagnosis:** Of the patients thought to have active Lyme disease, at least 52 had already been antibioticly treated before evaluation by the authors. Nonetheless, under the study protocols, lack of responsiveness to antibiotic therapy is a primary criterion for the determination that active Lyme disease is not present: Indeed, the scientists diagnosed fibromyalgia as opposed to Lyme disease solely on the basis of response or lack of it to antibiotic therapy—even though every one of the primary symptoms associated with fibromyalgia or chronic fatigue syndrome (persistent headache, fatigue, myalgias, arthralgias, sleep disturbance, etc.) are common in active Lyme disease and cannot be used for differential diagnosis.
5. 5. **Refusal to recognize treatment failure or relapse.** The paper states that temporary relapse following treatment is, in fact, the placebo effect that occurs when patients without real Lyme believe they are responding to medication. It also states that 20% of the study population had real Lyme that was cured by treatment but then went on to develop a variety of other illnesses, virtually all of which had identical symptoms to active Lyme disease. These conclusions ignored another interpretation-- that borreliac infection persisted after antibiotic treatment--even though culture-confirmed treatment failures now abound in the medical literature, sometimes even after long-term, high-dosage antibiotic therapy.^{xxxi[31] xxxii[32] xxxiii[33] xxxiv[34]}
6. 6. **Use of psychiatric symptoms to exclude the diagnosis of Lyme disease.** Controlled studies have indicated that a high percentage (66%) of seropositive Lyme disease patients report an episode of major depression during the course of their illness, most (90%) for the first time.^{xxxv[35]} A wide variety of minor

and major psychiatric disorders have been reported in Lyme disease,^{xxxvi[36] xxxvii[37]}
^{xxxviii[38]}similar to the findings in neurosyphilis .

Despite such objections, the viewpoint expressed in Steere's "Overdiagnosis" paper prevailed. It would, from the moment it was published, serve as a guide to family practitioners and pediatricians across the United States. For patients with late-stage, disseminated Lyme disease as well as those who just didn't respond to the traditional, four-week course of oral antibiotic, the results were disastrous. Although these patients often tested positive on DNA tests based on amplification of genetic material from blood or urine, and although they often showed immune response to Osp A and Osp B, they would not meet the standard for diagnosis set by Steere.

Section IV

Watershed At Dearborn

The watershed event making the redefinition of Lyme disease official occurred a year later, in Dearborn, Michigan, at the Second National Conference on Lyme Disease Testing, sponsored by the Association of State and Territorial Public Health Laboratory Directors (ASPHLD), the US Centers for Disease Control and Prevention (CDC), and the Michigan Department of Health, and co-sponsored by the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Council of State and Territorial Epidemiologists, and the National Committee for Clinical Laboratory Standards. It was at this pivotal meeting that Steere's reports (supplemented by others

based on patient cohorts with Lyme arthritis as well as neuroborreliosis) were accepted as the official surveillance criteria for Lyme disease by the CDC. To be accepted as an official case of Lyme disease for surveillance or research purposes, the committee decided, a patient would need to register positive or equivocal on an ELISA and then pass the acid test--light at least 2 of 3 IgM bands or 5 of the 10 IgG bands on the Western blot. Although these standards were not meant to serve as basis for diagnosis, participants like Nick Harris, president of IgenX, feared that the to general practioner, the distinction would not be clear. Recalling such concerns even back then, Harris reports the following points debated from the Conference floor^{xxxix[39] xl[40]}:

Point 1: Use of a fast and inexpensive ELISA test to prequalify patients for a definitive Western blot. If ELISA was negative, there would be no Western blot. If equivocal or positive, physicians would then go on to conduct the Western blot for definitive diagnosis.

The problem with this: ELISA has too many false negatives as well as false positives to act as a gateway for diagnosis. Studies conducted by the group responsible for Lyme disease proficiency testing for the College of American Pathologists (CAP), for instance, concluded that the currently available ELISA assays for Lyme disease do not have adequate sensitivity to be part of the two-tiered approach of the CDC/ASPHLD, where only ELISA-positive samples can be tested by Western blotting^{xli[41]}. And Dr. Alan Barbour had this to say about the ELISA in his application for US Patent # 5,582,990^{xlii[42]} ^{xliii[43] xliiv[44]}, filed with the US Patent Office just three weeks before he cast his vote as a member of the Planning Committee at Dearborn: “Conventional diagnostic tests for Lyme disease have used whole spirochaetal sonic extracts as test antigens in ELISA to detect antibodies to *B. burgdorferi*, but this test yields unsatisfactory low diagnostic sensitivity (20 to 60%) during the early stage of infection, ^{xliv[45] xlii[46]}possibly due to a

slow and late-appearing antibody response and to the inclusion of irrelevant cross-reacting antigens in the whole-cell preparations.”

Point 2: If an ELISA is equivocal or positive, look for 2 out of 3 accepted IgM bands on a Western blot to diagnose Lyme disease a month or less after the tick bite.

The problem with this: Studies from a number of research groups, including Allen Steere himself, found that IgM bands are important not just in the first month after the tick bite, but also thereafter. In cases of chronic or resistant Lyme, the IgG response is often nonexistent, and only the IgM remains. ^{xlvii[47]}, ^{xlviii[48]}, ^{xlix[49]}

Point 3: If an ELISA is equivocal or positive, look for 5 out of 10 acceptable IgG bands to diagnose Lyme disease a month or more after the tick bite.

The problem with this: Engstrom et al^{i[50]} and Aguero-Rosenfeld et al^{ii[51] iii[52]} confirmed that almost one-third of all Lyme patients are IgG negative during the first year. The Engstrom study also found that of those patients who DID express antibody, higher sensitivity and specificity --100% and 93-96%, respectively--could be achieved with criteria based on recognition of 2 of 5 IgG bands. It is notable that one author of the Engstrom study was Russel Johnson, a voting member of the Dearborn Planning Committee.

Point 4: Significant bands accepted by the planning committee specifically did not include those representing OspA or OspB.

The problem with this: OspA and OspB are so specific to the species *Borrelia burgdorferi* they should, according to a significant body of peer-reviewed literature, be considered significant when detected by Western blot. Indeed, attendees at the Dearborn conferences had published widely in this area. Writing in the *Journal of Clinical Investigation* in 1994, participant Steven Schutzer noted that “OspA has rarely been

detected less than 6 months after infection.” His paper went on to show, however, that the protein was merely bound up in immune complexes, present but unexpressed, from the earliest days of the erythra migrans rash. Yet another Planning Committee member, Raymond Dattwyler of Stony Brook, had just published an article on using OspA for Lyme disease diagnosis in Western blot.^{liii[53]} “Further resolution of the epitope specificity to determine humoral and cellular immune responses to OspA has implications for vaccine development and for the utility of this protein as a reagent in diagnostic testing for Lyme borreliosis,” Dattwyler wrote in July of 1994, just 3 months before the Dearborn meeting. His obvious suggestion: using a recombinant form of Osp-A for diagnosis. “A few years earlier, Planning Committee member Barbour had found that OspA and OspB were useful diagnostic markers for patients in Sweden.^{liv[54]} Both researchers nonetheless signed on to the plan for removing OspA from CDC criteria at Dearborn.

One reason it was important to define a case definition for Lyme disease was upcoming evaluation of two Lyme disease vaccines,^{lv[55]} planned for release by SmithKline Beecham Biologicals, Reixensart, Belgium; and the French and Canadian group of Pasteur Mérieux Connaught. Invented at Yale University in New Haven, the first generation vaccine was designed around OspA. Second generation vaccines might include OspB as well.

Point 5: The Planning Committee failed to accommodate a number of well-established and undisputed scenarios under which an infected individual might mount no immune response.

The problem with this: Individuals who clearly had Lyme disease but did not mount a strong immune response would not be diagnosed with, and thus treated for, the disease. A

1988 paper by Raymond Dattwyler and Russell Johnson, both voting members of the Planning Committee, for instance, showed that when Lyme is treated early but insufficiently, the antibiotic will abrogate the human immune response to *B. burgdorferi*.^{lvi[56]} Indeed, a more recent study from the same two authors shows that a majority of patients who fail early treatment and suffer clinical relapse are seronegative at the time of relapse.^{lviii[57]} Writing in 1990 in *Lancet*, Steven Schutzer showed that patients with Lyme disease may not test positive for exposure to *B. burgdorferi* because their antibodies to the organism are bound up in immune complexes.^{lviii[58]} Once steps are taken to dissociate these immune complexes, free antibody can be detected; however, this is not routinely done when performing serologic tests for Lyme disease.

Point 6: Reluctance to give appropriate credence to DNA-based diagnostic tests.

The problem with this: A significant body of literature shows the value of PCR technology. Studies by Goodman et al. found that 30% of their patients with early Lyme disease were positive by PCR.^{lix[59]} This percentage is comparable to blood culture data by others.^{lx[60]} Although some studies were unable to achieve PCR positive results from a percentage of patients with acute Lyme disease,^{lxi[61]} this was frequently contingent upon the status of antibiotic therapy. Manak et al. were able to detect 33% of early Lyme and 50% of late stage Lyme disease in patients not on antibiotic therapy.^{lxii[62]} Most of their patients became PCR negative within two weeks of commencing antibiotic therapy. They also found that during a relapse, patients might become PCR positive for a short period. Finally, using a combination of genomic and plasmid PCR, Bayer et al.^{lxiii[63]} found that 74% of patients with chronic (persistent) Lyme disease were PCR positive in urine samples. Indeed, writing in the *Journal of Clinical Microbiology* in 1989, Dearborn Planning Committee member Russell Johnson reported on "detection of antigens in urine

of mice and humans infected with *Borrelia burgdorferi*, etiologic agent of Lyme disease."^{lxiv}[64]

By the end of 1994, there existed two sets of divergent opinions from the same experts. One set was, for the most part, published in medical and scientific journals. The other set was, for the most part, handed down by official committee decree.

Reflecting on the Dearborn meeting, Nick Harris, Ph.D., President of IgeneX, a California laboratory that tests for Lyme disease, has this to say: "Although discussion of all these points occurred during the meeting, many observers felt that the planning committee's criteria and the conclusions to the meeting were predetermined, and that dissenting views were not seriously considered." "Most Planning Committee members said they would treat a patient with clinical signs and symptoms of Lyme disease, even if they had only 3 or 4 positive bands," Harris recalls. But the Committee did not seem to realize how difficult they were making that choice for the physician in an HMO, PPO, or even in private practice."^{lxv}[65]

Harris' worry has been borne out. Although the CDC and NIH insist that Lyme remain a clinical diagnosis, the Dearborn criteria has nonetheless been embraced by local physicians looking for cut and dried insight into this confounding disease. By imposing such rigid and questionable immunological markers on this complex and little-understood disease, the Planning Committee unilaterally refined a subset of Lyme patients out of existence. In the process, they redefined the disease itself. The Planning Committee also set the stage for a level of circular reasoning: If official studies of Lyme disease could now enroll only seropositive patients meeting the Dearborn criteria, then those studies would, de facto, reinforce the Dearborn profile and the requirements on which it was

based. It was a seemingly impenetrable wall of logic that excluded the sickest of patients, leaving their physicians outside the circle of acceptability required to integrate data of their own.

For those with chronic Lyme, the events of 1993 and 1994 were disastrous. Without OspA or OspB to serve as markers, many of those with the most chronic and hard-to-treat forms of Lyme disease no longer met *any* diagnostic standard. Likewise, “seronegative” patients could not be counted, even if physicians were able to find *Borrelia burgdorferi* DNA through genetic amplification techniques like PCR (polymerase chain reaction). Because many neurological symptoms were dismissed as psychiatric, those with neuroborreliosis found it difficult to get a diagnosis as well. Finally, even patients who met all the standards were told that if they had not recovered after four weeks of antibiotic therapy, it just wasn’t Lyme. Left to relapse without retreatment they joined their unfortunate brethren in the ranks of chronic disease.

Taking a skeptical approach to diagnosis, the new view asked physicians to accept that treatment failures virtually never occur, that those with real Lyme disease are rarely seronegative, that Lyme Lyme should rarely be diagnosed in patients without significant exposure in endemic areas, and that psychiatric symptoms may be used to exclude the Lyme diagnosis. This was a special trap for late stage patients, who often manifested psychiatric and neurological symptoms, and often expressed only OspA or B, or, frequently, no serological marker at all.

A year later, the new, circumscribed criteria seemed at odds not just with the views of vocal critics like Harris, but with the Dearborn architects themselves. Addressing the Senate Committee on Labor and Human Resources on October 18, 1995, ^{lxvi[66]} Dr. Allen Steere, lead investigator for the SKB vaccine, Lymerix, and author of the paper that

rendered the Dearborn Criteria, had this to say: “No serologic test distinguishes between active and past infection, and tests that identify the spirochete itself are greatly needed. ... Some patients continue to have symptoms after treatment. This is particularly troublesome since recent research has shown that the Lyme disease spirochete may sometimes persist in the nervous system for many years, as with the spirochete that causes syphilis. In addition, a genetically susceptible subset of patients with Lyme arthritis continues to have joint inflammation despite treatment with multiple courses of oral or intravenous antibiotics.”

And writing in his 1996 book, *Lyme Disease: The Cause, the Cure, the Controversy*,^{lxvii[67]} OspA patent holder and planning committee member Alan G. Barbour, MD, suggested there might be two sets of Lyme disease patients--one meeting the Dearborn definition and the other falling outside those parameters. “Can the viewpoints be reconciled?” Barbour asked in a volume that still stands as his last word on the topic. “At this time the answer is no, not completely. One reason is the difference in how Lyme disease is defined. The two groups may be talking about different groups of patients and therefore may be comparing apples and oranges. From this perspective, both groups are right. If the respective definitions are accepted on their own terms, then a comparatively short treatment is sufficient for people with illnesses fitting the more restrictive [Dearborn] definition, and longer treatment may be needed for some people whose illness meets the broader definition.”

In 1998, Columbia Presbyterian’s Brian Fallon answered Steere’s “Overdiagnosis” paper with one of his own: “The Underdiagnosis of Neuropsychiatric Lyme Disease in Children and Adults.”^{lxviii[68]} “Failure to recognize Lyme disease early in its course can result in the development of a chronic illness that is only temporarily or partially responsive to antibiotic therapy,” Fallon said. He acknowledged the findings of rheumatologists like

Steere, but went on to note that underdiagnosis of Lyme disease was a problem as well, “particularly when the symptoms are neuropsychiatric. In a survey of 193 patients with seropositive Lyme disease,” Fallon noted, “patients reported having been sick for approximately 1 year and having had to consult with a mean of two doctors before the diagnosis of Lyme disease was made. Prior to diagnosis, 42.5% of these seropositive patients were thought to have had only a psychiatric disorder. ...In conclusion, in endemic areas, although Lyme disease may be an overdiagnosed disorder in rheumatology clinics, it may be an underdiagnosed disorder in child and adult psychiatry clinics.”

But despite the caveats and equivocations, despite the avalanche of objection, the Dearborn Criteria stood.

Section V

The Lyme Disease Vaccine

After the Dearborn meeting, two companies --SmithKline Beecham (SKB) and Pasteur, Merieux, Connaught (PMC)—continued to move forward with their plans to market a human Lyme disease vaccine based on OspA. The new criteria were especially welcome to these companies for two reasons. First of all, without a well-defined case definition, their studies would never pass muster at FDA hearings. If the definition was too broad; if they could not say for sure who had Lyme disease and who did not; their data would be subject to challenge at every turn. Second, since the new criteria eliminated OspA and B from diagnostic consideration, the first and second generations of prospective vaccine products, which are made from these proteins, would not register as false positives on laboratory tests.

Indeed, SKB met with the CDC and FDA five months *before* the Dearborn meeting to go over requirements for the case definition of Lyme. At that Advisory Meeting, in June 1994, discussion included “various issues regarding clinical trial design,” according to Dr. Robert Pietrusko of SKB. Explaining the historical context for FDA Advisory Committee Members at the meeting on Lymerix in 1998, Pietrusko said, “This included the case definition of Lyme disease, and at that time it was determined that the CDC case definition would not be sufficient for the clinical trial evaluation.”^{lxix[69]}

“The case definition was essentially that that was agreed to by the Advisory Committee Meeting in [June] 1994 and finalized by agreement with the FDA,” Pietrusko told the group at the 1998 meeting. “In essence, this meant that, to be considered a definite case of Lyme disease, a person had to have clinical symptoms at the time they were seen by a physician. Usually these were manifestations of early Lyme disease, primarily erythema migrans. Also, it required laboratory confirmation of the infection, either through a positive skin biopsy culture or through Western blot serology using the Dearborn criteria of seroconversion.” While the Dearborn Criteria were voted into being in October of 1994, SmithKline Beecham, in agreement with the FDA and CDC, had embraced that very same standard, five months earlier, for use in the Lyme vaccine trials.

With new criteria established, SKB was able to move ahead. “Phase II studies were initiated in 1994. The pivotal Phase III efficacy trial began in early 1995 and was completed in late 1996,” Pietrusko explained. “After analysis of the data, the product license application and the companion establishment license amendment were submitted in 1997, and bridging studies for the final manufacturing scale-up were initiated in 1997.”

And that brings us to the FDA Hearing for approval of the Lyme disease vaccine, Lymerix, in the Versailles Rooms of the Bethesda Holiday Inn, May 1998.

To facilitate the hearing, the FDA hired eight expert consultants to supplement its usual team of evaluators. This is standard procedure. As also frequently occurs on such panels, these consultants presented with at least the appearance of conflict of interest, as defined by the FDA's own definition of conflict of interest^{lxx[70]}. The consultants are covered more extensively later in this report, but it is worth noting here that Allen Steere was not among them. Instead, he led the *corporate* team as lead investigator for the sponsor, SKB.

The complex issues discussed in the pages of this report were at the forefront of the FDA debate. When the votes were tallied, the vaccine was approved, but with great reservation. In fact, questions and doubts about the vaccine were so extensive that Committee Chairperson Christine Ferrieri had this to say: “It is fairly rare for a vaccine to be voted on with so much ambivalence by everyone with a stack of provisos.”

Part of the reservation stems from the unusual—actually, ingenious--theory behind the vaccine. While most vaccines create antibodies to infections in the human body, the Lyme vaccine was designed to kill *Borrelia burgdorferi* in the tick itself. Because Bb is so changeable, it expresses a different group of surface proteins from one organism to the next--and even from tissue type to tissue type within a single individual.

One phenomenon that scientists have long observed was the fact that while OspA is expressed in high quantities on the surface of the bacterium when the bacterium is located in the midgut of the tick, it is apparently “downregulated” as the bacterium transverses to the salivary glands of the tick. By the time *Borrelia burgdorferi* moves from those

salivary glands to the blood stream of the human host, OspA has receded and OspC has moved to the fore.

Given the sequence, scientists decided to marshal the dynamics of transition to build their vaccine. The idea: Inoculate humans with antibody to OspA. Then, when the tick takes its human blood meal, anti-OspA will rush from its mouth to its gut, killing *Borrelia burgdorferi* before it can make the journey back down the pathway to infect the human host.

As elegant as the concept was, its flaws remained a concern. Through the 1990s, for instance, an increasing amount of peer-reviewed literature showed that OspA was expressed in humans, after all--just a bit in some in the first months of illness, but with increasing intensity as infection disseminated and matured. Other studies showed that in individuals positive for the particular gene, HLA-DR4--some 30 percent of the population—there was increased risk for an especially chronic form of Lyme arthritis found to be refractory to antibiotics.

Some of the issues discussed that day, along with participant dialog, follow. We relay the discussion verbatim, with a brief comment of our own following each segment.

1. **1. QUESTION ONE**

Is the vaccine safe for those previously diagnosed with Lyme disease?

THE DIALOG

FROM DR. SCHOEN, SPONSOR REP: As investigators, we kept out of the study as much as possible anybody that we suspected had active infection at the onset of illness. So in an ideal world, nobody -- a few did, but nobody came into

this study with Lyme disease. So we didn't see late disease, which I think we would have seen if it was going to break through...

DR. DATTWYLER (Stony Brook and Brook Biotechnologies): "I think that is an issue that has to be studied very rigorously. If one looks at the question of autoimmunity and arthritis, it may be that ... having the bacterium in the joint is necessary for the development of significant chronic arthritis. And if you have that and you prime the T cells with this vaccine, you might cause some difficulty. So I think that ... needs to be studied quite rigorously.

DR. HALL: I am a little confused about the data that was presented that there seemed to be more unsolicited musculoskeletal events in those who had a history of Lyme disease, but that was not so in those who had confirmed serologic previous disease. Is that correct?

DR. PARENTI, SPONSOR: ... the people who had previous Lyme disease by their history, whether they received vaccine or placebo, had a higher rate of events. And that includes not only musculoskeletal. They had GI. They had psychiatric complaints as well.

CHAIRPERSON FERRIERI: What does that tell you?

DR. HALL: How can you explain that?. But if they had confirmed, that does not follow. I mean what is the dichotomy?

DR. PARENTI: I don't know if I want to throw out a hypothesis on that except that that is what the data were.

DR. LUFT: I don't think we have the numbers to say that there is real safety within that group. It is just too small of a group. I don't think we have the ... so I have some real reservations about using this vaccine in people who have had prior Lyme disease.

LDA COMMENT: They just don't know the answer. Without the Dearborn Criteria this issue would have been a deal breaker, since it would have been

impossible to know, in any official way, who had Lyme and who did not, especially in the endemic areas where the vaccine was to be used. Therefore, it would have been impossible to say for sure whether the vaccine was safe for *anyone*.

2. QUESTION TWO

Since the vaccine is not 100 percent effective, and, in fact, is just 50% effective after the second booster, vaccinated individuals in endemic areas stand a significant chance of contracting the disease. In such instances, does the vaccine change, and possibly worsen, the presentation and course of the disease? In other instances, will the vaccine literally mask the disease so that asymptomatic infection can smolder for years?

THE DIALOG

(Picks up with Pat Coyle of SUNY Stony Brook after the sponsor has suggested this question is of theoretical importance only.)

DR. COYLE: I think the possibility that vaccination might change the clinical picture of infection is of some concern. Really, the vaccine is not 100 percent effective. It is not just of theoretic interest. There are two distinct animal models that suggest that when this single protein vaccine is used, some of the hosts do get infected, but it is a smoldering infection that becomes more difficult to detect. Now vaccination is going to mess up serologic detection. I think in the monkey model, you had antigen and PCR and pathologic data of infection in some of the animals vaccinated. And in the rabbit model, you lost EM, which was a very good marker of infection. And this brings us back to the possible Lyme disease group, which is somewhat problematic.

DR. PIETRUSKO: Dr. Parenti, do we have some information on that topic as far as the latter part?

DR. PARENTI (Sponsor): I don't have any specific information about whether they were treated. My presumption is that they were, number one, told that they had seroconversion and that they were treated and the decision about treating clinical EMs was left up to the investigator. My presumption is that the vast majority, if not all of them, were treated. So, no, I don't think that we are going to have data on these "untreated" Lyme disease subjects.

LDA COMMENT

Since, as Dr. Parenti states above, the vast majority, if not all, vaccinees with clinical EM rashes or evidence of seroconversion were treated with antibiotics as soon as possible, SKB never addressed what might happen in the real world situation where a vaccinated individual becomes infected and is not treated promptly. Moreover, the SKB study team used the same standard in treatment of the placebo group, explaining why these individuals, too, had far less Lyme disease than a comparable group of people in the population at large. This laudable diligence to treatment separates what we see in the SKB study from a real world scenario.

1. 1. QUESTION THREE

Will vaccination with OspA affect our ability to diagnose subsequent Lyme disease in people who have been vaccinated?

THE DIALOG

DR. ELKINS, FDA:

DR. ELKINS: A note about the implication of vaccination with OspA for a diagnosis of subsequent Lyme disease itself. Many commercial ELISA kits use plates that are coated with whole *Borrelia burgdorferi*, and whole *Borrelia* grown in-vitro do express OspA on their cell surface. Thus, vaccination with OspA may lead to false positive ELISA results when this method is used for

detection of disease. However, the OspA band is not part of the standard criteria for interpretation of Western blots, and thus vaccination should not lead to false positive Western blot results when these criteria are applied. Further generation ELISA kits that will avoid this confusion are also under development. ...

DR. KOHL: The patients who were seropositive by Western blot and then developed Lyme disease, looking at the Western blots, did they have a band showing that they had antibody against OspA?

DR. SIKAND (Sponsor Rep): Well, the band against OspA is the 31 kilodalton band. They did not have that. And indeed, that is not one of the criteria which were used in the interpretation of the Western blot. So the 31 kilodalton band was not present. Indeed, one would also not have been able to determine if that band was present because that information was not available to investigators in order to keep them blinded.

LDA COMMENT

We believe that the removal of OspA and OspB from the Dearborn Criteria has done irreparable harm to chronic Lyme disease patients who present with those species-specific bands. Many patients have gone on to develop late stage, difficult-to-treat disease because, disregarding these markers as instructed by the CDC, diagnostic laboratories have consigned them to the negative category for Lyme. This is especially frustrating to the LDA in light of SKB's statement that the Criteria were generated in 1994 to facilitate the vaccine in the first place. To the degree that an OspA vaccine prevents *anyone* from being diagnosed and treated, we object and instead hold to the philosophy of "First, do no harm." This stance is especially relevant given the clear means to produce diagnostic tests for differentiating recombinant, vaccine-related OspA from infection-induced OspA.

Such products are now in the pipeline. We view distribution of OspA vaccine ahead of such tests as a rush to market.

2. 2. QUESTION FOUR

Will the vaccine induce autoimmune arthritis in some individuals due to production of OspA antibody? Specifically, researchers have associated treatment-resistant disease with the presence of Class II major histocompatibility genes, particularly certain DR4 and DR2 alleles. Are these people at risk when taking the OspA vaccine?

THE DIALOG, RIFF A

DR ELKINS, FDA: In the literature, an association between anti-OspA immune responses and the development of Lyme arthritis has been noted. Specifically, this association appears operative in treatment-resistant chronic Lyme arthritis, a rare complication of late Lyme disease, in which patients treated apparently appropriately with antibiotics to the point of eradication of the bacterium nonetheless continue with a course of arthritis. This has led to the suggestion that the arthritis has moved from an anti-bacterial response to an autoimmune response.

... FDA is aware of very recent data that further supports the hypothesis that cell-mediated immunity may be involved in the pathogenesis of treatment resistant late Lyme arthritis. In data that the sponsor will discuss in further detail today, it has been observed that synovial T cells from some people with treatment-resistant Lyme arthritis respond to full length OspA, particularly a particular peptide from OspA. This peptide binds to certain DR4 alleles, namely the same ones previously

associated with late Lyme arthritis, providing a molecular explanation for the recognition of OspA... It is not clear what, if any, implications these data, which relate to the natural history of disease, have for vaccination with OspA itself.

DR POLAND: In the discussion about the theoretical concern of the vaccine inducing any kind of rheumatologic problem in patients who are DR4 positive, what is the power of the study to determine those thresholds? If we said, well, the risk was 10 percent, for example, and we guessed that 10 percent of them carried the DR4 allele, what kind of power do we have to determine if the vaccine theoretically did induce any type of rheumatologic disorder? Do we know the answer to that question from your statisticians? In other words, clearly we are not seeing it at 20 months, but is that a type 2 error?

DR. PIETRUSKO: Dr. Krausse has some information.

DR. KRAUSSE: I am not sure that we have the answer to your question, Dr. Poland. Just to say that from a clinical point of view, I am not sure that it is relevant. I think it is of interest from an academic point of view. Of course, there is no way that we could screen people for HLA haplotype prior to vaccinating them. Even in a study, just a subset were done. Of the 40 people who were HLA haplotyped of the 100 sequential vaccine recipients -- people who got vaccine and had sufficient cells for HLA haplotyping -- six of them had DR alleles in question. So that would be a frequency of 18 percent, which is approximately equal to the numbers that are thought to be -- I think you said 10 percent and some people say 20 percent. So that probably is representative of the whole population, which probably was somewhat homogeneous from a demographic point of view.

DR. POLAND: It is a concern I think more than academic when and if this vaccine were to be delivered to millions of people as opposed to a small number. And I think there would be a study that could be done to get at this as has been

done with looking at vaccine failure with extended haplotypes for Hep B vaccine, and that is to prospectively immunize subjects who are known DR4's. And those are actually not -- because of the relatively high frequency of that allele in the U.S. population and the frequency with which people get typed, perhaps they are bone marrow donors or whatever, you actually could prospectively immunize a large group of DR4's and perhaps get at that issue.

DR. KRAUSSE: I don't mean to imply that safety issues are of academic issues only. It is just practical issues versus theoretical issues. I think it would be very difficult to type people and then to vaccinate them. It seems to me that what is important is the frequency of adverse events in the entire population. So as I say, within the power of this study, we did not detect a difference. And if there was an increased frequency of adverse events of 1 in 1,000, I think that one would need a study of about 40,000 to detect a significant difference. If the difference were 1 in 5,000, it would probably take several hundred thousand vaccinees to detect that difference.

THE DIALOG, RIFF B

DR. CLEMENTS-MANN: I guess one of the things we can't really answer in this study is what would happen to people who had the right -- who had the unfortunate allele who were vaccinated and then developed subsequent infection, maybe one of these milder ones that didn't get treated. And that would really be something that would have to be looked at, I think, under a totally different study design. It is not clear to me that the vaccine itself, at least based on the data we have seen, elicits this kind of adverse event, the chronic arthritis. And it may well be that it is really associated with the actual infection, which is more than just that one antigen exposure. So that that to me is going to be a separate question of whether the combination of vaccination and infection that would occur when it is

used on the wide scale without the surveillance could occur. And that would be another important question to look at in terms of safety.

CHAIRPERSON FERRIERI: Yes. Dr. Snider.

DR. SNIDER: Well, just to try to get back to the question and not dance around it as much. I agree with Mary Lou that we don't know for a fact that the vaccine has elicited any of these -- either one of these episodes of arthritis and paresthesias, but I think we are all worried about that. But when the question about safety is raised, it is always a relative term. And in this artificial environment of a clinical trial, we look at the placebo recipients as a comparison, but they really aren't going to be the comparison group in the real world in the sense that folks are not going to be followed so carefully. So, in fact, there will be in reality, I would suspect, cases in which EM occurs but it is not recognized, and so arthritis and neurologic effects occur. And this is what in the real world we have to balance against when we talk about the safety of the vaccine. It is the relative safety. And that is difficult for us to do because we don't have or at least I don't have the numbers from what happens in the real world of people who are not monitored in the context of a clinical trial.

CHAIRPERSON FERRIERI: Dr. Poland, did you have your hand up?

DR. POLAND: I was just going to say in regard to the DR question, that is a Phase V study. It is just not going to be done, I don't think, pre-licensure.

DR. FLEMING: When I look at the safety issue, I am inclined to break it out as to short term and long term. And I think the study conducted as it was in a high quality fashion has I think informed us quite a lot about short term. And what is apparent in short term as I see it is some level of safety, but relatively small. ... In terms of my more substantive concerns here, they are relative to the longer term issues... I am left with uncertainties about whether these two cases of paresthesia

that we are seeing are in fact a signal of something that we would have seen if we had been able to follow longer. So I am left with uncertainties on that regard.

LDA COMMENT

We'd like to excerpt a story from the June 14, 2000,^{lxxi[71]} issue of the (Newark) *Star-Ledger*, where reporter Edward R. Silverman wrote:

In October 1998, patients participating in a clinical trial for the forthcoming Lyme disease vaccine were asked to sign papers indicating a "theoretical possibility" existed that the vaccine might cause arthritis in certain genetically susceptible individuals, according to documents obtained by The Star-Ledger.

By January 1999, however, the Lymerix vaccine was approved by the Food and Drug Administration and the manufacturer, SmithKline Beecham plc, began marketing it. But the product labeling, or prescribing information, didn't mention the possibility that Lymerix may cause arthritis in people with a particular genetic profile.

Since then, dozens of people are claiming they developed severe arthritis-like symptoms after being vaccinated and, subsequently, some tested positive for the particular gene, HLA-DR4. This gene, which up to 30 percent of the population is believed to have, is the same one that has been linked, at least theoretically, to arthritis symptoms. SmithKline denies any link.

SmithKline spokeswoman Carmel Hogan said the company wasn't trying to hide the theoretical link to arthritis.

"It's been no secret," she said. "We knew this hypothesis was out there during clinical trials, and we presented it to monitoring boards and the FDA, and they concluded there was no clinical evidence" establishing a link.

Nonetheless, concern over a theoretical genetic link was raised just a few months before the 1998 informed consent letter sent to clinical trial patients by Yale University, which ran part of the trial. A panel of FDA advisers met in May of that year to review the vaccine's safety and effectiveness, and many panel members worried openly about the genetic issue.

In addition, a leading Lyme disease researcher, Allen Steere of Tufts University, who helped run SmithKline's clinical trials, shortly afterward published a scientific paper in which he noted the genetic link "is an issue of concern . . . ongoing surveillance will be important," according to an interview he subsequently gave to the journal Science.

Several lawsuits have recently been filed against SmithKline by people who claim they were harmed by the vaccine, including those who later tested positive for the HLA-DR4 gene. Their lawsuits charge that the information about the gene should have been disclosed in the labeling.

3. 3. CONCLUDING DISCUSSION AND THE VOTE

DR. KARZON: The safety issue here seems to me to be very complicated compared to any vaccine I know that has been licensed. And we have unearthed the -- those who did the trial have unearthed some very interesting sinister possibilities that may or may not be real. One is that we have excluded people

with arthritis. I don't know what percentage of arthritics have been excluded...

One of the problems I had or questions we can ask the manufacturers is whether they can initiate in any way a trial to answer further questions. And the possibility exists since the original exclusion has not been satisfied -- we still don't know theoretically whether arthritis patients will get into more trouble if they are vaccinated or not. We have said that we have excluded them. We have no data on it. And we can now say that to include them again, they need to be studied. How much or how long or in what way, I think we probably know those pathways.

There are a couple of other safety things that we don't know all the answers, and one is problems in AV function. As people get older, and we are going to have more people in this age group who will take this vaccine, AV dissociations [ventricular response that occurs over the atrioventricular node] are going to become more common. We don't know what impact the vaccination has on that system. We have some data. Maybe we need more data. And then something that has nothing to do with safety, but in a way it does, and that is how many further doses we need. We know that the half-life of antibody is short after one dose. The half-life from the curve shown may be a little flatter and may be a little longer after the second dose, which would fit as a physiological antigen administration. But we really don't know when and how many doses should be given and whether they offer any safety issues to be, if you will, hyperimmunized.

Another safety issue that is there but unresolved is the very interesting studies that Dr. Steere did to show what seems to be an autoantibody response. That, I think, has been very nicely pursued, but we don't know the final answer to that. We don't know the significance of DR4 in a statistical sense.

I see a lot of reasons why we have a lot of unsprung threats. I don't know myself how to best follow those -- what sort of follow-up we need for safety. And as I said earlier, rare events will become common when a million people are vaccinated. Furthermore, I can see all kinds of accusations or allegations of injury that aren't real in this sort of setting, and we have to clarify what is real and what isn't real. If somebody develops arthritis, well blame it on the vaccine. That is easy. But the big question I have in my mind is we need follow-up. How to do it is very difficult. I would like to hear others' opinions about how this could be done and what is realistic for the manufacturer. I am sure they are just as interested as anybody else to make sure their product is safe and sound and know all the contraindications and things that should be watched for.

CHAIRPERSON FERRIERI: Thank you, David. Those are very sobering thoughts and analyses. I don't see that we have better answers that have emerged from the table. There is a desire to try to balance a very reasonable response and analyze the data very rationally, but we heard emerging from several people at the table their concerns. No one has yet suggested that we have extension of the follow-up on the studies that have already been executed or that are in trials. Is there anyone who wants to add to what David has said... How do you feel, Dr. Dattwyler?

DR. DATTWYLER: Well, unfortunately I think it is like buying a computer. You know that there is always going to be something better next month, and the question is when to jump in. I am not sure. I think that they have done a very nice study that has shown that in this 20-month period in this population that there is a reasonable degree of safety. But the long-term effects of repeated immunizations and what is going to happen in subpopulations I think is something that needs to be studied. Can that be reasonably done as a post-licensing study or does that withhold licensing? That is a tough question and I am not sure I know the answer

to that. My overall answer to the question is, yes, there is enough there based on the data they supplied and then it becomes the agency's problem as far as what appropriate things to do are. So I am not -- I am hedging, obviously.

DR. CLEMENTS-MANN: I guess in the ideal world, it would be nice to follow vaccinated and placebo people for a very long time, but I don't think that that would altogether be ethical...it may be [depending on the number of boosters you require or receive] there is more modified disease in the vaccinated, or it may be enhanced, and that would be important information.

CHAIRPERSON FERRIERI: Thank you. We will start voting then -- yes or no or abstain. Starting with Dr. Dattwyler.

DR. DATTWYLER: Yes.

CHAIRPERSON FERRIERI: Dr. Coyle?

DR. COYLE: Well, I vote yes with the proviso that this is for a single cycle of three vaccinations. I can make no comment on the people that were excluded and I have a question mark about the elderly.

CHAIRPERSON FERRIERI: Fine. Dr. Luft?

DR. LUFT: I vote yes with a similar proviso as well as the group in regard to rheumatological conditions.

CHAIRPERSON FERRIERI: Thank you. Dr. Broome?

DR. BROOME: Yes with the same provisos. And I guess I think it is important to note that it is not going to be trivial to figure out what do you do about the ones that were excluded. I think that the endpoint we are talking about is common enough and poorly defined enough in terms of chronic arthritis that use of the vaccine in populations that were excluded from the trial is going to be difficult to assess.

CHAIRPERSON FERRIERI: Dr. Breiman?

DR. BREIMAN: Yes. And I guess we should just agree on the proviso, so we don't all have to say the same thing. But the one thing I would add to that, though, is that -- and I think Mary Lou may have mentioned this, but one thing that hasn't been talked about in great detail is the implications of vaccinating a patient that is currently infected or just has been infected within the last few weeks, which would have been another excluded criterion. But given the autoimmune issues and the possibility that there may be sort of antibody bug relationship there that could contribute, that is a concern too. And again, I am not sure how one would study that.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: The same provisional yes. I think my provisional relates to people with chronic arthritis and people with other serious underlying diseases who are clearly less likely to be exposed in the first place, and people who are beginning to approach that upper limit of age 70. I am not sure I have a good feel for the efficacy data by the time we get to the 65 to 70 age range.

CHAIRPERSON FERRIERI: So to summarize up to this point, these provisos that we are imposing and leading to provisional affirmative voting includes such issues of age, the data at the two ends of the spectrum, patients with arthritis, the suggestions earlier of special studies zeroing in on this age group as well as the other exclusions that have been mentioned regarding the recent infection. Dr. Fleming?

DR. FLEMING: Essentially similar provisos. Yes, short-term safety is established in those who met eligibility. So obviously additional information is needed in the chronic joint disease cohort and others who were excluded. We will talk about that in question 5. I would also say that this yes is also conditional on the duration of follow-up. So I remain with nontrivial concerns about whether the vaccine could be eliciting or inducing chronic infection over an interval of time

that would not have been detected with 12 to 20 months of follow-up. And again in question 5 we will come back to additional studies.

CHAIRPERSON FERRIERI: Did you mean chronic infection or chronic sequelae?

DR. FLEMING: Chronic sequelae -- excuse me, chronic arthritis or chronic sequelae. I am sorry I misspoke.

CHAIRPERSON FERRIERI: Fine.

DR. FLEMING: And obviously as well if there are different booster schedules, et cetera, that would have to be assessed for safety subsequently.

CHAIRPERSON FERRIERI: Steve Kohl?

DR. KOHL: Yes with all those provisos.

CHAIRPERSON FERRIERI: Dr. Karzon?

DR. KARZON: Yes. I can't imagine doing much better than these individuals that presented this today have done with a very difficult problem. So we have learned an extraordinary amount and I like it. But if we ever needed an intensive follow-up, call it Phase IV if you will, which has been worked over carefully and prescribed, that should be appended to that approval.

CHAIRPERSON FERRIERI: Absolutely. Mrs. Cole?

MS. COLE: My vote is yes also, but as everybody else has stated just limited to the groups that were tested in the trials that as far as I am concerned the safety is proven in. I would want to see a lot more work done on this.

CHAIRPERSON FERRIERI: Dr. Daum?

DR. DAUM: At the risk of being a little bit repetitive, yes, with the proviso that has gone all the way around. But I would also like to point out that it is my sense from hearing the discussion that almost certainly this vaccine is going to require additional dosing than the schedule that was used in the study. And thus I would like to put an additional proviso on that I think it should be evaluated, whether 4,

5, or 6 or who knows how many doses is equally safe or generates similar kind of data to what we have heard today.

CHAIRPERSON FERRIERI: Dr. Finkelstein?

DR. FINKELSTEIN: Just a couple of other provisos. One is that I would sort of -- I would like to have the age range actually shrunk in terms of something of the nature of 20 to 60, because there is not that much in the other extremes, and there is possibly -- especially in the elderly, it is possible there are side effects. And also just to point out that this is not that large a trial. So that some of the more rare side effects or complications wouldn't show up in this. So there is that aspect of it.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: I agree with all of the provisos, except I don't agree with the lower age range. I see no difference between a 15-year-old and an 18-year-old, and there have been over 300 people enrolled between 15 and 18. I do have the concerns about the older age group as have been mentioned.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: I vote yes, and I am not sure this proviso has been thrown out. But this vaccine has the potential to be like the inactivated measles vaccine, and that is to cause a late unanticipated event in people who were vaccinated with a different disease. So there needs to be very careful monitoring, even if there is no boosting of people over time -- over 5 and 10 years to make sure that they don't respond to a secondary infection in a different way.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: I would also vote yes and the provisos seem reasonable. But I think also we should be realistic that in the real world these provisos are probably not going to be very well adhered to. And particularly -- I can't find the entire list that I saw earlier of all the various exclusion criteria, but I think that would include a

great many people in our population, and I am not sure that that would be warranted even.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Well, like others I am not completely sure about the absolute long-term safety. But I will vote yes based on relative safety compared to the risk of people in endemic areas going unvaccinated. So I think the benefits are on the side of vaccination, at least in the short term. And as mentioned, we don't know in the long-term. And again I would emphasize, as others have, that although it is difficult, this seems to me to be one vaccine where we are going to have to find a way to do long-term follow-up. Because it appears that not only are we going to have to be concerned about chronic sequelae, but the potential need for more than one booster dose. One aspect of the exclusions that people haven't mentioned that is troubling to me has to do with -- I understand why I think certain groups were excluded, but it creates for me not only a practical problem but an ethical problem. And particularly with regard to children who are at high risk of disease. So I have to wonder what we are -- I mean, I know fortunately a trial is underway. But what is the ethics of making a vaccine available to certain select parts of the population and not other deserving parts of the population who are at risk. So for me it is a lesson of when thinking about designing trials to think about those aspects as well.

CHAIRPERSON FERRIERI: Thank you, Dixie. Dr. Huang?

DR. HUANG: I certainly vote yes, and I also support the extension of the vaccine to people 15 years of age.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: I support this. However, I do have some concerns. I think that we need to very carefully follow these individuals. We need to extend at both

ends and both age spectrum additional studies and we need to pursue the long-term follow-up very carefully.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Yes, subject to the provisos that will come up in question 5.

CHAIRPERSON FERRIERI: My vote is yes with great ambivalence and also in support of the provisos that have been mentioned with emphasis on the need for long-term follow-up and additional studies. I might comment that this is fairly rare for a vaccine to be voted on with so much ambivalence by everyone with a stack of provisos. Dr. Hardegree would be able to confirm whether or not this is relatively unprecedented. So that is all for the formal vote.

CDC Recommendations: OspA Reversal

A year later, in 1999, the CDC's Advisory Committee on Immunization Practices (ACIP), met according to regulation, to put its stamp of approval on the FDA findings by recommending a specific protocol for the vaccine. LDA has found one aspect of these proceedings and their aftermath important enough to emphasize here. Published in the *Morbidity and Mortality Weekly Report* on June 04,^{lxxii[72]} 1999, the ACIP report held that anti-OspA antibodies were simply not produced in natural Lyme disease infection. "Care providers and laboratorians should be advised that vaccine-induced anti-OspA antibodies routinely cause false-positive ELISA results for Lyme disease," the ACIP committee wrote. "Experienced laboratory workers, through careful interpretation of the results of WB, can usually discriminate between *B. burgdorferi* infection and previous rOspA immunization, because anti-OspA antibodies do not develop after natural infection."

Three and a half months later, on September 24, the CDC printed this correction^{lxxiii[73]}: "In 'Recommendations for the Use of Lyme Disease Vaccine: Recommendations of the

Advisory Committee on Immunization Practice (ACIP) ,’ in the section "Effect of Vaccination on the Serologic Diagnosis of Lyme Disease," on page 9 the statement that "anti-OspA antibodies do not develop after natural infection" is incorrect. Although antibody to OspA in patients with early Lyme disease is rarely evident, this antibody can be found in increasing amounts in patients with later stages of Lyme disease, particularly those with Lyme arthritis. Therefore, the paragraph should read: "Care providers and laboratorians should be advised that vaccine-induced anti-rOspA antibodies routinely cause false-positive ELISA results for exposure to *Borrelia burgdorferi* . Experienced laboratory workers, through careful interpretation of the results of immunoblots, can usually discriminate between *B. burgdorferi* infection and previous rOspA immunization. Although vaccination is expected to elicit antibody to OspA only, natural infection results in the production of antibody to additional diagnostic antigen bands in immunoblots."

The correction shows that the CDC now agrees that OspA antibody is, in fact, produced by patients with late-stage Lyme disease. But the correction calls for another: If the agency can admit, in the year 1999, that OspA antibody is, in fact, expressed as part of human Lyme disease pathogenesis, especially in late-stage disease, why can't that retraction extend back in time to the Dearborn meeting and the diagnostic criteria, too? Such a change would be meaningful to many patients who currently slip under the radar, unable to secure a diagnosis, treatment, or insurance coverage based on testing criteria as they stand today.

Vaccine Adverse Events

Questions about the OspA vaccine continue to emerge as trial participants and commercial recipients claim numerous adverse events. One physician now implicated in lawsuits and complaints is Westchester County Medical Center rheumatologist Gary

Wormser, who headed clinical trials for SmithKline Beecham's competitor, Pasteur Merieux Connaught. From 1995-1997, Wormser's lab served as test site for Pasteur, Merieux, Connaught's OspA vaccine. (PMC is now a subsidiary of the life sciences giant, Aventis, and has been renamed Aventis Pasteur.) Fee for this service is estimated at about \$1.5 million over the two years.

Connaught has pulled back from the OspA vaccine to develop more advanced versions, but for Wormser, the lawsuits remain. According to New York attorney Ira Maurer, representing three separate plaintiffs in a suit against Connaught and the Westchester County Medical Center, the clinical trials resulted in adverse reactions that he believes were further mishandled at the test site.

"There is evidence that some individuals who have been or are currently infected with the Lyme disease bacteria have experienced adverse reactions to the OspA based Lyme disease vaccines that far exceed the reactions stated as possible in the literature given to potential participants in the vaccine trials and to recipients of the licensed Lyme vaccine, Lymerix," Maurer notes.

One Maurer client was Marvin Fichter, who belonged to a sportsman's club near his home in Yorktown Heights. According to a *New York Newsday* article, Fichter, an avid outdoor person, sought out the vaccine as "a good idea," given his lifestyle. He went to Westchester County Medical Center, one of the sites in the Connaught clinical trial testing its Lyme disease vaccine, *Newsday* reported, and told the staff he had been treated for Lyme disease a decade before. He signed an informed consent, was entered into the study as number 5076, was given an injection and had blood drawn. A month later he returned for another shot.

Soon after, he started having pains in his spine, severe headaches, and scalp tenderness. "Since then, a series of what he believes are misdiagnoses and inappropriate treatments - all stemming from his alleged reaction to the vaccine - have left the 75-year-old unable to walk except on crutches," *Newsday* reported. "Because his hands are now curled like claws from severe nerve damage and he has constant pain in his joints, he can't dress himself and can barely feed himself, he said. "I'm not able to hunt and fish - that was my whole life. I have a two-acre parcel of grass; I'm not able to get out and cut it. That's the most distressing thing - not being able to do the things I used to do," he said.

Marvin Fichter died of an unrelated condition, but his estate is suing the study investigator, Dr. Gary Wormser as well as New York Medical College, which staffs Westchester County Medical Center, other doctors, and Connaught for \$1.2 billion. He's not the only one suing. Two other volunteers from the Westchester study site brought lawsuits against Wormser, New York Medical College, and Connaught for damages.

In Fichter's case, after he was given both shots and he developed symptoms, he was examined by Wormser. While an initial blood test showed he had been previously exposed to Lyme disease, another test three months later showed he was "off the charts positive" for Lyme, according to Maurer, his attorney. Nevertheless, he was told his symptoms were the result of a condition called polymyalgia rheumatica and he was sent by Wormser to see another doctor, who then put him on prednisone, a steroid known to suppress the immune system.

But, Maurer maintains, neither the patient nor the other doctor were told Fichter had tested positive for Lyme and Fichter was kept on the steroid, while his symptoms became worse.

Finally, Fichter went to his own doctor, who tested him for Lyme. He tested positive and was put on antibiotics. Within a short period of time, his symptoms were so severe he was in a wheelchair. "Our experts believe that the long course of treatment on the prednisone combined with the lengthy delay in getting antibiotics caused him to develop a serious peripheral nerve condition," Maurer said.

Two other cases are similar. Alison Schettini of Cortlandt Manor, who is suing for \$22 million, had been diagnosed with post-herpetic neuralgia, or chronic shingles, before she joined the study. She said she joined the trial to spare herself the possibility of getting Lyme disease. Instead, she says, the vaccine and subsequent misdiagnoses left her with an inflammatory arthritis condition that required two knee operations.

Albert Gambino of Southbury, Conn., volunteered to join the trial, he said, because he had had Lyme disease and symptoms consistent with chronic Lyme disease. He thought perhaps the vaccine would help. "I was clutching at straws," he said. Instead he broke out in hives, which still come back regularly three years later, and he believes his symptoms were exacerbated. "They're essentially all similar allegations, which assert that people were improperly introduced into research studies. We have denied this," said Thomas J. Martin, vice president and general counsel for New York Medical College.

"When participants in the studies were solicited, they were assured that the risk of adverse reactions were minimal. They were also promised that if, subsequent to vaccination, they were diagnosed with Lyme disease, they would be treated with appropriate antibiotics," Maurer says.

These new drug investigations are regulated by the FDA. The laboratories and principal investigators (doctors in charge of the trial at each location) are required to report to the FDA any adverse reactions that may reasonably be related to the vaccine. The FDA has the authority to shut down the vaccine trial if it receives reports from the laboratories testing the vaccines of adverse reactions being experienced by the trial participants in sufficient numbers or with serious medical consequences so as to cast the vaccine's safety in question."

Whether or not scientists at Westchester County Medical Center have falsely written off adverse events or data is subject to debate. However, it's clear that, by virtue of powerful conflicts of interest, the motivation arguably exists, Maurer states. "Vaccine trials mean millions of dollars in funding for participating labs and are a substantial source of revenue for study sites. Successful new drug investigations can bring invaluable prestige to the study site and principal investigator running the clinical trial."

"The problem with this setup is that we are trusting the children to self-monitor their trips to the cookie jar," says Maurer. "As Ralph Nader demonstrated decades ago, corporate greed can be a dangerous thing. Mix this with the egos of doctors who want to be associated with a successful Lyme vaccine and you have the makings for abuse."

Lymerix 2001

Today the controversies surrounding the Lyme disease vaccine, Lymerix, continue. A Washington Post reporter, present at the FDA's review of the product on January 31, 2001, summarized the situation on April 8 in the article, below:

Vanessa Raffio was a horsewoman and a veterinarian's helper who loved hiking and riding in the woods – hobbies that seemed to place the suburban New Jersey teenager at high risk for getting Lyme disease. So two years ago, Raffio, then 17, asked her doctor for the recently approved vaccine against the tick-borne infection.

"I'm the one who pushed for it," recalled her mother, Linda Scharf-Lurie. "It was the biggest mistake of my life."

Soon after she got her second dose of the vaccine in June 1999, Raffio began having pains in her ankles, she said. That autumn, she developed severe pain in her neck and back as well, and was eventually diagnosed with rheumatoid arthritis. She also permanently lost the peripheral vision in her left eye when her optic nerve became inflamed.

These days, Raffio, now a college freshman at the University of Missouri at Columbia, is able to ride a horse only for brief periods, and uses an electrical nerve stimulator to relieve her chronic pain.

"I have arthritis . . . pretty much everywhere but my knees," Raffio said. "I've learned to manage to the best of my ability. . . . My body is not like everyone else's body."

Raffio is one of more than 100 people whose arthritis or joint swelling is being investigated by the Food and Drug Administration because of possible links to the vaccine.

Such cases, and the questions they raise about the vaccine's safety, have renewed a debate on the risks and benefits of vaccines for illnesses, such as Lyme disease, that are treatable or avoidable by other means.

"This is what some people have called a 'boutique vaccine,' " said Robert Daum, a professor of pediatrics at the University of Chicago who chaired the FDA advisory committee that reviewed the vaccine.

Sidney M. Wolfe, director of the Public Citizen Health Research Group, a consumer group, said that the "vaccine is being grossly overpromoted to people who don't live in parts of the country where [Lyme disease] happens very much."

Carmel Hogan, a spokeswoman for GlaxoSmithKline Inc., which makes the vaccine, defended its safety record and the company's marketing policies. The company has distributed 1.4 million doses of the vaccine and continues to sponsor follow-up research on its safety, she said. "Based on clinical trials to date and postmarketing surveillance . . . there is no causal link between this vaccine and arthritis," Hogan said.

When the FDA approved the vaccine, called LYMERix, in 1998, the agency concluded that the product was safe after reviewing extensive studies sponsored by GlaxoSmithKline, including a two-year trial involving almost 11,000 healthy adults and adolescents. Neither that study nor a separate safety trial in people with a previous history of Lyme disease found evidence that the vaccine could cause arthritis or other serious adverse effects.

However, members of the FDA advisory committee that reviewed LYMERix expressed concern at the time that the vaccine might have the potential to provoke arthritis in some recipients. The committee asked GlaxoSmithKline to conduct a large follow-up study after approval, and urged long-term monitoring of the health of vaccine recipients.

Earlier this year, the same committee heard emotional testimony from Scharf-Lurie and others who believe that the Lyme vaccine made them or their family members sick. What they didn't hear, either from the company or from the FDA, was sufficient scientific evidence to settle the question of whether the vaccine caused the illnesses, Daum said.

"Your heart went out to these folks who came" to testify, he said. "And yet, where's the science? The committee was presented with what they thought was less than the science that they had hoped for – from everybody."

More than 16,000 cases of Lyme disease were reported in 1999, making it the most common illness transmitted by insects, ticks or spiders in the United States. Yet, most cases are concentrated in about 115

counties in the eastern and north-central United States where animals (chiefly mice and deer) have high infection rates with the disease-causing bacteria, increasing the likelihood that a tick bite will transmit the infection to humans.

Maryland reported 899 cases of Lyme disease in 1999, or about 18 cases per 100,000 population. (For comparison, Connecticut, with the highest rate of any state, had 98 cases per 100,000 population.) Virginia reported 122 cases, or about 2 cases per 100,000, in 1999. The District reported six cases, about 1 per 100,000. Fairfax County in Virginia and 13 counties in Maryland (including Montgomery and Prince George's), as well as Baltimore City, are considered high-risk areas based on the frequency of reported cases and the prevalence of infected ticks, according to the federal Centers for Disease Control and Prevention.

People spending time outdoors in such areas can usually avoid tick bites by taking simple precautions. If infection does occur, it generally responds promptly to antibiotics. In a minority of cases, Lyme disease causes persistent arthritis, nerve abnormalities or other long-lasting symptoms.

GlaxoSmithKline has marketed the vaccine aggressively, with advertisements presenting ticks as a threat to people in many states who garden, golf or cook on the outdoor barbecue.

However, the vaccine – which costs about \$200 for a series of three doses – does not provide complete protection, and recent studies suggest that periodic boosters are needed to maintain immunity. It should be considered only by people living in high-risk areas who engage in high-risk activities, according to guidelines issued by the CDC.

Hogan said the company's view on who should get the Lyme vaccine "is that people who live, work or travel in endemic areas should consider it."

The company is continuing to fund the follow-up study that was requested two years ago, although patient recruitment has been slow, and has reported all cases of suspected adverse reactions to the FDA, she added.

Scientific concerns about a possible link between the vaccine and arthritis arise from the fact that the vaccine is made from the same protein, found on the surface of the Lyme disease bacterium, that has been implicated in causing persistent arthritis in some people with the infection. The bacterial protein, Osp A, is similar to a human protein found on blood cells. High levels of antibodies to Osp A correlate with

severity of joint swelling in people with Lyme arthritis, suggesting that the body's immune response against the infection somehow triggers an attack on its own joint tissues. People whose tissues carry a cell-surface protein known as HLA DR4 are more likely than others to develop persistent arthritis from Lyme disease (and some experts believe they may also be more prone to complications from the vaccine.)

Arthritis and neurological disorders are among the medical problems that have been reported to the FDA by some recipients of LYMErix, but there is no clear pattern to suggest that the vaccine was the cause, said Robert Ball, the agency's acting chief of vaccine safety. However, he cautioned, "the way we receive [reports], it's usually difficult or impossible to determine if a vaccine is causing adverse events" without doing additional studies.

A total of 1,048 adverse events in people who received LYMErix were reported to the agency from December 1998 through October 2000, representing about 0.07 percent of the approximately 1.4 million doses of the vaccine distributed. There were 133 reports of arthritis or joint swelling, but symptoms did not occur in any consistent pattern in relation to when people received the vaccine. There were 13 cases of facial paralysis (an occasional feature of Lyme disease) and 37 reports of possible allergic reactions. FDA reviewers concluded that the vaccine was probably responsible for some allergic reactions, but that most cases of facial paralysis had other possible causes.

Ball said the FDA is examining the arthritis cases in greater detail and plans to conduct a study to investigate whether arthritis is a possible side effect of the vaccine. In individual cases, it is very difficult to determine whether joint inflammation has been produced by the vaccine, by Lyme disease, or by some other cause of arthritis.

The study will take time, and meanwhile the agency isn't sure what to make of cases such as Raffio's, said Susan Ellenberg, director of the office of biostatistics and epidemiology in the FDA's Center for Biologics Evaluation and Research.

"When you get these reports, it looks very compelling. We are very concerned," she said. "These people are suffering."

Daum said the continuing uncertainty about the Lyme vaccine should serve as a reminder that even extensive testing can't guarantee that a new drug or vaccine will not produce unexpected side effects, and demonstrates the need for closer safety monitoring after products are approved.

"How big should the clinical trials be?" he asked. Even if studies involve more than 10,000 participants, as the LYMERix trial did, "they will not pick up something that occurs in 1 in a million people."^{lxxiv}⁷⁴

PART TWO: LYME DISEASE AS BUSINESS MODEL

Section VI **Why Lyme Had To Be Redefined in Order for Products to Reach Market**

Those entering the Lyme disease arena for the first time find it difficult to comprehend the virulence of the debate. If acne can be treated with antibiotics for two years or more, why can't we do the same for someone with chronic Lyme disease? In the face of myriad clinical accounts showing the efficacy of such an approach, it seems reasonable to try. This is especially true in light extensive peer-reviewed literature showing persistence of infection, as well as recent findings that some 30% of the ticks carrying Lyme contain coinfections, including Babesia and Ehrlichia. Physicians treating the triad of tick-borne infections--including those recognized only in the last few years--find that a combination of antibiotics prescribed over time will bring relief, even in those who have been sick for years.

Some scientists at the National Institutes of Health and elsewhere now suggest those with chronic Lyme suffer not from persistent infection, but from autoimmune damage the killed-off spirochete has left behind. In fact, there is no more evidence for this pet theory in the literature than for the theory that the *Borrelia burgdorferi* spirochete simply persists, hiding and reproducing in the cells of the organs, central nervous system, and the brain. Indeed, given the enigma the disease presents, it seems reasonable to suppose that both factors play a role. Why all the *Sturm und Drang* over an honest disagreement in

science? Until we have a definite answer about the pathogenesis of this disease--which no one claims to understand--can't we find a middle ground?

The impasse appears to make sense, at least in part, in the context of a series of U.S. and international patents that suggest the potential for a staged product rollout of vaccines and associated diagnostic tests, produced in lockstep. The reason new vaccines must be developed in tandem with lab test products is clear: Vaccines change the immunological profile of the vaccinated, thus rendering previous diagnostic tests inaccurate or useless for anyone who has been given the vaccine. So that the vaccinated can always be "seronegative," there is an accepted need for new tests with new versions of a vaccine. This is simply protocol.

But why would the product lineup require a redefinition of Lyme disease itself? It didn't happen with measles, or polio, or hepatitis B. What can be gained from dismissing the possibility of seronegative Lyme disease, asymptomatic or subclinical Lyme disease, Lyme that persists after four weeks of antibiotic medication (like other spirochetal illness), or Lyme that provokes an antibody response through OspA and B (found in nature in *Borrelia burgdorferi* and nowhere else)? Why is PCR technology based on amplification of DNA deemed precise enough to send someone to the electric chair but *not* reliable enough to document diagnosis of Lyme disease? Why have standards voted by committee despite serious reservation in 1994 become the final word on the evolving and complex pandemic of Lyme?

One possibility is that any other course would have compromised the business model. After all, how would you know whether you are vaccinating someone who is or is not infected if Lyme disease can be seronegative? If researchers at Glaxo SmithKline and Aventis admit it's impossible to know whether they're vaccinating already-infected

patients, it would be impossible to interpret their data. The FDA, moreover, would be hard-pressed to permit clinical trials where unknown numbers of patients are inoculated but may well be infected, too.

Well aware of this, SmithKline Beecham, the FDA, and CDC met to decide upon a viable case definition for Lyme disease, one that would enable their data to have meaning and permit their clinical trials to move forward, ultimately passing review at the FDA.

The criteria adopted for the SmithKline Beecham vaccine were ultimately also adopted to define Lyme disease in general, in Dearborn, Michigan, in 1994. A stringent serological definition of Lyme disease, one that seemed to settle, once and for all, who had Lyme and who did not, was essential for products to be approved.

Indeed, if the case definition for Lyme disease is either broad or serologically uncertain, one may have to concede the existence of:

1. 1. seronegative Lyme disease;
2. 2. asymptomatic or subclinical Lyme disease with the potential to become symptomatic or chronic up the road;
3. 3. persistent infection that may not be cured by four weeks of standard treatment in many individuals;
4. 4. the reality of antibodies to OspA and B as specific immunological markers of Lyme disease;
5. 5. the existence of many unknowns, including the variability of some 300 strains and strong evidence of rapid mutation inside the host; and
6. 6. the possibility that, since we know so little, genetically engineered antigens of the pathogen may have unforeseen effects.

If one accepts these possibilities, then one cannot accept:

1. 1. that those who test negative for Lyme disease by current standards are definitely free of the disease;
2. 2. that vaccinating an infected individual is absolutely safe;
3. 3. that the vaccinated will never harbor late-stage infection without knowing it, especially if they present only with immune marker for OspA;
4. 4. that a vaccine made from genetically engineered parts of the pathogen in question is benign, or that *Borrelia burgdorferi* pathogenesis is understood well enough to justify vaccinating ourselves with genetically engineered antigens derived from it; and
5. 5. that even the most rigorously designed study can prove the vaccine safe or unsafe.

In short, without enactment of the Dearborn Criteria, the OspA vaccine and all the second and third generation vaccines and associated test kits would be waiting in line at the FDA pipeline, still unmarketable and/or unapproved.

These days, no one questions the right of university scientists or even governments to patent their inventions and generate revenues. As long as the conflicts of interest are fully disclosed, and as long as they are not allowed to influence policy, these groups and individuals are within their rights. In the case of Lyme disease, however, the appearance of conflict of interest among some of those charged with setting medical policy and standards requires a closer look.

Section VII:

Lyme Disease Products and Companies

A series of products have emerged to capitalize on the market for Lyme disease tests and vaccines. The products are rooted in patents filed by industry, government, and academia. Many of the patents have been funded in part or almost completely by the US government, including such agencies as the NIH and the CDC. When government agencies hold rights to revenue from the inventions, they must be considered in any discussion concerning conflict of interest as well. As can be seen below, a number of the products are related to each other, with vaccines and tests coming out in tandem. An increasingly complex series of vaccines represent second, third, and fourth generations of the initial launch, a vaccine invented by Yale University and developed by SmithKline Beecham.

In the listing below, we present four categories of Lyme disease products, grouped by corporate affiliation, where possible.

1. 1. Track A: GlaxoSmithKline Products and Offshoots

1. 1. **Glaxo SmithKline** vaccine, Lymerix. First generation based on OspA and invented by **Yale University**
2. 2. **Imugen**, Patent # 6,045,804, OspA-Less Western blot diagnostic test for the vaccinated and tests for Babesia and Ehrlichia, *recipient of US patent grant. **(Steere/Tufts; Persing/Mayo Clinic)**
3. 3. **Corixa**. Provides Adjuvants to Glaxo SmithKline (was SKB) for Lyme disease vaccine. Provides antigens to Imugen. *Special note here: Glaxo SmithKline is an equity stakeholder in Corixa, and Corixa has

rights to revenue whenever its adjuvant products are used in an SKB vaccine. This is the case due to Glaxo SmithKline's equity investment in RIBI Immunochem, which held rights to the patents until RIBI was purchased by Corixa in 1999.^{lxxv[75]}

4. 4. **NYS Department of Health.** Provides antigens to Imugen.
 5. 5. **Sunrise Labs, NY:** distributes Imugen products.
 6. 6. **Brook Biotechnologies,** Stony Brook, NY; products include 20-minute Lyme test and OspA-negative Elisa, US Patent # 5,571,718, recipient of US patent grant. **(SUNY Stony Brook Spin-off, Datwyller and Luft.)**
 7. 7. **Brook Biotech** partner: **Chembio,** NY; manufactures Brook Elisa, US grant recipient.
 8. 8. **Wampole/Carter Wallace;** distributes Brook Bio Elisa.
 9. 9. **L2 Diagnostics. (Yale University Spin-off.)** US patent numbers : 5,807,685; 5,747,294; 5,656,451.
-
2. 2. **Track B: Aventis Pasteur Products and Offshoots.**
 1. 1. **Aventis Pasteur** (formerly Pasteur, Merieux, Connaught) OspA vaccine abandoned in wake of lawsuits. Special note: Since the original patent for OspA used in the Glaxo product is registered by Aventis, **Aventis derives revenue from every dose of the Glaxo vaccine that is sold.**
 2. 2. Second-generation vaccines based on Symbicom patents and licensed to Aventis Pasteur: US Patent #'s 6,143,872, 6,090,586, 5,777,095, 5,688,512,
 3. 3. 6,083,722, 5,582,990. **(Barbour/Bergstrom)** *recipient of US patent grants.

4. 4. **Vical**, US Patent #: 5,846,946, naked DNA vaccine, produced in partnership with Aventis-Pasteur. (**Barbour**)
5. 5. **Medimmune**. Decorin-binding protein vaccine produced in partnership with Aventis Pasteur. US Patent #: 5,853,987, (**U of Texas**)
*recipient of US patent grant
6. 6. **Avant Immunotherapeutics**, vaccine adjuvants. Licensed to Aventis Pasteur for Lyme vaccine. US patent #'s: 5,855,895, 5,562,909, 5,814,704.

3. 3. **Track C: Stand-alone technologies**

1. 1. **Roche Molecular**, US Patent # 5,912,117, PCR Test, *recipient of US patent grant
2. 2. **Mayo Clinic**, PCR Test, US Patent # 6,087,097, Persing. Licensed to IGenX.
3. 3. **Gen-probe**, RNA-based test, US patent #: 6,074,826.
4. 4. **RX Technologies**, ultrasound vaccine, US Patent #: 5,582,829.
*recipient of US patent grant.
5. 5. **Abbott Labs**, tests spirochete flagella, US Patent #: 5,643,733.
6. 6. **Immunetics**, Products: Qualicode and Codacel, Automatic Western blot. US Patent #: 5100626. Recipient of US patent grant.. * Can be used to differentiate between OspA infected and OspA vaccinated. Is available for canine Lyme diagnosis.
7. **Viro Dynamics**, Osp-BmpC as diagnostic assay, immunodots, recipient US grant, **Westchester County Medical Center Spin-off**.
8. **Medimmune and Human Genome Sciences**, polynucleotide sequences and vaccines derived therefrom. Assignees include both Human Genome and Medimmune.

9. **Alexon-Trend** DotBlot testing for Lyme disease is an EIA membrane strip format that allows separate results for IgG and IgM in less than two hours. Test gives separate results for whole borrelia, HMW (P83-100), Flagellin (P41), BmpA (P39), and OspC antigen These products do not rely on OspA reactivity for interpretation.^{lxxvi[76]}
10. **Hycor Biomedical Inc.** User-Defined Software for the Hy-Tec 288 Plus automated immunoassay system complements its basic instrument software package, which permits testing of up to 25 autoimmune tests or more than 900 specific allergies. The Windows-based system can handle 50 patient samples and 288 tests per run.^{lxxvii[77]}
11. **Boston Biomedica.** BBI Clinical Laboratories of New Britain, Conn. New antibody test for Lyme disease — the C6 Lyme Peptide ELISA (VlsE^{lxxviii[78]}). Invented by Dr. S. J. Norris and coworkers at the University of Texas, and by Dr. Mario Philipp and his group at Tulane University. The newly discovered protein, VlsE, has the ability to change its structure, thus avoiding the patient's immune response. VlsE consists of both variable and invariable parts. One of the invariable parts, C6, produces a strong antibody response in patients with Lyme disease and can distinguish between patients with Lyme disease and those who have been vaccinated to help prevent the disease. Tests without looking at OspA.
12. **Biomerieux.** This company is partner with the CDC in ownership of **WO 99/35272** "RECOMBINANT P37/FlaA AS A DIAGNOSTIC REAGENT"^{lxxix[79]} Inventors include CDC scientists Robert Gilmore and Barbara Johnson.
13. **Gen-bio**^{lxxx[80]}. "Immunodot" system to replace the elaborate Western blot.

Unlike Western blots, Borrelia DotBlot tests show separate results for whole borrelia, HMW (P83-100), Flagellin (P41), BmpA (P39) and OspC antigens. No reliance on OspA reactivity for interpretation.

4. **4. Track D: Animal Vaccines.**

1. **American Home Products**, Fort Dodge, LymeVax. US Patent #: 4,721,617 ^{lxxxix[81]}. Assignee is **University of Minnesota** and inventor is U of Minnesota Professor Russel Johnson. Patent forms basis for later patents defining human Lyme vaccine.
2. **Schering-Plough**, Galaxy®Lyme, canine Lyme vaccine
3. **Aquila Biopharmaceuticals, Inc.**, canine Lyme vaccine.

Section VIII

Lyme Disease Patents

It's unpleasant to think that physicians and scientists entrusted with the public good would redefine the parameters of a disease to enable approval and marketing of the products on which their patents and entrepreneurial ventures are based. But a review of the patent list below suggests the appearance of this possibility in Lyme. It turns out that many of those who hold rights to the patents, either directly or through investment, license, or marketing agreement, are the same individuals and organizations who sit on official committees that determine the fate of those patents. They do so by their ability to determine diagnostic criteria, standard of care, and--in some situations--approval of the patent itself. The devil is always in the details. In that spirit, we present the patents defining the Lyme disease product roll-out, below. A review of the assignees, inventors,

and partners suggests the potential for an appearance of conflict of interest, as defined by either government agency or other ethical standards, in many instances.

US PATENTS FOR LYME DISEASE VACCINES AND DIAGNOSTIC TESTS

#	invention	assignees & partners	inventors
Patent pending & 5,922,614	Oralscreen collector method Oral diagnostic test for lyme	Avitar Incorporated (Canton, MA)	Cesarczyk; Edward J. (North Easton, MA)
5,855,895	Polyphosphazene polyelectrolyte immunoadjuvants	Assignee: Virus Research Institute (Cambridge, MA,) now known as Avant Immunotherapeutics. Partner: Aventis Products: Adjumer, Micromer, used in vaccines for Lyme disease And respiratory syncytial virus (RSV). January 5, 1999	Andrianov; Alexander K. (Belmont, MA); Payne; Lendon G. (Arlington, MA); Sargent; Jonathan R. (Somerville, MA); Sule; Sameer S. (Woburn, MA)
5,814,704	Recovery of polyphosphazene polyacids or acids salts thereof September 29, 1998	Assignee: Virus Research Institute	Andrianov; Alexander K. (Belmont,

		(Cambridge, MA,) now known as Avant Immunotherapeutics. Partner: Aventis Products: Adjumer, Micromer, used in vaccines for Lyme disease And respiratory syncytial virus (RSV).	MA); Sargent; Jonathan R. (Los Angeles, CA); Sule; Sameer S. (Marlboro, MA)
5,562,909	Phosphazene polyelectrolytes as immunoadjuvants Market for adjumer vaccines estimated at \$900 million per year.	Assignees: Virus Research Institute, now called Avant Immunotherapeutics Massachusetts Institute of Technology (Cambridge, MA) The Penn State Research Foundation (Cambridge, MA) Partner for Lyme vaccine: Aventis	Allcock; Harry R. (State College, PA); Andrianov; Alexander K. (Belmont, MA); Langer; Roberts (Newton, MA); Visscher; Karyn B. (State College, PA).

Products: vaccine
 adjuvants adjuver
 And micromer, used
 for Lyme disease as
 well as And
 respiratory syncytial
 virus (RSV).

6,143,872	Bb OSPA/OSPB proteins and immunogenic peptides	7-Nov-00	assignee: Symbicom corporate developer: Aventis Pasteur Hansson; Lennart (Umea, SE) Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX)
6,090,586	66 kDa antigen from Borrelia	18-Jul-00	assignee: Symbicom corporate developer: Aventis Pasteur Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX)
6,083,722	Borrelia antigen	4-Jul-00	assignee: Symbicom corporate developer: Aventis Pasteur Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX) Magnarelli; Louis A. (Durham, CT)
5,846,946	compositions and methods		assignees: Huebner; Robert C. (Stroudsburg, PA)

	for administering naked DNA	8-Dec-98	Vical Inc. (San Diego, CA) Aventis Pasteur, FR The Texas A & M University System (College Station, TX)	Norman; Jon A. (Poway, CA) Liang; Xiaowu (La Jolla, CA) Carner; Kristin R. (San Diego, CA) Barbour; Alan G. (San Antonio, TX) Luke; Catherine (San Antonio, TX)
5,777,095	OspA and B sequences of strains ACA1 and IP90.	7-Jul-98	assignee: Symbicom corporate developer: Aventis Pasteur	Bergstrom; Sven (Umea, SE) Hansson; Lennart (Umea, SE)
5,688,512	Borrelia antigen	18-Nov-97	assignee: Symbicom corporate developer: Aventis Pasteur	Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX)
5,582,990	DNA encoding Bb OspA and a method for diagnosing Bb infection	10-Dec-96	assignee: Symbicom corporate developer: Aventis Pasteur	Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX) Magnarelli; Louis A. (Durham,
5,523,089	Borrelia antigen		assignee: Symbicom	Bergstrom; Sven (Umea, SE) Barbour; Alan G. (San Antonio, TX)

		4-Jun-96	corporate developer: Aventis Pasteur	Magnarelli; Louis A. (Durham,
5,853,987	Decorin binding protein compositions and methods of use			Guo; Betty (Houston, TX)
	next generation vaccine	29-Dec-98	assignee: The Texas A & M University System (College Station, TX) corp. developers: Aventis, Medimmune Gov: NIH grants A120524 HL47313, AR41507	Hook; Magnus (Houston, TX)
5,583,038	Bacterial Expression Vectors Containing DNA encoding secretion of lipoproteins		assignee: MedImmune, Inc. (Gaithersburg, MD) development: Aventis Pasteur	Stover; Charles K. (Silver Spring, MD)
5,585,102	Flagella-less borrelia		assignee: Board of Regents, The University of Texas System 17-Dec-96 (Austin, TX) devel: Aventis Pasteur NIH grant # A124424	Barbour; Alan G. (San Antonio, TX) Sadziene; Adriadna (San Antonio, TX) Bundoc; Virgilio G. (Newbury Park, CA)
6,113,914	OSPA proteins of Bb subgroups encoding genes and vaccines		assignee: Smithkline Beecham *used in tandem with	Kramer; Michael (Frieburg, DE) Simon; Markus (Frieburg, DE) Schaible;

		Yale patents to develop Product.	Ulrich (Frieburg, DE) Wallich; Reinhard (Heidelberg, DE) Schaible; Ulrich (Frieburg, DE)
		5-Sep-00	
5,178,859	Vaccine against Lyme disease	assignees: Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. (Gottingen, DE); Deutsches Krebsforschun Zentrum Stiftung des Offentlichen Rechts (Heidelberg, DE) corporate developer: Smithkline Beecham *used in tandem with Yale patents to develop Product.	Wallich; Reinhard (Heidelberg, DE) Eichmann; Klaus (Freiburg, DE) Simon; Markus (Frieburg, DE) Schaible; Ulrich (Frieburg, DE) Kramer; Michael (Frieburg, DE)
		12/1/93	
5,942,236	encoding genes and vaccines of OSPA proteins of Bb supgroups, encoding genes,	assignees: SmithKline Beecham Biologicals (GB) Max-Planck-Gesellschaft zur Forderung der Duetsches Krebsforschungszentrum Stiftung	Kramer; Michael (Frieburg, DE) Schaible; Ulrich (Frieburg, DE) Simon; Markus (Frieburg, DE)

	and vaccines	24-Aug-99	Offentlichen Rechts (Heidelberg, DE) corporate developer: Smithkline Beecham *used in tandem with Yale patents to develop Product.	Wallich; Reinhard (Heidelberg, DE)
5,780,030	Passive vaccine against Lyme disease SKB OSP A	14-Jul-98	assignees: Max-Planck- Gesellschaft zur Forderung der Wissenschaften e.V. (Gottingen, DE); Deutsches Krebsforschun Zentrum Stiftung des Offentlichen Rechts (Heidelberg, DE) corporate developer: SmithKline Beecham *used in tandem with Yale patents to develop Product.	Eichmann; Klaus (Freiburg, DE) Simon; Markus (Frieburg, DE) Kramer; Michael (Frieburg, DE) Reinhard; Wallich (Heidelberg, DE)
5,856,447	Hybridomas producing antibodies specific for lyme disease antigens OspA and OspB	5-Jan-99	assignee: Max-Planck- Gesellschaft zur Forderung der Wissenschaften (Heidelberg, DE)	Schaible; Ulrich (Frieburg, DE) Simon; Markus (Frieburg, DE) Kramer; Michael (Frieburg, DE)

		<p>corporate developer: Smithkline Beecham</p> <p>*used in tandem with Yale patents to develop Product.</p>	<p>Reinhard; Wallich (Heidelberg, DE) Eichmann; Klaus (Freiburg, DE)</p>
<p>5,571,718</p>	<p>Cloning and expression of soluble truncated variants of Borrelia OspA, OspB and Vmp7</p> <p>Product: Prevue</p>	<p>assignee: Associated Universities, Inc. (Washington, DC) (Patents licensed to Brook Biotech by Brookhaven National Lab and NY State)</p> <p>corporate developers: Brook Biotechnologies: Principles Raymond Dattwyler and Benjamin Luft of Stony Brook Chembio Wampole Laboratories Carter Wallace</p> <p>university association: SUNY Stony Brook</p> <p>government claim: DOE/Brookhaven contract #: DE-AC02-76CH0001</p> <p>NIH Small Business Grants: grant #: NIAID: 1R43AI38724- 01 2R44AI38724-02 5R44AI38724-03</p>	<p>Dunn; John J. (Bellport, NY) Barbour; Alan G. (San Antonio, TX)</p>

		4 R44 AI44572-02 NIH Small Bus: 29146	
		5-Nov-96	
5,807,685	OspE, OSPF, and S1 polypeptides in Bb	assignee: Yale University corporate developer: SmithKline Beecham L-2 Diagnostics (Yale Spin-off)	Lam; Tuan T. (San Jose, CA) Flavell; Richard A. (Killingworth, CT) Kantor; Fred S. (Orange, CT) Fikrig; Erol (Guilford, CT) Barthold; Stephen W (Madison, CT)
		15-Sep-98	
		government claim: HHS Grant # A130548	
5,747,294	comp. And methods for the dx and prevention of Lyme disease	assignee: Yale University corporate developer: Smithkline Beecham L-2 Diagnostics (Yale Spin-off)	Barthold; Stephen W (Madison, CT) Fikrig; Erol (Guilford, CT) Flavell; Richard A. (Killingworth, CT) Kantor; Fred S. (Orange, CT)
		5-May-98	
		government claim: HHS Grant # 26815	
5,656,451	OspE, OspF, and S1 polypeptides in borrelia burgdorferi	assignee: Yale University corporate developer: SmithKline Beecham L-2 Diagnostics (Yale Spin-off)	Fikrig; Erol (Guilford, CT) Flavell; Richard A. (Killingworth, CT) Berland; Robert (Kingston, NY) Lam; Tuan T. (San Jose, CA)
		12-Aug-97	
		government claim: NIH Grant # AI30548	Kantor; Fred S. (Orange, CT) Fikrig; Erol

5,618,533	<p>Flagellin-based polypeptides</p> <p>for the diagnosis of lyme disease</p> <p>8-Apr-97</p>	<p>assignee: Yale University</p> <p>corporate developer: Smithkline Beecham</p> <p>L-2 Diagnostics (Yale Spin-off)</p>	<p>(Guilford, CT)</p> <p>Flavell; Richard A. (Killingworth, CT)</p> <p>Berland; Robert (Kingston, NY)</p>
5,434,077	<p>Borrelia burgdorferi strain 257</p> <p>Osp A or Osp B vaccine</p>	<p>assignees:</p> <p>Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. (Gottingen, DE);</p> <p>Deutsches Krebsforschun Zentrum Stiftung des Offentlichen Rechts (Heidelberg, DE)</p> <p>corporate developer: SmithKline Beecham</p> <p>*used in tandem with Yale patents to develop Product.</p>	<p>Kramer; Michael (Frieburg, DE)</p> <p>Schaible; Ulrich (Frieburg, DE)</p> <p>Schaible; Ulrich (Frieburg, DE)</p> <p>Simon; Markus (Frieburg, DE)</p> <p>Wallich; Reinhard (Heidelberg, DE)</p>
6,045,804	<p>Method for detecting B. burgdorferi infection</p> <p>4-Apr-00</p> <p>Test to go with OspA vaccines</p>	<p>assignee:</p> <p>Mayo Foundation for Medical Education and Research (Rochester, MN)</p> <p>Imugen (Allan Steere, David Persing)</p> <p>Sunrise Labs</p>	<p>Persing; David H. (Rochester, MN)</p>

		Government Claims through grant #'s: CDC#U50/CCU-510343 PHS#A1-32403 4-Apr-00 PHS#BAA-9431 PHS#AR-40452 PHS#A1-30548 PHS#A1-41497	
5,489,511	Specific and sensitive diagnostic test for Lyme disease test using plasmid DNA	6-Feb-96 assignee: The United States of America as represented by the Department of Health (Washington, DC)	Schwan; Tom (Hamilton, MT) Garon; Claude (Hamilton, MT) Rocky Mt. Labs
5,470,712	Antigenic proteins of borrelia burgdorferi	6-Feb-96 assignee: 28-Nov-95 none listed Inventors employees of NIH: Rocky Mountain Labs Laboratory of Vectors, Pathogens	Simpson; Warren J. (Hamilton, MT) Schwan; Tom (Hamilton, MT) Garon; Claude (Hamilton, MT) Rocky Mt. Labs
5,403,718	Methods and antibodies for the immune capture capture and detection of Borrelia	government claim: NIH assignee: none listed	Simpson; Warren J. (Hamilton, MT) Schwan; Tom

	burgdorferi	4-Apr-95	Inventors employees of NIH: Rocky Mountain Labs Laboratory of Vectors, Pathogens	(Hamilton, MT) Dorward; David W. (401 N. 7th St., Hamilton, MT 59840) Rocky Mt. Labs
5,308,753	Methods for purifying and detecting IGM antibodies	3-May-94	Rocky Mountain Labs Laboratory of Vectors, Pathogens	Garon; Claude (Hamilton, MT) Huguene; Edward D. (Guilford, CT) Dorward; David W. (Hamilton, MT) Davis; Gary (Millford, CT) Rocky Mountain Labs Rosa; Patricia A. (Hamilton, MT)
5,279,938	Sensitive diagnostic test for Lyme disease		assignee: The United States of America as represented by the Department of Health (Washington, DC) government claim: NIH	Rocky Mt. Labs
5,217,872	Method for detection of Borrelia burgdorferi antigens	8-Jun-93		Dorward; David W.

			(Hamilton, MT) Schwan; Tom (Hamilton, MT) Garon; Claude (Hamilton, MT) Rocky Mountain Labs
6,013,460	Modified western blot membrane and method for detecting lyme disease and other tick-borne diseases 11-Jan-00 products: Qualicode CodaXcel	Immunitics, Incorporated (Cambridge, MA) NIH Small Business Grant	Levin; Andrew E. (Wellesley, MA)
5,100,626	Binding assay device with removable cassette and manifold 31-Mar-92	Immunitics, Incorporated (Cambridge, MA) NIH Small Business Grant	Levin; Andrew E. (Wellesley, MA)
5,965,702	Bb antigens and uses thereof 12-Oct-99	assignee: Abbott Laboratories	Robinson; John M. (Gurnee, IL) Pilot-Matias; Tami J. (Libertyville, IL)
5,643,733	Bb antigens and uses thereof 1-Jul-97		Hunt; Jeffrey C. (Lindenhurst, IL)

5,427,930

Amplification of target nucleic acids using

gap filling ligase chain reaction

27-Jun-95

works for a number of organisms

assignee: Abbott Laboratories

Birkenmeyer;
Larry G.
(Chicago, IL)
Carrino; John
J. (Gurnee, IL)
Dille; Bruce J.
(Antioch,
Hu; Hsiang-
Yun
(Libertyville,
IL)
Kratochvil; Jon
D. (Kenosha,
WI)
Laffler;
Thomas G.
(Liberty
ville, IL)
Marshall;
Ronald L.
(Zion, IL)
Rinehardt;
Laurie A.
(Kenosha, WI)
Solomon;
Natalie A.
(Buffalo
Grove, IL)

5,582,829

RxTechnologies
Garden City, NY

DARPA
Grant No. N0014-90-J-
2032

	Sonicated Bn vaccine multi-valent vaccine produced by exposing Bb to ultrasound	NIH, under a CRADA research: NYU Medical Center and the NIH in cooperation with Georgetown University, Department of Biochemistry and Molecular Biology, pursuant to a contract with the Defense Department's Advanced Research Projects Agency (ARPA).	Alliger; Howard M. (Melville, NY) Frey; Alan (Highland Park, NJ)
		10-Dec-96	
6,074,826	nucleic acid amplification oligonucleotides and probes to Lyme disease associated Borrelia	Gen-Probe Incorporated (San Diego, CA)	Hogan; James J. (Coronado, CA) Yang; Yeasing (San Diego, CA) Carter; Nick (San Diego, CA)
		13-Jun-00	
6,087,097	PCR detection of Borrelia burgdorferi Detects Bb DNA	assignee: Mayo Foundation for Medical Education and Research (Rochester, MN) licensee: GeneX, Inc.	Persing; David H. (Rochester, MN)
		11-Jul-00	
		government claim:	

		NIH Grant Nos. AI30548 and AR41497	
5,977,339	Methods and compositions for diagnosing lyme disease 2-Nov-99		LeFebvre; Rance B. (Davis, CA) Perng; Guey- Chen (San Gabriel, CA)
5,817,460	Nucleic acid probes specific to the spirochete <i>B. burgdorferi</i> associated with lyme disease PCR tech. 6-Oct-98	assignee: La Region Wallonne (Brussels, BE)	Godfroid; Edmond (Brussels, BE) Bollen; Alex (Itterbeek, BE)
5,932,220	Diagnostic tests for a new spirochete, <i>Borrelia lonestari</i> sp. nov 3-Aug-99	Assignee: Board of Regents University of Texas System (Austin, TX) government claim: NIH grant number AI24424	Barbour; Alan G. (San Antonio, TX); Carter; Carol (Bulverde, TX)
5,912,117	Method for diagnosis of lyme disease Using RNA 15-Jun-99	assignee: Roche Molecular Systems, Inc. (Branchburg, NJ)	Dodge; Deborah E. (Albany, CA) White; Thomas J. (Oakland, CA)
5,854,395	Cloned <i>borrelia burgdorferi</i> virulence protein	assignee: The Regents of the University of California (Oakland, CA)	Champion; Cheryl I. (Culver City, CA); Lovett; Michael A.

	protein for vaccine or diagnostic test	Oakland CA Government claim: NIH Grant # AI-29733	(Los Angeles, CA); Haake; David A. Lovett; Michael A. (Los Angeles, CA) Haake; David A. (Culver City, CA) Miller; James N. (Northridge, CA) Blanco; David R. (Beverly Hills, CA)
5,620,862	Methods for diagnosing early Lyme disease using Osp C	15-Apr-97 assignee: University of Connecticut (Storrs, CT) government claims: US Public Health Service Grant # 5R29-AR39361	Padula; Steven J. (Simsbury, CT)
5,466,577	Nucleic acid probes for the detection of Lyme disease spirochetes	assignee: Amoco Corporation	Weisburg; William G. (Milford, MA)
5,385,826	Diagnostic assay for lyme disease culture test	31-Jan-95 Gundersen Medical Foundation, Ltd. (Lacrosse, WI)	Schell; Ronald F. (Madison, WI) Steven M. (Onalaska, WI)
5,283,175	Genus-specific oligomers of	The Research Foundation of State University of New York	

	Borrelia and methods of using same. PCR tech to amplify Bb flagellin 1-Feb-94	(Albany, NY)	Wise; Darla J. (Blacksburg, VA) Weaver; Terry L. (Fredonia, NY)
5,246,844	Virulence associated proteins in Borrelia burgdorferi (BB) useful diagnostic antigens 21-Sep-93	assignee: Board of Regents, The University of Texas System (Austin, TX) government claims: NIH grant #'s AI 24424 and AI 29731	Norris; Steven J. (Houston, TX) Barbour; Alan G. (San Antonio, TX)
5,155,022	Assay for lyme disease differentiates cross-reactive antibodies 13-Oct-92	assignee: Becton, Dickinson and Company (Franklin Lakes, NJ)	Naqui; Ali (Sparks, MD) Gossett; Liane F. (Morrisville, NC) Mapes; James P. (Raleigh, NC)
5,554,371	Recombinant vaccine against Lyme disease September 10, 1996	Regents of the University of Minnesota (Minneapolis, MN)	Caputa; Anthony C. (Nanuet, NY); Bey; Russell F. (Arden Hills, MN); Murtaugh; Michael P. (Roseville, MN)

4,721,617	<p>Vaccine against lyme disease</p> <p>January 26, 1988</p>	<p>Assignee: Regents of the University of Minnesota (Minneapolis, MN)</p> <p>Partners: MGI Pharma and American Health Products.</p> <p>Product: Lymevac For dogs</p> <p>Public Health Service Grant AM 34733.</p>	<p>Johnson; Russell C. (St. Paul, MN)</p>
5,985,595	<p>Early detection of Borrelia infection</p> <p>November 16, 1999</p> <p>1st test to work weeks 3-6, based on polymorphonuclear leukocytes (PMNs)</p>	<p>Assignee: The University of Connecticut (Storrs, CT)</p> <p>Licensee: Bio- Investigation Ltd., the Madison, Conn</p> <p>Manufacture and marketing: Aventis Pasteur</p>	<p>Krider; Hallie M. (Willimantic, CT); Bushmich; Sandra Lee (Hebron, CT)</p>

5,187,065

Method and materials for
detecting lyme disease: antigen
decomplexing

Schutzer;
Steven E. (21
Canterbury
Rd., Great
Neck, NY
11021)

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

**INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT
COOPERATION TREATY (PCT)**

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1. [\(WO 00/65064\) PEPTIDES AND ASSAYS FOR THE DIAGNOSIS OF LYME DISEASE AND COMPOSITIONS USEFUL FOR THE PREVENTION THEREOF](#)
THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND 1430
Tulane Avenue, New Orleans, LA 70112-2699
PHILIPP, Mario, T. 248 Shaunell Drive, Mandeville, LA 70448 ; LIANG,
Fang, Ting 7 Lurline Drive, Apt. 9, Covington, LA 70433
2. [\(WO 00/63386\) PREVENTION, DIAGNOSIS AND TREATMENT OF LYME DISEASE](#)
BOSTON MEDICAL CENTER CORPORATION One Boston Medical
Center Place, Boston, MA 02118
DONTA, Sam 127 Pembroke Street, #3, Boston, MA 02118 ;
CARTWRIGHT, Mark 472 Waltham Street, West Newton, MA 02465
3. [\(WO 00/06745\) USES OF THE BORRELIACIDAL EPITOPE\(S\) OF BORRELIA *BURGDORFERI* OUTER SURFACE PROTEIN C \(OSPC\) AS VACCINE](#)
GUNDERSEN LUTHERAN MEDICAL FOUNDATION, INC. 1836 South
Avenue, LaCrosse, WI 54601
CALLISTER, Steven, N. 2050 Grandview Boulevard, Onalaska, WI 54650
LOVRICH, Steven, D. 1626 Keller Ct., Onalaska, WI 54650
SCHELL, Ronald, F. 157 Nautilus Drive, Madison, WI 53705
JOBE, Dean, A. 3324 Hanson Ct., LaCrosse, WI 54603
4. [\(WO 99/61048\) CORRELATIVE PROTECTION USING OspA ANTIBODY TITERS](#)
SMITHKLINE BEECHAM CORPORATION One Franklin Plaza,
Philadelphia, PA 19103
SMITHKLINE BEECHAM BIOLOGICALS 89, rue de l'Institut, B-1330
Rixensart; (BE). PARENTI, Dennis 453 Printer Way, Lansdale, PA 19446
LOBET, Yves 89, rue de l'Institut, B-1330 Rixensart;
(GILLET, Marc 89, rue de l'Institut, B-1330 Rixensart

5. [\(WO 99/60009\) IMPROVED METHODS FOR DETECTING A TARGET NUCLEIC ACID FRAGMENT](#)
 IGENEX, INC. 797 San Antonio Road, Palo Alto, CA 94303
 SHAH, Jyotsna, S. 14 Preserve Drive, Nashua, NH 03060
 HARRIS, Nick, S. 420 University Avenue, Los Gatos, CA 95030
6. [\(WO 99/40200\) RECOMBINANT LIPIDATED PsaA PROTEIN, METHODS OF PREPARATION AND USE](#)
 CENTER FOR DISEASE CONTROL AND PREVENTION 1600 Clifton Road, N.E., Atlanta, GA 30333;
 ADES, Edwin, W. 4432 Whitewater Creek Road, Atlanta, GA 30327
 CARLONE, George, M. 5243 Sandy Shoals Lane, Stone Mountain, GA 30087
 DE, Barun, K. 2530 Blyth Lane, Snellville, GA 30078
 SAMPSON, Jacquelyn, S. 4220 Greentree Lane, College Park, GA
 HUEBNER, Robert, C. 860 Queen Street, Stroudsburg, PA 18360
7. [\(WO 99/32602\) CULTURE MEDIUMS](#)
 PHILLIPS, Steven, E. Suite 2, 10 Roberts Lane, Ridgefield, CT 06877
 MOAYAD, Hamid Suite 311, 1305 Airport Freeway, Bedford, TX 76021
 MATTMAN, Lida, H. 319 Rivard Road, Grosse Point, MI 48230
8. [\(WO 99/14345\) MEDICAMENT FOR TREATING A MANIFESTED LYME DISEASE](#)

 MAX- PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.
 H ofgartenstrasse 2, D-80539 München ;
 SIMON, Markus, M. Sebastian-Kneipp-Strasse, D-79104 Freiburg ;
 ZHONG, Weimin Sundgau Allee 12, D-79106 Freiburg ;
 WALLICH, Reinhard Hermann-Löns-Weg 52, D-69118 Heidelberg
 KRAMER, Michael, D. Bergstrasse 85, D-64319 Pfungstadt
9. [\(WO 99/13057\) CLASS I-TYPE LYSYL-tRNA SYNTHETASE](#)
 YALE UNIVERSITY Office of Cooperative Research, 155 Whitney Avenue, New Haven, CT 06520-8336
 SÖLL, Dieter 145 Dessa Drive, Hamden, CT 06517
 IBBA, Michael 192 Edward Street,
 New Haven, CT 06511
10. [\(WO 99/12960\) P13 ANTIGENS FROM BORRELIA](#)
 SYMBICOM AB Tvistevägen 48, S-907 36 Umeå; (SE). [SE/SE]. (for all designated states except US)
 BERGSTRÖM, Sven Marmorvägen 95, S-907 42 Umeå; (SE) [SE/SE].
11. [\(WO 99/00413\) SURFACE ANTIGENS AND PROTEINS USEFUL IN COMPOSITIONS FOR THE DIAGNOSIS AND PREVENTION OF LYME DISEASE](#)

THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND 1430
Tulane Avenue, New
Orleans, LA 70112-2699 ; (US). [US/US]. (for all designated states except US)

PHILIPP, Mario, T. 248 Shaunell Drive, Mandeville, LA 70448 ; (US)
[US/DE].

12. [\(WO 98/59071\) LYME DISEASE VACCINES](#)

HUMAN GENOME SCIENCES, INC. 9410 Key West Avenue, Rockville, MD
20850 ; (US). [US/US]. (for
all designated states except US) MEDIMMUNE, INC. 35 West Watkins Mill
Road, Gaithersburg, MD
20878 ; (US). [US/US].
CHOI, Gil, H. 11429 Potomac Oaks Drive, Rockville, MD 20850 ; (US)
[US/KR]. ERWIN, Alice, L. 5101
Connecticut Avenue, N.W., Washington, DC 20008 ; (US) [US/US]. HANSON,
Mark, S. 5962 Camelback
Lane, Columbia, MD 21054 ; (US) [US/US]. LATHIGRA, Raju 19051 Steeple
Place, Germantown, MD
20874 ; (US) [US/IN].

13. [\(WO 98/58943\) BORRELIA *BURGDORFERI* POLYNUCLEOTIDES AND SEQUENCES](#)

HUMAN GENOME SCIENCES, INC. 9410 Key West Avenue, Rockville, MD
20850 ; (US). [US/US]. (for
all designated states except US) MEDIMMUNE, INC. 35 West Watkins Mill
Road, Gaithersburg, MD
20878 ; (US). [US/US].

FRASER, Claire 11915 Glen Mill Road, Potomac, MD 20854 ; (US) [US/US].
WHITE, Owen, R. 886
Quince Orchard Boulevard #202, Gaithersburg, MD 20878 ; (US) [US/US].
CLAYTON, Rebecca 6706 B.
Polor Avenue, Takoma Park, MD 20912 ; (US) [US/US]. DOUGHERTY,
Brian, A. 10 Rosemary Lane,
Killingworth, CT 06419 ; (US) [US/US]. LATHIGRA, Raju 19051 Steeple
Place, Germantown, MD 20874 ;
(US) [US/IN]. SMITH, Hamilton, O. 8222 Carrbridge Circle, Towson, MD
21204 ; (US) [US/US].

14. [\(WO 98/39028\) LYME COMBINATION COMPOSITIONS AND USES](#)

MERIAL LIMITED 115 Transtech Drive, Athens, GA 30601 ; (US). [US/US].
JARECKI-BLACK, Judy 467 Ware Road, Carnesville, GA 30521

15. [\(WO 98/06850\) IMMUNOLOGICALLY ACTIVE PROTEINS OF BORRELIA *BURGDORFERI*, CODED NUCLEIN ACIDS OF SUCH AND THEIR USE IN TEST KITS AND VACCINES](#)

MIKROGEN MOLEKULARBIOLOGISCHE ENTWICKLUNGSGMBH
Westendstrasse 125, D80339 München; MOTZ, Manfred Gatterburgstrasse 7, D-

80689 München; (DE)
SOUTSCHEK, Erwin Enzianweg 49, D82335 Berg; (DE)

16. [\(WO 97/47197\) COMPOSITIONS AND METHODS FOR ADMINISTERING BORRELIA DNA](#)

PASTEUR MERIEUX SERUMS ET VACCINS 58, avenue Leclerc, F69007 Lyon ; (FR). [FR/FR].ORM=)

VICAL, INC. Suite 100, 9373 Towne Center Drive, San Diego, CA 92121 ; (US). [US/US]. TEXAS HEALTH

SCIENCE CENTER, UNIVERSITY OF, AT SAN ANTONIO 201 West 7th Street, Austin, TX 78701 ; (US).

[US/US].

HUEBNER, Robert, C. 860 Queen Street, Stroudsburg, PA 189601941 ; (US). NORMAN, Jon, A. 11602 Via

Tavito, San Diego, CA 92128 ; (US). LIANG, Xiaowu 5851 Desert View Drive, La Jolla, CA 92037 ; (US).

CARNER, Kristin, R. 17161 Alva Road #2733, San Diego, CA 92127 ; (US). BARBOUR, Alan, G. 404

Charles Road, San Antonio, TX 78209 ; (US). LUKE, Catherine, J. 5903 Danny Kaye Drive #3006, San Antonio, TX 78240 ; (US).

17. [\(WO 97/42325\) B. BURGDORFERI POLYPEPTIDES EXPRESSED IN VIVO](#)

YALE UNIVERSITY 451 College Street, New Haven, CT 06520 ; (US). [US/US]. (for all designated states except US)

FIKRIG, Erol 101 Coventry Way, Guilford, CT 06437 ; (US) [US/US]. SUK, Kyoungho 47, WondaeIdong

Seogu, Taegu 703031 ; (KR) [KR/KR]. BARTHOLD, Stephen, W. 18 Little Hollow Road, Madison, CT

06443 ; (US) [US/US]. FLAVELL, Richard, A. 283 Moose Hill Road, Guilford, CT 06437 ; (US)

18. [\(WO 97/42221\) NOVEL OSPC DERIVED PEPTIDE FRAGMENTS](#)

STATENS SERUMINSTITUT Artillerivej 5, DK2300 København S ; (DK). [DK/DK]. (for all designated states except US)

MATHIESEN, Marianne, Jartved Strandvejen 94, 1. th., DK2900 Hellerup ; (DK) [DK/DK]. THEISEN,

Michael N.J. Fjords Allé 20, 4. th., DK1957 Frederiksberg C ; (DK) [DK/DK]. HOLM, Arne Margrethevej

19, DK2840 Holte ; (DK) [DK/DK]. ØSTERGAARD, Søren Sandbjerggade 54,

3. th., DK2200
København N ; (DK)

19. [\(WO 97/27301\) DECORIN BINDING PROTEIN COMPOSITIONS AND METHODS OF USE](#)

THE TEXAS A & M UNIVERSITY SYSTEM 310 Wisenbaker, College Station, TX 778433369; (US).

[US/US]. (for all designated states except US) MEDIMMUNE INCORPORATED 35 W. Watkins Mill Road, Gaithersburg, MD 20878; (US). [US/US].

GUO, Betty, P. 7900 Cambridge, No. 202G, Houston, TX 77054; (US)
HÖÖK, Magnus 4235

Oberlin, Houston, TX 77005; (US) [US/US]. HANSON, Mark 5962 Camelback Lane, Columbia, MD 21045

20. [\(WO 97/26273\) BORRELIA *BURGDORFERI* OUTER MEMBRANE PROTEINS](#)

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA 22nd floor, 300 Lakeside Drive, Oakland, CA

946123550 ; (US). [US/US]. ORM(=) SLOANKETTERING INSTITUTE FOR CANCER RESEARCH

1275 York Avenue, New York, NY 10021 ; (US). [US/US].

SKARE, Jonathan, T. 502 Hensel Road, Bryan, TX 77801 ; (US). SHANG, Ellen, S. 1247 Stoner Avenue #305,

Los Angeles, CA 90025 ; (US). CHAMPION, Cheryl, I. 4900 Overland Avenue #262, Culver City, CA 90230 ;

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90077 ; (US). MIRZABEKOV, Tajib, A. 3301 Sepulveda Boulevard #16, Los Angeles, CA 90034 ; (US).

KAGAN, Bruce, L. 655 Haverford Avenue, Pacific Palisades, CA 90272 ; (US).

TEMPST, Paul Apartment 4C,

402 East 64th Street, New York, NY 10021 ; (US).

21. [\(WO 97/26006\) COMPOSITIONS AND METHODS FOR ADMINISTERING BORRELIA *BURGDORFERI* ANTIGENS](#)

THE UNIVERSITY OF TEXAS SYSTEM 201 West 7th Street, Austin, TX 70701 ; (US). [US/US].

(72)

BARBOUR, Alan, G. 404 Charles Road, San Antonio, TX 78209 ; (US). LUKE, Catherine, J. 5903 Danny

Kaye Drive, #3006, San Antonio, TX 78240

22. [\(WO 97/15600\) TICK \(*IXODES SCAPULARIS*\) VECTOR SALIVAINDUCTION](#)

LYME DISEASE SPIROCHETE (BORRELIA *BURGDORFERI*) ANTIGENS AS VACCINE CANDIDATES

THE BOARD OF GOVERNORS FOR HIGHER EDUCATION, STATE OF RHODE ISLAND AND

PROVIDENCE PLANTATIONS 199 Promenade Street, Providence, RI 02908 ; (US). [US/US].

NELSON, David, R. 13 Mulberry Drive, Wakefield, RI 02879 ; (US). MATHER, Thomas, N. 215 Kings Ridge

Road, Wakefield, RI 02879 ; (US). SCORPIO, Angelo 9238 Moonfire Place, Columbia, MD 21045

23 (WO 99/35272) RECOMBINANT P37/FlaA AS A DIAGNOSTIC REAGENT

BIOMERIEUX, INC. 800 Hingham Street, Rockland, MA 02370 ; (US).

[US/US]. (for all designated states

except US)

(72)(75)

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INVENTORS ARE BOTH EMPLOYEES OF THE CDC. Rights accrue to the CDC, the National Center for Infectious Diseases, and the Department of Health and Human Services.

Section IX

Estimating the Size of the Market for Lyme Disease Vaccines and Serological Tests

Lyme disease has attracted a significant amount of funding and attention. But most grant and investment monies have gone into vaccines and diagnostics as opposed to the search for more effective treatment.

This has occurred even though, according to the government's risk-benefit analysis,^{lxxxii[82]} underwriting the cost of a Lyme vaccine doesn't make economic sense. "At an assumed cost of vaccination of \$100/person/year, a vaccine effectiveness of 0.85, a probability of 0.85 of correctly identifying and treating early Lyme disease, and an assumed incidence of Lyme disease of 1,000/100,000 persons/year, the net cost of vaccination to society was \$5,692/case averted and \$35,375/complicated neurologic or arthritic case avoided," according to the CDC. "Using these same baseline assumptions, the societal cost of vaccination exceeds the cost of not vaccinating, unless the incidence of Lyme disease is greater than 1,973/100,000 persons/year. Of the variables examined, the incidence of Lyme disease had the greatest impact on cost-effectiveness of vaccination. The likelihood of early diagnosis and treatment also has a substantial impact on vaccine cost-effectiveness because of the reduced incidence of sequelae when Lyme disease is diagnosed and patients are treated early in the disease.

"Most disease-endemic states and counties report Lyme disease incidence that is substantially below 1,000/100,000 persons/year. For example, in 1997, the highest reported state incidence was 70/100,000 persons in Connecticut, and the highest

reported county incidence was 600/100,000 population in Nantucket County, Massachusetts. However, some studies document that approximately 10%-15% of physician-diagnosed cases of Lyme disease are reported to state authorities in highly endemic areas. Epidemiologic studies of populations at high risk in the northeastern United States have estimated annual incidence of greater than 1,000/100,000 persons/year in several communities.”

Many experts agree that Lyme disease is spreading out from endemic areas, but given the numbers, government economists suggest individuals be asked to purchase their own Lyme vaccine, if they so desire, instead of depending upon the government to pitch in. “Individuals may wish to use their own money and resources to pay for their own vaccine,” says CDC economist Martin Meltzer. “In such a case, they might base their decision on their personal valuation of the risk of contracting Lyme disease, their physician recommendations, and the FDA’s guidelines regarding the use of the vaccine.”

If the vaccine won’t save society any money, and if experts claim Lyme is so easily treated and cured for most individuals, why do federal grants reveal government investing so heavily in Lyme disease products? Indeed, the US government holds revenue claims to more Lyme disease vaccine and test-kit patents than any other single entity, as shown in the patent list above.

One possibility is that, for the US government, like other investors and developers, the business model of Lyme makes sense as financial investment, even if not as social policy. As long as it does not have to underwrite the cost of purchasing the product for consumers thereafter, the US government may have made a wise investment in a line of popular and promising products, much like Aventis Pasteur or GlaxoSmithkline.

Projections for revenue and profitability come from the companies producing the products, and are easily accessible in corporate literature and especially in applications for NIH grants. Below, are just some of the projections:

1. The total market for serological assays (Western blots) for the diagnosis of Lyme disease is estimated to be 2,000,000 units per year in the US and a similar number in Western and Eastern Europe. NIH Grant # 5R01AI43063-02, Cabello, Felipe, Regulation of Expression of *Borrelia Burgdorferi* Bmpc_
1. The estimated market for a Babesia test should be similar to that for Lyme disease testing both in the US and worldwide. Current estimates for this market are \$30-\$50 million a year but could be greater if blood bank testing is mandated even on a regional basis. NIH Grant # 2R44AI41840-02, Houghton, Raymond L., Novel Antigens for the Serodiagnosis of Human Babesiosis
2. “In the US and Europe, about 5 million Lyme (ELISA) tests are performed each year. When OspA-based Lyme vaccines come on the market, essentially the entire diagnostic market will be open to the first company with an approved assay that can detect *B. burgdorferi* infection regardless of vaccination status.” -- NIH Grant # 5R44AI38724-03, John Glass, research director of Brook Biotechnologies.
1. 1. Vaccines will be even more profitable. Current versions require a yearly booster, after all. And if we assume the average cost of the vaccine per year per

person to be \$100, in line with estimates of the CDC, one can see that vaccinating just one percent of the US population--now at 276 million--would yield enormous revenue. To wit: 2.8 million vaccinations @\$100 per year equals almost \$280 million in revenue. Economists anticipate equivalent revenue in Europe.

Without attempting a formal financial analysis, and in the absence of a marketing study, we'd like to do some simple extrapolation. In a rough rule of thumb analysis, assuming a the conservative reach of one percent of the population in the US and Europe, the per annum revenue for vaccines and test kits for Lyme disease, Ehrlichia, and Babesia would be between approximately \$500 million and \$1 billion a year, within 5 years, if the products succeed. As the diseases and knowledge about them spread, and as automation renders screening tests more useful, those numbers will increase. The revenue potential of the vaccine will fuel the need for new and improved tests and large-scale clinical trials. Each new version of a vaccine will engender the need for more clinical trials and additional test kits, bringing money into universities and smaller biotech companies, respectively. The phenomenon of global warming, which pushes the number of ticks and the occurrence of vector-borne disease higher with each new season, is a stimulant to this industry as well.

It goes without saying that the inventors and assignees of the patents fueling this industry may see huge economic windfalls if their products come to market and succeed.

PART THREE: CONFLICTS OF INTEREST IN LYME DISEASE POLICY

In the case of Lyme disease treatment guidelines, laboratory tests, and vaccines, individuals with the appearance of conflict of interest have helped to set policy in line with associated corporate agendas or special interests through prominent roles in the following critical committees and working groups:

1. 1. **Laboratory Diagnostics:** Conference on the Laboratory Diagnosis of Lyme Disease, March 1998, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID,) the Centers for Disease Control and Prevention (CDC,) and the Office of Rare Diseases (ORD.) ^{lxxxiii[83]}
2. 2. **Laboratory Diagnostics:** Second National Conference on the Serological Diagnosis of Lyme disease, 27-29 October 1994, Dearborn, MI, sponsored by the CDC and the Association of State and Territorial Public Health Laboratory Directors. ^{lxxxiv[84]}
1. 1. **Vaccine Approval:** United States of America Department of Health and Human Services Food and Drug Administration, Center for Biologics Evaluation and Research, Vaccines and Related Products Advisory Committee Meeting, Tuesday, May 26, 1998. Conference for approval of the Smithkline Beecham OspA-A Lyme disease vaccine, Lymerix. ^{lxxxv[85]}
1. 1. **Vaccine Guidelines:** Recommendations of the Advisory Committee on Immunization Practices (ACIP,) June 4, 1999. ^{lxxxvi[86]}

1. **Treatment Guidelines** From The Infectious Diseases Society Of America. 2000.

lxxxvii[87]

Section X

Defining Conflict of Interest

What is a conflict of interest? It seems that every university, government agency, and corporation has its own definition. But since the committees we cover here have been setting federal policy, we refer to precise US law. The laws covering conflict of interest are explained in the section below, excerpted from the summary put together by the staff of Committee on Government Reform.

Laws Governing Advisory Committees^{lxxxviii[88]}

Federal law requires that advisory committees be balanced in terms of points of view of their members and that they conduct their business in public. The law also requires that advisory committee members disclose their financial interests and recuse themselves from matters in which they have an interest. The following is a brief description of the requirements of these laws:

1. Federal Advisory Committee Act (FACA)^{lxxxix[89]}:

The FACA, signed into law by President Richard Nixon in 1972, regulates advisory committees, task forces and councils established by either the President, the federal agencies or Congress. These increasingly influential advisory bodies have been considered by many to be the fifth branch of government.^{xc[90]} It is important to note, however, that the FACA does not address the conflict of interest of committee members; these are addressed in a separate statute and dealt with by individual agencies in the Code of Federal Regulations.^{xcii[91]} The

FACA's most significant requirements fall into three basic categories:

a.) Scope of Committees: The statute clearly states that the function of advisory committees is to be advisory only. They provide advice and recommendations that may or not may be adopted. The final determination is to be made by the official or agency involved.^{xcii[92]}

b.) Requirement of Openness: The second important issue addressed by the FACA is the need for openness in the proceedings of advisory committees. With very few exceptions, all advisory committee meetings are to be open to the public and the materials distributed at the meetings, including working papers, studies agendas, etc..., are to be made available to the public for inspection.^{xciii[93]}

c.) Balanced Representation: Perhaps the most controversial provision of the FACA is the need for a membership that is fairly balanced in terms of the points of view represented and the functions of the committee.^{xciv[94]} The statute specifically forbids the committees to be inappropriately influenced by special interests.^{xcv[95]}

2. Conflicts of Interest Statutes.^{xcvi[96]}

The ethics guidelines for the advisory committees are set by the agencies in accordance with federal statute, specifically 18 U.S.C. [Section 202-209. Under the statute, advisory committee members are considered "Special Government Employees," or SGEs. SGEs provide temporary services to the U.S. government, not to exceed 130 days a year. As SGEs, advisory committee members must comply with Federal conflict of interest laws. 18 U.S.C. Section 202-209 broadly prohibits employees, including SGEs, from participating in a decision-making process when they have a personal interest in the matters discussed, absent a waiver from the relevant parties.^{xcvii[97]} The types of waivers found in the statute are:

a.) (b)(1) waivers: The employee may participate when the appointing official

determines that the financial interest is not so substantial as to be deemed likely to affect the integrity of the services that the Government may expect.^{xcviii[98]}

b.) (b)(2) waivers: Employee may participate if the interest is so remote or inconsequential that it will not have a special or distinct effect on the employee or his employer.^{xcix[99]}

c.) (b)(3) waivers: specifically applicable to advisory committee members, this waiver will allow them to participate in matters for which he would have been disqualified, if it is determined that the need for the employee's services outweigh the potential conflict of interest created by the employee's financial interest.^{ci[100]} Factors that may be considered include: type of interest, identity of the person, uniqueness of the individual's qualifications, difficulty of locating a similarly qualified individual without a disqualifying interest, the dollar value of the interest- including its value relevant to the member's assets, and the extent to which the financial interest will be affected by the actions of the committee.

3. Code of Federal Regulations (CFR) & Office of Government Ethics (OGE): Since most advisory committee members are considered special government employees, the provisions in 18 U.S.C. Section 201-219 that address conflicts of interest apply to them. However, the statute only provides broad guidelines, so that it is up to the individual agencies to provide the specific rules governing conflict of interest.^{ci[101]} In the case of the Department of Health and Human Services (DHHS), these regulations can be found at 5 C.F.R. Section 2635 and in 5 C.F.R. Section 2640. Under the DHHS regulations, an advisory committee member may not participate, absent a waiver, in matters in which they have a financial interest. These are divided into the following categories:

a.) Particular matter: includes matters that involve deliberation, decision, or action focused on the interests of specific persons, or a discrete and identifiable class of persons.^{cii[102]}

b.) Particular matter involving specific parties: the code defines this term to include proceedings, applications, requests for determination, contracts, claims, controversies and/or investigations involving specific parties. The term typically involves a specific proceeding affecting the legal rights of the parties, or an isolatable transaction or related set of transactions between identified parties.^{ciii}

^[103] This term will generally refer to the particular issue, vaccine and or company that will be directly affected by the advisory committee discussions.

c.) Particular matter of general applicability: the code defines this term as a particular matter that is focused on the interests of a discrete and identifiable class of persons, but does not involve specific parties.^{civ[104]} This definition becomes relevant in the discussion of companies that may be indirectly affected by the proceedings of an advisory committee. In this report, the companies under this category will be referred to as affected companies.

d.) A direct and predictable effect on their financial interest: a direct effect on a financial interest is defined as a close causal link between any decision or action to be taken in the matter and any expected effect of the matter on the financial interest.^{cv[105]} According to the CFR, the effect may actually be considered direct even though it does not occur immediately. However, the CFR also specifies that the link will not be direct in instances where the chain of causation is attenuated or is contingent upon the occurrence of events that are speculative.^{cvi[106]} On the other hand, predictable is defined in the code as a situation where there is a real possibility that the matter will be affected.

e.) Affected interests: according to the CFR, the disqualifying financial interests include: salary, indebtedness, job offer, or any other similar interests that could be affected by the matter discussed.^{cvi[107]} It also includes the interests of persons other than the advisory committee members, such as a spouse, children, general partner, place of employment, organizations where the advisory committee

member serves as officer, director and/or trustee, and prospective employers.^{cviii}

[108]

f.) Interests in securities: The CFR specifically addresses the potential conflicts that may arise out of interests in securities, such as stock holdings. The guidelines provided for in the CFR include:

(1) De minimis exemption: This exemption applies to publicly-traded or long-term Federal/ municipal securities. The CFR states that persons having holdings in the specific parties involved of \$5,000 or less or holdings in the affected companies of \$25,000 or less will be allowed to participate in the proceedings of the advisory committee. These financial interests are deemed to be of low involvement and do not require a waiver, but a simple disclosure on the forms required by the particular agency or department.

(2) Employment exemption: Under the DFR, SGEs may participate in the advisory committee discussions on matters of general applicability so long as the otherwise disqualifying financial interest arises only from the committee member's non-Federal employment or prospective employment and so long as the matter does not have a special or distinct effect on the employee or employer other than as part of a class. In other words, under these circumstances, employees will be granted an automatic waiver.

g.) Teaching, speaking and writing on subject of meeting: SGEs are prohibited from receiving compensation for teaching, speaking, and writing on subjects related to the employee's official duties on the advisory committee.^{cix[109]}

The Code also stipulates that an SGE may not participate in matters that are likely to have a direct and predictable effect on the financial interests of ...a person with whom he has a covered relationship, including members of his household, close friends or employer.^{cx[110]} This type of

conflict requires that the member disclose the potential conflict and that said conflict be waived by the agency designee.

Section XI Laboratory Diagnosis and Conflict of Interest

Two meetings served to simplify the serological profile of Lyme disease, in the process eliminating OspA (used to make the first and second generation vaccines) from the diagnostic profile while, at the same time, clearing the path for commercialization of OspA-based Lyme disease patents and products, among others.

Second National Conference on the Serological Diagnosis of Lyme Disease, 1994

Held on October 27-29, 1994, in Dearborn, Michigan, this conference was sponsored by the CDC and the Association of State and Territorial Public Health Laboratory Directors. This watershed meeting changed the face of Lyme with a new and far more stringent definition of the disease. Participants included state health departments, diagnostic laboratories, universities, and government agencies. But it was a planning committee of 16 that heard all the evidence and decided policy for the group. This controversial meeting stirred great debate among the participants, and many questions and objections from the floor. However, when all was said and done, the committee passed, almost without change, the diagnostic criteria they had originally proposed.

The committee consisted of 7 regular members and 9 consultants added for their expertise on Lyme. The 7 regular members, largely hailing from state health departments and other government agencies, gave the floor to the consultants, whose expertise guided the plans. These consultants included:

Alan G. Barbour, MD, Univ. of TX Health Sciences Center, San Antonio, TX.

Among factors that may contribute to the appearance of conflict of interest, according to Federal guidelines:

1. Rights to multiple patents related to Lyme vaccines and tests (see patent table, above.)^{cxii[111]}
2. Inventor of the vaccine technology used by Aventis Pasteur to manufacture its second (and third and beyond) generation vaccines. ^{cxiii[112]}

Allen C. Steere, MD, Professor of Medicine/Chief of Rheumatology, Tufts-New England Medical Center, Boston, MA.

Among factors that may contribute to the appearance of conflict of interest, according to federal guidelines:

1. 1. Lead researcher for the SmithKline Beecham Lyme disease vaccine, Lymerix.^{cxiii[113]}
2. 2. On the consulting staff on Imugen, a biotechnology company whose product lines hinge, in large part, on success of the OspA vaccine.^{cxiv[114]}

Other facts of interest:

3. 3. Steere published articles on the genetic marker theoretically associated with extreme vaccine adverse events for OspA vaccine, yet still worked to have the vaccine approved at the 1998 FDA hearing. ^{cxv[115]}
4. 4. Former employee of both the CDC and Yale University.

Raymond J. Dattwyler, MD, SUNY at Stony Brook, School of Medicine, Stony Brook, NY. , CEO, Brook Biotechnologies, Stony Brook, New York.

Among factors that may contribute to the appearance of conflict of interest, according to Federal guidelines:

1. 1. Company develops Lyme test kit and vaccine products tied, in part, to serological definition of Lyme disease established at Dearborn.^{cxvi[116]}
2. 2. Working under federal grant money to commercialize patent # 5,571,718, licensed from Brookhaven Laboratory in New York, to create a series of diagnostic tests, including one that differentiates those vaccinated with the SmithKline Beecham OspA vaccine product from those with infection.^{cxvii[117]}
3. 3. Worked with Glaxo on Ceftin and served as consultant and investigator to Roche on Rocephin, one of the recommended drugs.^{cxviii}

[118]

Duane Gubler, Sc.D, DVBIID/CDC, Fort Collins, CO.

Among the factors that may contribute to the appearance of conflict of interest, according to Federal guidelines: Employer, the CDC, filed for rights to a Lyme disease diagnostic test through the World International Property Organization in 1999 (Application Number: WO 99/40200, Title: Recombinant Lipidated PsaA Protein, Methods Of Preparation And Use). The new CDC patent can be used for diagnostic tests and vaccines. CDC also has rights to **WO 99/35272**^{cxix[119]}, **entitled** “Compositions and methods for serological immunoassay for the detection of *Lyme disease* infection using recombinant P37/FlaA

protein antigen and methods for producing such protein antigen.” This work may be used for diagnostic tests or for creation of future generations of the OspA vaccine. Assignee is BIOMERIEUX, INC, of Rockland, MA. Biomerieux has recently merged with Cambridge Biotech to form Aquila Biopharmaceuticals, a major manufacturer of Lyme vaccines and diagnostic tests for animal health. Aquila Biopharmaceuticals is a partner of SmithKline Beecham and Aventis Pasteur, the two major manufacturers of Lyme disease for humans.^{cxix[120]} (See, also, patent and product listings, above.)

Barbara Johnson, Ph.D., DVVID/CDC, Fort Collins, CO. Chief, Molecular Biology Section, DVVID, CDC, NCID, Fort Collins, CO.

Among factors that may contribute to the appearance of conflict of interest, according to Federal guidelines:

1. Her employer, the CDC, filed for rights to a Lyme disease diagnostic test through the World International Property Organization in 1999 (Application Number: WO 99/40200, Title: Recombinant Lipidated P₃₇/FlaA Protein, Methods Of Preparation And Use). The new CDC patent can be used for diagnostic tests and vaccines.
2. Johnson is named as inventor on WO 99/35272,^{cxix[121]} entitled “Compositions and methods for serological immunoassay for the detection of *Lyme disease* infection using recombinant P₃₇/FlaA protein antigen and methods for producing such protein antigen.” This work may be used for diagnostic tests or for creation of future generations of the OspA vaccine. Assignee is BIOMERIEUX, INC, of Rockland, MA. Biomerieux has recently merged with Cambridge Biotech to form Aquila Biopharmaceuticals, a major manufacturer of Lyme vaccines and diagnostic tests for animal health. Aquila Biopharmaceuticals is a partner of GlaxoSmithKline and Aventis Pasteur, the

two major manufacturers of Lyme disease vaccines for humans.^{cxixii[122]} Indeed, in addition to Aquila's internal product development programs, Aquila has seven corporate partners that have licensed its Stimulon® adjuvants for a variety of human diseases: SmithKline Beecham, p.l.c.; Wyeth-Lederle Vaccines and Pediatrics; Aventis Pasteur; Bristol Myers–Squibb (Progenics Pharmaceuticals, Inc.); VaxGen, Inc.; Elan Corporation, plc.; and Korea Green Cross Corporation. In return for rights to use Stimulon® adjuvants for specific diseases, the corporate partners have agreed to pay Aquila license fees, milestone payments, and royalties on product sales. Aquila has retained worldwide manufacturing rights for QS-21. In addition to corporate partners, Aquila has developed a number of academic collaborations to test potential product formulations containing QS-21.^{cxixiii[123]} It is also notable that although Aquila will maintain its identity, it was recently purchased by Antigenics, a company specializing in producing antigens of specific use in a wide variety of Western blot and ELISA tests. Finally, Biomerieux's patented technology has recently been used by the CDC, in the peer-reviewed literature, to argue against research in opposition to the Dearborn Criteria while the specifics, defended as patent-protected by Biomerieux, are not revealed.^{cxixiv[124]} Note this comment in the *Journal of the American Medical Association (JAMA)* from authors who cannot respond to CDC criticisms because the Biomerieux technology on which those criticisms are based are patent-protected: "It is difficult to respond to the issue of the true-positive rate of the test, as performed in the laboratory of Schrieffer et al., in the absence of a defined cutoff point for a positive test result and information on how the cutoff point for the first tier was computed (e.g., proprietary to the manufacturer of the Biomerieux VIDAS machine used for their assay). Without this information,

no direct comparisons can be made. We endorse and plan further collaborative evaluations in this serious and costly disease.”^{cxv[125]}

Dr. David Dennis, Chief, Bacterial Zoonoses Branch, CDC, NCID, Division of Vector-Borne Infectious Diseases, Fort Collins, CO.

Among factors that may contribute to the appearance of conflict of interest:

1. His employer, the CDC, filed for rights to Lyme disease diagnostic test and vaccine technology through the World Intellectual Property Organization. Application Numbers: WO 99/40200, entitled “Recombinant Lipidated PsaA Protein, Methods Of Preparation And Use” and WO 99/35272,^{cxvi[126]} entitled “Compositions and methods for serological immunoassay for the detection of *Lyme disease* infection using recombinant P37/FlaA protein antigen and methods for producing such protein antigen.” Both patents are the culmination of ongoing work at the CDC, including collaboration between CDC and industry.

Russell Johnson, Ph.D., U of MN. Among factors that may contribute to the appearance of conflict of interest: Inventor of the patent behind the popular and profitable canine Lyme vaccine, LymeVac, which is licensed to MGI Pharma and sold by American Home Products through its subsidiary, Fort Dodge Laboratories.^{cxvii[127]} Johnson’s employer, the University of Minnesota, is assignee on this patent. This patent is of pivotal importance to work on human Lyme disease vaccines as well, as evidenced by the fact that 6 crucial patents for human Lyme vaccine reference this work, including US Patent #'s:

1. 6,083,7 Borrelia antigen

- | | | | |
|----|----|----------------|------------------------------------|
| | 2. | <u>5,747,2</u> | <u>Compositions and methods</u> |
| | | <u>94</u> | <u>for the prevention and</u> |
| | | | <u>diagnosis of lyme disease</u> |
| 1. | 3. | <u>5,656,4</u> | <u>OspE, OspF, and S1</u> |
| | | <u>51</u> | <u>polypeptides in borrelia</u> |
| | | | <u>burgdorferi</u> |
| | 4. | <u>5,582,8</u> | <u>Sonicated borrelia</u> |
| | | <u>29</u> | <u>burgdorferi vaccine</u> |
| | 5. | <u>5,554,3</u> | <u>Recombinant vaccine</u> |
| | | <u>71</u> | <u>against Lyme disease</u> |
| | 6. | <u>5,530,1</u> | <u>Method for the purification</u> |
| | | <u>03</u> | <u>of PC protein from Borrelia</u> |
| | | | <u>burgdorferi</u> |

Dr. Arthur Weinstein, Department of Rheumatology, George Washington University Medical Center, Washington, D.C.

Among factors that may contribute to the appearance of conflict of interest, according to Federal guidelines: Ran clinical trials for Lyme disease vaccines. Is being sued by patients who claim he negligently handled their adverse reactions during clinical trials.^{cxxviii[128]}

Raymond Ryan, Ph.D., U of Conn.

Among factors that may contribute to the appearance of conflict of interest, according to Federal guidelines: Ryan's employer holds two pivotal patents for the diagnosis of Lyme disease.^{cxxix[129]}

Conference on the “Laboratory Diagnosis of Lyme Disease, 1998”

Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID,) the Centers for Disease Control (CDC), and the Office of Rare Diseases, this conference aimed to set guidelines for diagnosis. One major recommendation served to promote commercialization of the SmithKline Beecham OspA vaccine: “Only bacterial antigens derived from OspA-deficient mutant of *Borrelia burgdorferi* be used in all diagnostic assays to circumvent false positive reactions likely to result from the use of OspA Lyme vaccines.”

Participants:

Dr. Maria Agüero-Rosenfeld, Clinical Laboratories, Westchester County Medical Center, Valhalla, NY . Factor that could contribute to the appearance of conflict of interest: Her employer participated in vaccine trials for Connaught (now Avenitis Pasteur.)

Dr. Phillip J. Baker, DMID, NIAID, NIH, Bethesda, MD. Among factors that may contribute to the appearance of conflict of interest: NIH inventors hold the rights, in full, to 6 patents related to vaccine and diagnostic test development. (See patent chart, above.) Moreover, the NIH has rights to numerous additional Lyme-related patents, including those central to the creation of first and second generation vaccines and associated diagnostic tests. (Again, see patent chart in this report.)

Dr. Alan G. Barbour, Department of Microbiology & Molecular Genetics, College of Medicine, University of California, Irvine Among factors that might contribute to appearance of conflict of interest: Same as above.

Dr. Felipe C. Cabello, MD, Viro Dynamics, New York, NY. CEO, Viro Dynamics. Among factors that may contribute to the appearance of conflict of interest: Company

devoted to Lyme disease testing.^{xxxx[130]} Employee of Westchester County Medical Center, recipient of sizable grants from pharmaceutical industry to study Lyme disease.

Dr. Patricia Coyle, SUNY at Stony Brook, Department of Neurology. Stony Brook, NY. Among factors that may contribute to the appearance of conflict of interest: Her employer, SUNY at Stony Brook, is recipient of government grants to study Lyme disease and has an interest in products dependent upon launch of OspA vaccines.

Dr. Raymond J. Dattwyler, SUNY at Stony Brook, School of Medicine, Stony Brook, NY. CEO, Brook Biotechnologies, Stony Brook, New York. Factors that may contribute to the appearance of conflict of interest, listed above.

Dr. Eugene A. Davidson, Chair, Department of Biochemistry & Molecular Biology, Georgetown University School of Medicine, Washington, D.C. Among factors that might contribute to the appearance of conflict of interest: Employer is recipient of sizable government and pharmaceutical industry grants to study Lyme disease vaccines and diagnostic tests.

Dr. David Dennis, Chief, Bacterial Zoonoses Branch, CDC, NCID, Division of Vector-Borne Infectious Diseases, Fort Collins, CO. Factors that might contribute to the appearance of conflict of interest, listed above.

Dr. Dennis Dixon, DMID, NIAID, NIH. Factors that may contribute to the appearance of conflict of interest: NIH inventors hold the rights, in full, to 6 patents related to vaccine and diagnostic test development; moreover, the NIH has rights in at least 11 additional Lyme-related patents, including those central to the creation of first and second generation vaccines and associated diagnostic tests. (See patent listing, above.)

Dr. Robert D. Gilmore, Molecular Biology Section, DVVID, CDC, NCID, Fort Collins, CO. Factors that may contribute to the appearance of conflict of interest: Employer, the

CDC, filed for rights to a Lyme disease diagnostic test through the World Intellectual Property Organization in 1999. (Application Number: WO 99/40200, entitled “Recombinant Lipidated Psaa Protein, Methods Of Preparation And Use.) The new CDC patent can be used for diagnostic tests and vaccines.” In addition, Gilmore himself is named as inventor on **WO 99/35272**^{cxxxii[131]}, entitled “Compositions and methods for serological immunoassay for the detection of *Lyme disease* infection using recombinant P37/FlaA protein antigen and methods for producing such protein antigen.” This work may be used for diagnostic tests or for creation of future generations of the OspA vaccine. Assignee is BIOMERIEUX, INC, of Rockland, MA. Biomerieux has recently merged with Cambridge Biotech to form Aquila Biopharmaceuticals, a major manufacturer of Lyme vaccines and diagnostic tests for animal health. Aquila Biopharmaceuticals is a partner of GlaxoSmithkline and Aventis Pasteur, the two major manufacturers of Lyme disease for humans.^{cxxxiii[132]} Indeed, in addition to Aquila's internal product development programs, Aquila has seven corporate partners that have licensed its Stimulon® adjuvants for a variety of human diseases: SmithKline Beecham, p.l.c., Wyeth-Lederle Vaccines and Pediatrics, Aventis Pasteur, Bristol Myers–Squibb, (Progenics Pharmaceuticals, Inc.), VaxGen, Inc. , Elan Corporation, plc., and Korea Green Cross Corporation. In return for rights to use Stimulon® adjuvants for specific diseases, the corporate partners have agreed to pay Aquila license fees, milestone payments, and royalties on product sales. Aquila has retained worldwide manufacturing rights for QS-21. In addition to corporate partners, Aquila has developed a number of academic collaborations to test potential product formulations containing QS-21.^{cxxxiiii[133]} In addition to corporate partners, Aquila has developed a number of academic collaborations to test potential product formulations containing QS-21. It is also notable that although Aquila will maintain its identity, it was recently purchased by antigenics, a company specializing in producing antigens of specific use in a wide variety of western blot and ELISA tests.

Dr. John Glass, Research Director, Brook Biotechnologies, Inc., Stony Brook, NY.

Factors that may contribute to the appearance of conflict of interest: Research Director of Brook Biotechnologies, which manufactures Lyme diagnostic tests in lockstep with vaccines. The success of Brook Biotechnologies hinges, in part, on the serological definition of Lyme disease.

Dr. Marc Golightly, University Hospital/Immunology Laboratory, SUNY at Stony Brook, Stony Brook, NY. Factors that may contribute to the appearance of conflict of interest: Golightly's employer, SUNY Stonybrook, holds the rights to diagnostic technology for Lyme disease.

Dr. Jesse Goodman, Department of Internal Medicine, University of Minnesota, Minneapolis, MN. Factors that may contribute to the appearance of conflict of interest: Goodman's employer, the University of Minnesota, holds the patent to the popular and profitable canine Lyme vaccine, Lymevac, which is licensed to MGI Pharma and sold by American Home Products through its subsidiary, Fort Dodge Laboratories. Goodman himself is named as inventor on US Patent #s 5,955,359 and 5,928,879^{xxxxiv[134]}, with University of Minnesota as assignee. The patents relate to Ehrlichia, a tick-borne illness that is transmitted by the same species of tick that transmits Lyme disease.

Dr. Duane Gubler, Director, DVVID, CDC, NCID, Fort Collins, CO. Factors that may contribute to the appearance of conflict of interest, as detailed above

Dr. Jacob Ijdo, Section of Rheumatology, Yale University School of Medicine, New Haven, CT. Factors that may contribute to the appearance of conflict of interest: Ido's employer, Yale University, invented the Osp-A Vaccine being sold by Smithkline Beecham. A line of additional Lyme disease patents form the business model for Yale's new spin-off company, L2 Diagnostics.

Dr. Barbara Johnson, Chief, Molecular Biology Section, DVVID, CDC, NCID, Fort Collins, CO. Factors that might contribute to the appearance of conflict of interest, listed above.

Dr. Mark Klempner, Department of Medicine, Tufts-New England Medical Center. Factors that may contribute to the appearance of conflict of interest: Runs clinical trials for vaccine companies.

Dr. Scott Lesley, Research and Development, Promega Corporation, Madison, WI. Factors that might give the appearance of conflict of interest: Supplies high-tech biologicals to the biotech, pharmaceutical and diagnostic industries.^{xxxxv[135]} As such, its interests are tied up with those of other conference attendees. Received more than \$1.5 million in federal grants in 1997, with two specifically related to Lyme disease and others of associated relevance.^{xxxxvi[136]}

Dr. Andrew E. Levin, Scientific Director, Immunetics, Inc., Cambridge, MA. Factors that might contribute to the appearance of conflict of interest: His company, Immunetics, markets Lyme disease diagnostic tests using Western blot technology. It is funded by the NIH as well as a British Virgin Islands company known as the Blotto Corp.,^{xxxxvii[137]} for investors who wish to remain anonymous.

Dr. Benjamin Luft, SUNY at Stony Brook, Department of Medicine, Stony Brook, NY. Principal, Brook Biotechnologies, Stony Brook, New York.

Factors that might contribute to the appearance of conflict of interest: His company manufactures Lyme diagnostic tests in lockstep with vaccines. Products depend, in part, on case definition—especially the serological standard—established for Lyme disease in 1994. Currently working under federal grant money to commercialize patent # 5,571,718, licensed from Brookhaven Laboratory in New York, to create a series of

diagnostic tests, including one that differentiates those vaccinated with the SmithKline Beecham OspA vaccine product from those with infection. (See documentation for Dattwyler, above.) **Dr. Adriana Marques**, LCI, NIAID, NIH, Bethesda, MD. Factors that might contribute to the appearance of conflict of interest: Dr. Marquez's work is based on the theory that Lyme disease is an autoimmune problem. Her employer is NIH. NIH inventors hold the rights, in full, to six patents related to vaccine and diagnostic test development. (See patent chart, above.) NIH has rights to at least 11 additional Lyme-related patents, including those central to the creation of first and second generation vaccines and associated diagnostic tests. (See patent chart, above.)

Dr. Michael V. Norgard, Professor & Vice Chair. Factor that might contribute to the appearance of conflict of interest: Norgard's employer, the University of Texas, is assignee to valuable vaccine and diagnostic test patents for Lyme disease. (See patent chart, above.)

Dr. David Persing, Laboratory Medicine/Pathology, Mayo Foundation, Rochester, MN. Factors that might contribute to the appearance of conflict of interest: Works as Director of Diagnostics Development, Corixa Corporation, and Infectious Disease Research Institute, Seattle Life Sciences Center, Seattle, Washington. Is also inventor of pivotal patents for Lyme vaccines and tests. (See patent chart above.)

Dr. Richard R. Porwancher, Infectious Disease Consultants, P.C., Trenton, N.J.

Dr. Marty Schriefer, Research Microbiologist, Diagnostic & Reference Section, Bacterial Zoonoses Branch, DVVID, CDC, NCID, Fort Collins, CO. Factors that might contribute to the appearance of conflict of interest: Employer, the CDC, filed for rights to a Lyme disease diagnostic test through the World International Property Organization in 1999 (Application Number: WO 99/40200, Title: Recombinant Lipidated PsaA Protein, Methods Of Preparation And Use). The new CDC patent can be used for diagnostic tests

and vaccines. CDC inventors also hold title to **WO 99/35272**^{cxviii[138]}, “compositions and methods for serological immunoassay for the detection of *Lyme disease* infection using recombinant P37/FlaA protein antigen and methods for producing such protein antigen.”

Dr. Steven Schutzer, Department of Medicine, UMDNJ-New Jersey Medical School, Newark N.Y. Holds patent # *5,187,065* for decomplexing antigens prior to testing for early Lyme disease.

Dr. Ira Schwartz, Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, NY 10595. His employer ran trials for the PMC OspA Lyme disease vaccine.

Dr. Roxanne G. Shively, DHHS/FDA/CDRH/ODE/DCLD, Rockville, MD.

Dr. Aravinda de Silva, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT. Factors that might lead to the possible appearance of conflict of interest: de Silva’s employer, Yale University, invented the OspA vaccine being sold by SmithKline Beecham. A line of additional Lyme disease patents form the business model for Yale’s new spin-off company, L2 Diagnostics. de Silva reports directly to one of the primary patent holders of the OspA vaccine. De Silva has also worked directly on OspA through an NIH grant.^{cxix[139]}

Dr. Allen C. Steere, Professor of Medicine/Chief of Rheumatology, Tufts-New England Medical Center, Boston, MA. Factors that might lead to the possible appearance of conflict of interest, detailed above. Also of interest: Steere is the scientist who documented the association between naturally acquired treatment-resistant Lyme disease arthritis, certain HLA-DR4 genetic subtypes, and high levels of antibody to OspA of naturally acquired *Borrelia burgdorferi*. While this certainly does not constitute a conflict of interest, it is notable that he nonetheless worked with SKB

toward approval of their vaccine in 1998.. Steere is also a former employee of both the CDC and Yale University.

Dr. Ralph Timperi, Director, State Laboratory Institute, Department of Public Health, Boston, MA. We have found no appearance of conflict of interest in the Lyme disease area for Dr. Timperi. However, we present the following as general information, only: Timperi was, at the time of this meeting, a defendant in a lawsuit involving conflict of interest and laboratory policy. This suit, brought by Neo Gen Screening, Inc., a private, for-profit Pennsylvania corporation whose business is the medical screening of newborn children, charged Timperi and his employer, the Massachusetts Department of Health, with “monopolizing, attempting to monopolize and/or conspiring to monopolize ‘newborn screening services’ in Massachusetts and surrounding states,” providing babies with inferior testing at higher price. While the United States Court of Appeals for the First Circuit ultimately relegated the decision back to the Commonwealth of Massachusetts, that same court notes a relevant conflict of interest: “It may be, as Neo Gen charges, that the defendants' actions reflect a cozy arrangement that gives newborns inferior screening at higher cost and that everyone--except possibly the Screening Program--would be better off if hospitals could contract competitively for screening services, just as they procure drugs, bandages, and other resources. The state, in turn, says that its contract provides for extra research and follow-up that Neo Gen fails to provide; such cross-subsidy arguments are traditional defenses for monopoly but not invariably without merit. At bottom, this is a policy matter to be resolved by the Commonwealth.”^{exl[140]}

Ms. Marilyn Tuttleman, DMID, NIAID, NIH, Bethesda, MD. Possible Appearance of Conflict of Interest: NIH inventors hold the rights, in full, to at least six patents related to Lyme disease vaccine and diagnostic test development; moreover, the NIH has rights to

at least 11 additional Lyme-related patents, including those central to the creation of first and second generation vaccines and associated diagnostic tests.

Dr. Arthur Weinstein, Department of Rheumatology, George Washington University Medical Center, Washington, D.C. Possible Appearance of Conflict of Interest, detailed above.

Dr. Gary Wormser, Professor of Medicine, Division of Infectious Diseases, Westchester County Medical Center, Valhalla, NY. Possible Appearance of Conflict of Interest: Ran clinical trials for Lyme disease vaccines. Is being sued by patients who claim he negligently handled their adverse reactions during clinical trials.^{cxli[141]}

Section XII Vaccines and Conflict of Interest

Vaccines are generally approved for market under specific guidelines through two separate committees.

The first committee is the Vaccines and Related Products Advisory Committee (VRBPAC), which is appointed by and reports to the United States of America Department of Health and Human Services Food and Drug Administration (FDA.) It is the job of VRBPAC to accept or reject the vaccine based on an examination of the data.

The second committee is the CDC's Advisory Committee on Immunizations Practices (ACIP). ACIP gets involved once VRBPAC has given approval. It is the job of ACIP to decide who should get a vaccine, under what circumstances, and at what dose.

Participating in both committees is considered a conflict of interest since the notion of peer review requires that one body have the oversight of another.

To understand the dynamic, LDA reviewed the actions of each Committee member evaluating the SmithKline Beecham Lyme disease vaccine, Lymerix, on both FDA and CDC panels. Specifics follow below, but in a nutshell, our investigation has revealed:

1. 1. Members who served on both FDA and CDC committees, in violation of conflict of interest rules.
2. 2. Members whose products and companies would fail or fly based on approval of the vaccine in question.
3. 3. Members who depended upon the vaccine industry for research grants and professional survival.
4. 4. Members who had direct financial relationships with the vaccine manufacturer –or its direct competitor-- at the time they served on the Committee.
5. 5. Members who either did not understand the issues or voted for approval despite an unprecedented degree of reservation.

The FDA Hearing: VRBPAC on Lyme

Reviewing FDA actions for its August 21, 2000 report on the rotovirus vaccine in “Conflicts of Interest in Vaccine Policy,” the Committee on Government Reform, U.S. House of Representatives ,^{cxlii[142]}provides excellent insight into how the Vaccines and Related Products Advisory Committee actually functions. We excerpt relevant sections, below:

Description of the Committee:

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) advises the Commissioner of the Food and Drug Administration in discharging her

responsibilities as they relate to helping ensure safe and effective biological products, including vaccines.^{cxliiii[143]} It reviews and evaluates the data concerning the safety, effectiveness, and the appropriate use of vaccines and related biological products. In short, the VRBPAC advises the FDA on whether or not to license new vaccines for commercial use.

Membership of the Committee

The VRBPAC has 15 voting members, including the Chair, who are selected by the Commissioner of the FDA or her designee. The FDA seeks members who are “authorities” in the fields of immunology, pediatrics, infectious diseases and related fields. The charter also suggests that there be a member who is identified with consumer interests. VRBPAC meets approximately 6 times a year.

Terms: VRBPAC members serve overlapping terms of four years. A member may serve after the expiration of the member’s term until a successor has taken office. Under the DHHS policy, members may not serve continuously for more than four years or more than eight years within a twelve-year period. Additionally, members may not serve on more than one committee within the agency at the same time. Vacancies are announced at least once a year in the Federal Register. The selections are made by Dr. Linda Suydam, Senior Associate Commissioner of the FDA, who also considers and grants all conflict of interest waivers.

Temporary voting members

Members of other scientific and technical FDA advisory committees—not to exceed 4 members—may vote on the VRBPAC when: (a) expertise is required that is not available among current voting members or, (b) their presence is needed to comprise a quorum.

Conflict of Interest Review and Waivers by the FDA

Scope: Conflict of interest statutes and regulations generally prohibit the participation of advisory committee members in official matters where that person has a financial interest and their participation will have a direct and predictable effect on that interest.^{cxliv[144]}

Many factors are considered by the Department in determining whether a conflict of interest exists and, if it does, whether it may be waived to allow participation. A conflict may either be an actual or apparent conflict. An actual conflict is the situation where a direct, identifiable conflict exists. An apparent conflict is where there is an appearance of a lack of impartiality.^{cxlv[145]}

There are many steps in the FDA's procedure to clear potential conflict of interests in VRBPAC. Prior to a scheduled VRBPAC meeting, FDA officials will review the agenda and other assignments. Entities with a financial interest in the matter to be discussed are identified by the staff of the Center for Biologics Evaluation & Research, as are the products to be used in conjunction with the product being reviewed, and competing products. Advisory committee members are required to fill out a Confidential Financial Disclosure Statement (FDA form 3410) prior to each meeting. FDA staff compares financial disclosure information compiled for each VRBPAC member with the issues on the agenda for the upcoming meeting to determine who has conflicts. Based on the information provided, the member can be found to have: (a) no conflict of interest, (b) a conflict of interest that is minimal and thus, justifiable, or (c) a conflict of interest so substantial that recusal or a waiver is the only course of action. If there is a substantial conflict of interest, it must be detailed.

Some of the factors and criteria used in determining whether a waiver is appropriate include:

6. 6. Agenda topic: Where the subject of the meeting is of general scientific presentations and not of particular products, or to review research with no direct or predictable effect on outside interests, waivers are not needed.^{cxlvi[146]}
7. 7. Net worth of member: The amount of the financial interest will be considered in relation to the net worth of the SGE.^{cxlvii[147]}
8. 8. Employment: Situations where the SGE's university employer has a grant or a contract with either the sponsoring company or any other affected companies will be taken into consideration during the waiver process.^{cxlviii[148]}
9. 9. Amount of grant or contract: The amount of the grant or contract given to the university employer of a member, as well as the member's involvement (i.e. principal investigator, department chair) will be considered in determining whether the financial interest arises to the point of conflict.^{cxlix[149]}
10. 10. Competing products: The member's financial interest in competing products or otherwise affected companies will be taken into consideration by the agency in determining whether a waiver may be granted.^{cl[150]}

As the rules stand, members may not vote on any matter where a committee recommendation could benefit financially either the member or his/her immediate family. A waiver may not be granted where the member's own research is involved. The level of involvement of the member with either a sponsoring or an affected company, as measured by the amount of compensation received, will also be considered.^{cli[151]} As in the previous categories, the level of involvement of the particular member will be measured by the amount of compensation received from the sponsoring or affected companies.^{clii[152]} If the Director of the division determines that the member's services are too important, despite a substantial conflict of interest, he must provide the necessary

justification for a waiver. Where the financial interest is relatively large it is essential that the justification be particularly strong.^{cliii[153]}

Finally, if a waiver is contemplated, it must be reviewed by the FDA's ethics staff, who will make a recommendation to the approving official regarding the waiver. They may also consult with the Office of General Counsel in the Department or the Office of Government Ethics. Final approval of waivers is given by Dr. Linda Suydam, Senior Associate Commissioner of the FDA. In addition to a full participation waiver, the Department may also grant limited Waivers, enabling the individual to participate but placing restrictions on his or her right to vote.^{cliv[154]} Potentially, a limited waiver could also restrict a member's participation to answering factual questions about the matter being discussed by the committee.

Disclosure

In cases where the financial interest is not deemed to be substantial, it will be disclosed in the public record with the expectation that other participants will take them into consideration as they evaluate the opinions expressed by the member. The Agency in some cases deems that such disclosure is sufficient in addressing the potential for an actual or apparent conflict of interest.^{clv[155]} Finally, members are expected to recuse themselves from the committee proceedings in cases where they deem that the financial interest may interfere with their ability to be impartial.

Approving Lymerix: The Meeting Itself

It is against the backdrop of VRBPAC rules and regulations that the group met on May 26, 1998 to approve the SmithKline Beecham Lyme disease vaccine, Lymerix. The LDA

investigation reveals numerous conflicts of interest and ethical questions that require further scrutiny.

Present at the meeting were^{clvi[156]}:

REGULAR VOTING MEMBERS

Patricia L. Ferrieri, M.D., Chair: University Of Minnesota Medical School
and the Chair of the Vaccines and Related Biological Products Advisory
Committee

Nancy Cherry, Executive Secretary

Mary Lou Clements-Mann, M.D., Member, Johns Hopkins University

Rebecca E. Cole, Member, Consumer Representative, Chapel Hill, North Carolina

Robert S. Daum, M.D., Member, University Of Chicago

Kathryn M. Edwards, M.D., Member, Vanderbilt University, Nashville

Dianne M. Finkelstein, Ph.D., Member

Harry B. Greenberg, M.D., Member, Stanford University and the Palo Alto VA
Hospital

Caroline B. Hall, M.D., Member

Alice S. Huang, Ph.D., Member, Caltech

Steve Kohl, M.D., Member, University Of California, San Francisco

Gregory A. Poland, M.D., Member: Mayo Clinic, Rochester

Dixie E. Snider, Jr., M.D., M.P.H., Member, Centers for Disease Control and
Prevention.

CONSULTANTS

Robert Breiman, M.D., FDA Consultant, National Vaccine Program Office

Claire Broome, M.D., FDA Consultant

Patricia Coyle, M.D., FDA Consultant, State University of New York at Stony Brook

Raymond Dattwyler, M.D., FDA Consultant, State University of New York at Stony Brook

Theodore Eickhoff, M.D., FDA Consultant, University of Colorado

Thomas Fleming, Ph.D., FDA Consultant, University of Washington, Seattle

David Karzon, M.D., FDA Consultant, Vanderbilt University, Nashville

Benjamin Luft, M.D., FDA Consultant, State University of New York at Stony Brook

Karen Elkins, Ph.D., FDA Speaker, Office of Vaccines, FDA

Daniel R. Lucey, M.D., FDA Speaker, Office of Vaccines, FDA

NON-VOTING MEMBERS

Yves Lobet, Ph.D., Sponsor Rep, SKB

Dennis Parenti, M.D., Sponsor Rep, SKB

Robert Pietrusko, Pharm.D., Sponsor Rep, SKB

Robert Schoen, M.D., Sponsor Rep, Yale University

Vijay Sikand, M.D., Sponsor Rep, family practice, East Lyme, CT

Allen Steere, M.D., Sponsor Rep, Tufts

Howard R. Six, Ph.D., Public Comment, Pasteur Merrieux Connaught

Karen Vanderhoof-Forschner, MBA, MS, CLU, CPCU, Lyme Disease Foundation

Dani Degrave, SKB

Carolyn Hardegree, M.D.

David Krausse, M.D., SKB

Frank Rockhold, Ph.D., SKB

Elke Sennewald, Dr. , Kendall GMI in Munich

One key here is to look at the voting consultants chosen by the CDC.

The VRBPAC charter states that the number of temporary members (i.e., consultants) is normally not to exceed four, yet in the case of Lymerix, eight were appointed; this is particularly notable because, according to policy, when a quorum cannot be constituted from the duly appointed members, a meeting should be canceled until the quorum can be achieved. But it is especially notable because some of the consultants chosen came with conflicts of interest so clear and blatant that their participation should never have been permitted under any interpretation of the rules.

VRBPAC Consultants: Eight out of Eight Present Conflicts of Interest or Ethical Concerns

Raymond Dattwyler, M.D., FDA Consultant, SUNY at Stony Brook CEO, Brook Biotechnologies, Stony Brook, New York. Disclosed conflict of interest, for which a waiver was provided: At the time of meeting, in negotiation with the sponsor to present a general lecture. Not mentioned in text of meeting transcript, but potentially presenting the appearance of conflict of interest: Manufactures Lyme diagnostic tests in lock-step with vaccines. Working under federal grant money to commercialize US Patent # 5,571,718, licensed from Brookhaven Laboratory in New York, to create a series of diagnostic tests, including one that differentiates those vaccinated with the Smithkline Beecham Osp-A vaccine product from those with infection. Dattwyler's business model, as reflected in grant proposals to the NIH, depended upon approval of the Osp-A vaccine. Dr. Dattwyler was involved in this business venture, one funded by the US government itself, at the same time he was voting on vaccine approval for the US government.

Benjamin Luft, M.D., FDA Consultant, State University of New York at Stony Brook
And principal, Brook Biotechnologies, Stony Brook, New York. Factors that might present the appearance of conflict of interest: Company manufactures Lyme diagnostic tests in lock-step with vaccines. Currently working under federal grant money to commercialize patent # 5,571,718, licensed from Brookhaven Laboratory in New York, to create a series of diagnostic tests, including one that differentiates those vaccinated with the Smithkline Beecham Osp-A vaccine product from those with infection. Luft's business model, as reflected in grant proposals to the NIH, depended upon approval of the Osp-A vaccine. Dr. Luft was involved in this business venture –one funded by the US government itself- at the same time he was voting on vaccine approval for the US government.(See patent and product charts, above.)

Robert Breiman, M.D., FDA, Consultant, National Vaccine Program Office, Centers for Disease Control and Prevention. Factors presenting the potential appearance of conflict of interest: Dr. Breiman was involved in both development of evaluations for the FDA and recommendations for the CDC –both VRBPAC and ACIP. Thus, he was able to influence the process of vaccine approval and then the process of recommendation, activities inherently in conflict according to the FDA and CDC. This is especially notable since Dr. Breiman is an employee of the CDC. In 1999 the CDC filed Application Number WO 99/40200, Title: Recombinant Lipidated PsaA Protein, Methods Of Preparation And Use^{clviii[157]} with the World Patent Organization. The CDC patent may be useful for companies involved in Lyme immunology.

Claire Broome, M.D., FDA Consultant, Centers for Disease Control. Conflict of Interest: Like Dr. Breiman, Dr. Broome's affiliation with the CDC creates the potential for the appearance of conflict of interest with respect to agency patents. Of interest, as

well, is her role in another controversial disease, Chronic Fatigue Syndrome. Although this suggests no conflict of interest whatsoever in terms of Lyme disease, we present the following, general information: Just two months after participation in the Lyme vaccine hearing, Dr. Broome, at the time acting director of the CDC, was accused of participation in diversion of money from chronic fatigue to diseases the agency considered more worthy. According to Science magazine, at the root of the controversy was “\$22.7 million that Congress earmarked for CFS research in 1995. In 1998, William Reeves, the agency's top CFS researcher and director of the Viral Exanthems and Herpesvirus Branch, filed a whistle-blower complaint charging that his superior, Brian Mahy, who heads the Division of Viral and Rickettsial Diseases, had used a large part of the special funds for other purposes. ... The report also said that CDC's acting director, Claire Broome, had provided lawmakers with "inaccurate and potentially misleading" data about the program.”^{clviii[158]} In 2001, CDC's Mahy has been “reassigned” and Claire Broome no longer holds the post of CDC director, acting or otherwise, but her actions regarding chronic fatigue syndrome raise the possibility that she may have a predisposed bias against controversial diagnoses like Lyme.

Patricia Coyle, M.D., FDA Consultant, SUNY at Stony Brook. Factors presenting the potential for the appearance of conflict of interest, detailed above.

Theodore Eickhoff, M.D., FDA Consultant, University of Colorado Health Sciences Center. Factors presenting the potential for the appearance of conflict of interest: Eickhoff had no personal conflict, but his employer, the University of Colorado, is currently listed as a participant in 79 NIH clinical trials. The University of Colorado Health Sciences Center has 11 current NIH grants, and received \$107 million dollars in NIH grant money in 1999 alone.

Thomas Fleming, Ph.D., FDA Consultant. Factors presenting the potential for the appearance of conflict of interest: Dr. Fleming was involved in development of both the

FDA evaluation and the CDC recommendations for Lymerix. Thus, he was able to influence the process of vaccine approval and then the process of recommendation, activities inherently in conflict.

David Karzon, M.D., FDA Consultant. Professor at Vanderbilt University. Factors presenting the potential for the appearance of conflict of interest: Dr. Karzon is a frequent consultant and/or temporary voting member to the VRBPAC, voting on a variety of issues. While no apparent conflicts of interest were reported by Dr. Karzon personally, his employer, Vanderbilt University, receives extensive grants and contracts from pharmaceutical companies. Vanderbilt University also received more than \$111 million in grant money from the NIH in 1999.^{clix[159]} Of special note is Vanderbilt's close relationship with Lyme vaccine manufacturer Aventis Pasteur for heading clinical trials on its AIDS vaccine.^{clix[160]}

Regular voting members present with conflicts of interest, too, as follows:

Patricia L. Ferrieri, M.D., Chair: University Of Minnesota Medical School And The Chair Of The Vaccines And Related Biological Products Advisory Committee. Factors presenting the potential for the appearance of conflict of interest: Ferrieri's employer, the University of Minnesota, holds the patent to the popular and profitable canine Lyme vaccine, Lymevac, which is licensed to MGI Pharma and sold by American Home Products through its subsidiary, Fort Dodge Laboratories. (See patent and product charts, above.)

Dixie E. Snider, Jr., M.D., M.P.H., Centers for Disease Control and Prevention. Factors presenting the potential for the appearance of conflict of interest: Dr. Snider was involved in development of both evaluation for the FDA and recommendations for the CDC. Thus, he was able to influence the process of vaccine approval *and then* the process of

recommendation, activities inherently in conflict according to ethics experts. Dr. Snider is an employee of the CDC, which holds the rights to world patent # WO 99/40200, Recombinant lipidated psaa protein, methods of preparation and use, of potential value for Lyme disease vaccines and diagnostic tests.

Greg Poland, Mayo Clinic, Rochester. Factors presenting the potential for the appearance of conflict of interest: His employer, the Mayo Clinic, is assignee on US patents number 6,087,097 and 6,045,804. The latter's success is contingent upon approval of the OspA vaccine. (See patent and product charts, above.)

Mary Lou Clements-Mann, M.D., Member, Johns Hopkins University. Factors presenting the potential for the appearance of conflict of interest: In 2000, Johns Hopkins University received more grant money from the NIH than any other single institution in the world, a total of \$ 419,345,194 .^{clxi[161]}As the principal investigator at Johns Hopkins University's AIDS Vaccine Evaluation Group (AVEG),^{clxiii[162]} Clements-Mann received NIH grant money year after year.^{clxiii[163]} (Note: AVEG also had ties to Bristol-Myers Squibb/Oncogen, MicroGeneSys, Genentech, Wyeth-Lederle Vaccines and Pediatrics, Immunex, and VaxGen, among many others.^{clxiv[164]}) She also had ties to Smithkline Beecham's premiere competitor in the Lyme disease field, Pasteur Merieux Connaught, now known as Aventis Pasteur. As principal investigator of the first trial of the canarypox-gp120 vaccine for AIDS from that company, she was instrumental in making Aventis a leader in the AIDS vaccine field. Interviewed by the Committee on Government reform, FDA staff stated that when the VRBPAC is deliberating the licensure of a vaccine, a company is considered an affected company if it is a direct competitor of the manufacturer of the vaccine being considered.^{clxv[165]}AVEG including such companies as

Robert S. Daum, M.D., Member, University of Chicago. Factors presenting the potential for the appearance of conflict of interest: Robert Daum was lead researcher in clinical trials for the pneumococcus vaccine, working with Lyme vaccine manufacturer Connaught (now Aventis) and colleagues at Yale.^{clxvi[166]} Interviewed by the Committee on Government reform, FDA staff stated that when the VRBPAC is deliberating the licensure of a vaccine, a company is considered an affected company if it is a direct competitor of the manufacturer of the vaccine being considered.^{clxvii[167]}

Kathryn M. Edwards, M.D., Member, Vanderbilt University, Nashville. Factors presenting the potential for the appearance of conflict of interest: Dr. Edwards is currently funded by two NIH grants. In one, she is examining a range of new vaccine candidates^{clxviii[168]}, and in another she is studying prostaglandin metabolites.^{clxix[169]} She has been criticized for conflicts of interest by consumer groups in recent years^{clxx[170]}. For instance, Wyeth Lederle paid her \$255,023 per year from 1996 to 1998 for the study of vaccines for pneumococcal infections, which can cause earaches, meningitis, blood poisoning and pneumonia. The vaccine she studied, Prevnar, was ultimately approved for use despite significant concerns, and Dr. Edwards now serves as national editor for the Wyeth's Web site, "Pneumo.com." In that capacity, she participates in an Internet bulletin board, answering questions and easing fears regarding adverse reactions for parents and doctors. Finally, Dr. Edward's employer, Vanderbilt University, received more than \$111 million in grant money from the NIH in 1999.^{clxxi[171]} Also of special note: Vanderbilt's close relationship with Lyme vaccine manufacturer Aventis Pasteur for heading clinical trials on its AIDS vaccine.^{clxxii[172]}

Caroline B. Hall, M.D., Member. Factors presenting the potential for the appearance of conflict of interest: Dr. Hall's employer, the University of Rochester, received more than \$87 million in grant money from the NIH in 1999^{clxxiii[173]}. She herself has been recipient

of many millions in grant money from the federal government and pharmaceutical companies over the 25 years she has specialized in conducting some 40 clinical trials. She has also received grant money to participate in clinical trials for a vaccine for respiratory syncytial virus (RSV^{clxxiv[174]}) from Medimmune. Medimmune has exclusive rights^{clxxv[175]} to the patent for the Decorin-binding protein^{clxxvi[176]} essential to Aventis Pasteur's second generation Lyme disease vaccine, and is a partner with Aventis in creating that vaccine. The Medimmune-Aventis vaccine will be far more likely to be approved on the heels of approval for the first generation vaccine from SmithKline Beecham, representing a direct conflict of interest according to FDA standards. Also of note is the University of Rochester's close relationship to Aventis for clinical trials of its AIDS vaccine.^{clxxvii[177]} Finally, the University of Rochester has accepted money to conduct clinical trials for canine Lyme vaccine manufacturer, Aquila Biopharmaceuticals, Inc., although for a product in the human arena.^{clxxviii[178]}

Harry B. Greenberg, M.D., Member, Stanford University and the Palo Alto VA Hospital. Factors presenting the potential for the appearance of conflict of interest: At around the time of the meeting, Dr. Harry Greenberg owned \$120,000 of stock in Aviron,^{clxxix[179]} a vaccine manufacturer. The relationship was made official in September 2000, when he was named senior vice president, research and development and chief scientific officer.^{clxxx[180]} The relationship between Dr. Greenberg and Aviron is especially notable given that fact that in 1997, the fiscal year directly prior to the Lymerix meeting, Aviron's entire income accrued from research support and its relationship with Lymerix vaccine manufacturer, SmithKline Beecham.^{clxxxi[181]} Indeed, Aviron and SmithKline have been partners on development of vaccines for Epstein Barr virus since 1995. Dr. Greenberg was also was a paid member of the board of advisors of Chiron, another vaccine manufacturer, and owned \$40,000 of stock.

Sponsor Rep.

Allen Steere, MD, Tufts University. Lead Investigator for the Vaccine. Since Dr. Steere represented the sponsor, he presented with no conflict of interest at this hearing. As a point of interest, however, it is notable that during the hearing he helped the sponsor assert that adverse reactions to the vaccine were minimal. Yet nine months after the release of the vaccine, in September 1999, he published an article entitled "Association of Antibiotic Treatment-Resistant Lyme Arthritis with T Cell Responses to Dominant Epitopes of Outer Surface Protein A of *Borrelia burgdorferi*" in *Arthritis and Rheumatism*, the official journal of the American College of Rheumatology. In that article, Dr. Steere and his colleagues conclude that "both the severity and duration of Lyme arthritis after antibiotic treatment are associated with T cell responses to dominant epitopes of OspA. This may be critical in the pathogenesis of antibiotic treatment-resistant Lyme arthritis." Clearly, this was relevant during the vaccine hearing, and should have resulted in at least a warning label for the product. None exists to this day.

Specifics on Waivers and Disclosure

The following individuals were granted waivers permitting them to participate fully in the committee discussions on the inclusion of a boxed warning on package inserts for vaccines (a section of the Hearing not, in fact, devoted to Lyme specifically): Drs. Clements-Mann, Edwards, Ferrieri, Greenberg, Hall, Poland, Finkelstein, Kim and Daum. In addition, Dr. Daum disclosed a potential conflict of interest that was deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest. A written appearance determination under 5 C.F.R. 2635.502 of the Standards of Ethical Conduct was granted to permit Dr. Daum to participate in the discussions of Lyme

disease. Dr. Edwards received a waiver for discussion of the Lyme disease vaccine as well. Additionally, the FDA remarked, "It should be noted for the record that Dr. Raymond Dattwyler is negotiating to present a general lecture on Lyme disease supported by SmithKline. We should also note that Dr. Patricia Coyle consulted on one occasion with SmithKline in 1995. At that time, she reviewed monkey data pertinent to the vaccine which is not expected to come before this committee. She did not review human vaccine data." No one mentioned Dattwyler's other conflict of interest--his venture-backed biotech company, whose main product line was a diagnostic test kit developed for the OspA vaccine.

CDC Recommendations: ACIP on Lyme

The Advisory Committee on Immunizations Practices (APIC) met in June 1999 to review the findings of the VRBCAP and other research and recommend how the newly-approved Lymerix should be used. To better understand ACIP and associated conflicts of interest, it is instructive to read the following excerpt from an August 1999 staff report by the Committee on Government Reform:

Practices and Procedures of the Advisory Committee on Immunization Practices (ACIP):

Purpose of the ACIP: ACIP provides advice and guidance on vaccine policy to the Secretary of DHHS, the Assistant Secretary for Health, and the Director of the CDC. The ACIP develops written recommendations, subject to the approval of the Director of the CDC, for the routine administration of vaccines to the pediatric and adult populations,

along with schedules regarding the appropriate periodicity, dosage, and contraindications applicable to the vaccines.

The recommendation for routine use of a vaccine is tantamount to a federal mandate for vaccine use. HHS regulations require that all grants for childhood immunizations be subject to the states' implementation of procedures to ensure routine vaccination. To receive federal funding the states must, among other things, require a plan to systematically immunize susceptible children at school entry through vigorous enforcement of school immunization laws.^{clxxxii[182]}

Additionally, the ACIP has been given a mandate from Congress by the Omnibus Budget Reconciliation Act of 1993, to establish and periodically review and, as appropriate, revise a list of vaccines for administration to children in the Vaccines for Children Program (VFC), along with schedules regarding the appropriate periodicity, dosage, and contraindications applicable to the pediatric vaccines.^{clxxxiii[183]} The VFC program provides for public purchase of vaccines for children without health insurance coverage. Under the VFC program, \$474 million has been obligated to pay for the purchase of vaccines in fiscal year 2000.

Membership of the ACIP:

1. The ACIP has three different categories of membership consisting of voting members, ex-officio members and liaison representatives. **Voting Members of the ACIP:** The ACIP has twelve voting members, including the Chair, all approved by the Secretary of DHHS or her designee. ACIP members are selected based upon their expertise in the field of immunization practices.^{clxxxiv[184]} The membership consists of U.S. citizens who have multidisciplinary expertise in public health, and expertise in the use of vaccines and immunologic agents in both clinical and preventive medicine.

The ACIP membership is required by FACA and agency guidelines to be fairly balanced in terms of point of view represented and the committee's function. Specifically, the CDC attempts to select members from diverse backgrounds including geographic areas, gender, ethnic and minority groups, and the disabled.

New members are nominated to the ACIP on an annual basis. Suggestions for membership to the committee are sought from a variety of sources, including current and former ACIP members, professional societies, vaccine manufacturers and the general public. A panel of government officials screens the candidates for nomination to the committee and submits a slate of possible nominees to the director of the CDC. With approval of the CDC director, a nomination package is prepared for the Secretary of DHHS, who makes the official appointments to the committee.

Committee members are nominated to serve overlapping four-year terms. Members may serve after the expiration of their terms until their successors have taken office.^{clxxxv[185]}

1. 1. **Ex Officio Members of the ACIP:** The ACIP charter designates seven nonvoting ex officio members to the committee from the following federal agencies:
 1. 1. Deputy Director, Division of Vaccine Injury Compensation, Bureau of Health Professions, Health Resources and Services Administration,
 2. 2. Deputy Director for Scientific Activities, Office of the Assistant Secretary of Defense,
 3. 3. Under Secretary for Health, Department of Veterans Affairs,
 4. 4. Director, National Center for Drugs and Biologics, Food and Drug Administration (FDA),
 5. 5. Medical Advisor, Medicaid Bureau, Health Care Financing Administration (HCFA),

6. 6. Director, Microbiology and Infectious Diseases Program,
National Institute of Allergy and Infectious Diseases, HHS, and
7. 7. Director, National Vaccine Program Office, CDC.^{clxxxvi[186]}

Generally, designees of the officials listed above hold the ex officio positions. In contrast to regular voting members, who are expected to voice their personal opinions, ex-officio members are expected, to the extent possible, to represent the position and views of their sponsoring organizations.^{clxxxvii[187]}

2. 2. **Liaison Members:** In addition to the voting members and ex-officio members, the ACIP charter specifies 16 additional nonvoting liaison representatives from professional societies and organizations responsible for the development and execution of immunization programs for children and adults. Like ex officio members, liaison members are expected, to the extent possible, to represent the positions and views of their sponsoring organizations. Liaison members are expected to contribute to committee discussions when issues of importance to their organizations are being discussed. These members can serve as appointed consultants to working groups and subcommittees to provide expert advice and apprise the working group of the position their organization endorses.^{clxxxviii[188]}

Decision-Making Process of the ACIP:

When deemed appropriate by the Executive Secretary and the Chair of the ACIP, working groups may be formed to prepare draft policy recommendations to be submitted to the full ACIP for its consideration. The working groups must: 1) include one or more regular voting members, 2) include CDC staff members, 3) may include ex officio members and liaison representatives and other consultants. Vaccine manufacturer's

official representatives may not serve on working groups but, at the discretion of the chair, may be consultants to a working group.^{clxxxix[189]}

Generally, working groups range from six to fifteen members.^{exc[190]} The working group is charged with reviewing all pertinent information relative to the recommendation for use of a vaccine. No notice is given to the public of working group meetings and discussions of the group are held in private. No minutes are taken at the meetings.

Upon drafting a proposed recommendation, the chair will submit the draft proposal to the ACIP for consideration. The ACIP members review the proposal and suggest revisions to the working group. This process is generally repeated numerous times. The process for making a final recommendation to the full ACIP generally takes eighteen to twenty-four months. The work that the working group does contributes in large part to the recommendations for use of a vaccine submitted to the Director for approval.

Regularly scheduled meetings are usually held three times a year, at the discretion of the CDC, with meeting dates announced six to twelve months in advance. Notices of each meeting, along with agenda items that may be discussed, are published in the Federal Register in accordance with the requirements of FACA. Potential topics for ACIP consideration can be suggested by anyone, but are most often proposed by CDC program staff, ACIP members, and vaccine manufacturers.^{exci[191]}

The meetings of the ACIP are held in public and are widely attended by representatives from government, industry, and other interested parties. Frequent votes are taken to decide on a given policy matter at hand. Whenever six or more members are not eligible to vote by reason of financial conflict of interest, the Executive Secretary has the authority to temporarily designate the ex-officio members as voting members.

Final Recommendations for Vaccine Use

ACIP recommendations are submitted to the agency for approval. Upon acceptance by the agency, ACIP recommendations are published in the *Morbidity and Mortality Weekly Report* published by the CDC. While the recommendations by the ACIP to the CDC are subject to agency approval, longtime CDC officials do not remember an ACIP recommendation that was not approved by the agency.

What the CDC Considers a Conflict of Interest in ACIP

According to the Committee on Government Reform, as an SGE, every member of the ACIP is required to file a standard confidential financial disclosure report once a year. New members of the ACIP must file a new entrant report no later than 30 days after assuming their position. All reports must cover the 12 months preceding the date of filing.

Members must report specific sources of earned income over \$200 for the filer and \$1,000 for the filer's spouse. ACIP members must report all honoraria received in excess of \$200, along with the date services were provided. The \$1,000 threshold for spousal earned income does not apply to honoraria, because of special concerns about that form of income. They must also report all assets held for investment or the production of income with a fair market value greater than \$1,000 at the end of the reporting period. The filer does not have to report the dollar amount or values for any asset or income.

ACIP Waiver Process

The Committee on government reform states that “waivers are granted to each and every member of the ACIP whether or not they have conflicts of interests listed” on their form. In fact, the Committee found, ACIP issues limited waivers “on an annual basis to

members who have potential conflicts of interest. The waivers allow members to participate in all matters that come before the ACIP, with the provisos that: (1) members recuse themselves from voting on matters involving vaccine-related entities where they have a current direct financial interest and (2) that they publicly disclose all relevant financial interests at the beginning of each ACIP meeting.”

The waiver states that the members are under statutory obligation to refrain from participating in any deliberation that involves a particular matter having a direct and predictable effect on a financial interest attributed to them. They provide that the deputy ethics counselor has the authority to grant a waiver permitting the ACIP member to participate in such matters as deemed appropriate.

Waivers are requested by the Executive Secretary of the ACIP, Dr. Dixie Snyder, Jr. CDC Legal Counsel Kevin Malone concurs that the waiver is appropriate and the Deputy Ethics Counselor, Mr. Joseph R. Carter, is responsible for approving the waiver. In interviewing these individuals, the Committee staff was told, “We generally give them to everyone...we give them out freely.” The CDC representatives explained, it is “the nature of the industry that they will have conflicts...we will allow you to participate if you disclose your conflicts...we will let you discuss but not vote.”

The Executive Secretary prepares a work sheet prior to every ACIP meeting detailing the conflicts of interest that members may have pertaining to the topics on the agenda. The work sheet is only for his use and is not disclosed to the public. The documents are considered informal and are not saved by the CDC.

The Committee on Government Reform has found “serious weaknesses” in the CDC’s policing of conflicts of interest on ACIP. Problems included these:

1. **1.** Many members do not fully disclose conflicts of interest.
2. **2.** CDC ethics officials conceded to Committee staff that they have been lax in compelling the ACIP members to provide complete and thorough information.

Every member of the ACIP is granted a waiver for the entire year. The CDC grants blanket waivers to the ACIP members each year that allow them to deliberate on any subject, regardless of their conflicts, for the entire year. (In contrast, the FDA grants waivers on a meeting by meeting basis, taking into consideration the issues on the agenda and the affected companies discussed. Moreover, the FDA provides a list of parties that will be affected by their vote so their members clearly understand when they cannot participate.) "The CDC's policy of issuing annual waivers creates an environment where people do not take the conflict of interest issue as seriously as they should," states the Committee on Government Reform. "This policy, in concert with sloppy monitoring of the completeness of members' financial disclosure statements, allows for a clubby environment where ethical concerns are downplayed."

The Committee on Government Reform found, in their investigation, that "ACIP members are allowed to vote on vaccine recommendations, even when they have financial ties to drug companies developing related or similar vaccines."

For example, in the case of rotavirus vaccine, the vaccine before the advisory committee was developed by Wyeth-Lederle. However, Merck and SmithKline Beecham had rotavirus vaccines under development. A recommendation for Wyeth-Lederle's vaccine would help pave the way for future recommendations for the products of Merck and SmithKline Beecham.

"While ACIP members with ties to Wyeth-Lederle were not allowed to vote on

recommendations for the rotavirus vaccine, those with ties to Merck and SmithKline Beecham were allowed to vote. This stands in stark contrast to the policies of the FDA. In discussions with FDA staff on this specific issue they informed the Committee staff that when the VRBPAC is deliberating the licensure of a vaccine, a company is considered affected [an affected company is one with a direct interest] if they are direct competitors of the manufacturer of the vaccine being considered. They further clarified that this policy was in place because of the competing interest of the affected company and not because of concerns about the release of proprietary information. Moreover, if a VRBPAC member has a direct interest with a competing firm they are automatically disqualified from participation.”

ACIP Committee that Evaluated Lymerix

LDA has found that some ACIP members were allowed to participate in the recommendation process for the Lyme disease vaccine despite the potential for the appearance of a conflict of interest.

Members of the APIC for the SmithKline Beecham Lyme disease vaccine included

Voting Members:

CHAIRMAN: John F. Modlin, M.D., Professor of Pediatrics and Medicine, Dartmouth Medical School, Lebanon, New Hampshire.

EXECUTIVE SECRETARY: Dixie E. Snider, Jr., M.D., M.P.H, Associate Director for Science, Centers for Disease Control and Prevention, Atlanta, Georgia.

Richard D. Clover, M.D., University of Louisville School of Medicine, Louisville,
Kentucky

David W. Fleming, M.D., Oregon Health Division, Portland, Oregon.

Mary P. Glode, M.D., The Children's Hospital, Denver, Colorado

Marie R. Griffin, M.D., M.P.H. , Vanderbilt University Medical Center
Nashville, Tennessee

Fernando A. Guerra, M.D. , San Antonio Metropolitan Health District
San Antonio, Texas

Charles M. Helms, M.D., Ph.D. , University of Iowa Hospital and Clinics
Iowa City, Iowa

David R. Johnson, M.D., M.P.H. , Michigan Department of Community Health,
Lansing, Michigan

Chinh T. Le, M.D. , Kaiser Permanente Medical Center, Santa Rosa, California.

Paul A. Offit, M.D. , The Children's Hospital of Philadelphia, Philadelphia,
Pennsylvania.

Jessie L. Sherrod, M.D. , King Drew Medical Center , Los Angeles, California

Bonnie M. Word, M.D. , Monmouth Junction, New Jersey

EX-OFFICIO MEMBERS (Non-voting)

Robert F. Breiman, M.D. , Centers for Disease Control and Prevention,
Atlanta, Georgia

William Egan, Ph.D. , Food and Drug Administration, Rockville, Maryland

Geoffrey S. Evans, M.D. , Health Resources and Services Administration ,
Rockville, Maryland

T. Randolph Graydon, Center for Medicaid and State Operations, Baltimore,
Maryland.

Regina Rabinovich, M.D., National Institutes of Health. Bethesda, Maryland.

Kristin Lee Nichol, M.D., M.P.H. , VA Medical Center , Minneapolis, Minnesota

David H. Trump, M.D., M.P.H. , Office of the Assistant Secretary of Defense (Health
Affairs,) Falls Church, Virginia

LIAISON REPRESENTATIVES

American Academy of Family Physicians, Richard Zimmerman, MD, Pittsburgh,
Pennsylvania,

American Academy of Pediatrics, Larry Pickering, M.D., Norfolk, Virginia and Jon
Abramson, M.D. Winston-Salem, North Carolina,

American College of Obstetricians and Gynecologists, Stanley A. Gall, M.D.
Louisville, Kentucky.

American College of Physicians, Pierce Gardner, M.D. , Stony Brook, New York

American Hospital Association, William Schaffner, M.D. , Nashville, Tennessee.

American Medical Association, H. David Wilson, M.D. , Grand Forks, North Dakota

Association of Teachers of Preventive Medicine, W. Paul McKinney, M.D.,
Louisville, Kentucky

Biotechnology Industry Organization, Yvonne E. McHugh, Ph.D.,
Emeryville, California

Canadian National Advisory Committee on Immunization, Victor Marchessault,
M.D., Cumberland, Ontario, Canada

Hospital Infection Control Practices Advisory Committee, Jane D. Siegel, M.D. ,
Dallas, Texas

Infectious Diseases Society of America, Samuel L. Katz, M.D. ,
Durham, North Carolina

National Immunization Council and Child Health Program, Mexico
Jose Ignacio Santos, M.D. , Mexico City, Mexico

National Medical Association, Rudolph E. Jackson, M.D. ,
Atlanta, Georgia

National Vaccine Advisory Committee, Georges Peter, M.D.
Providence, Rhode Island

The following CDC staff members prepared this report:

David T. Dennis, M.D., M.P.H.

Edward B. Hayes, M.D.

Kathleen A. Orloski, D.V.M., M.S., Division of Vector-Borne Infectious Diseases

Martin I. Meltzer, Ph.D., Office of the Director, National Center for Infectious
Diseases

Potential for the Appearance of Conflicts of Interest, voting members:

Richard D. Clover, M.D.: University of Louisville School of Medicine, Louisville, Kentucky. Factors contributing to the potential for the appearance of conflict of interest: Dr. Clover has received educational grants from the vaccine manufacturer, SmithKline Beecham.^{excii[192]}

David W. Fleming, M.D., Factors contributing to the potential for the appearance of conflict of interest: Dr. Fleming was involved in both development of vaccine recommendations for the CDC and vaccine evaluations for the FDA. Thus, he was able to influence the process of vaccine approval and then the process of recommendation, activities inherently in conflict.

Chinh T. Le, M.D. , Among factors contributing to the potential for the appearance of conflict of interest: Kaiser Permanente Medical Center, Santa Rosa, California. Conflict of Interest: Dr. Le's employer, Kaiser Permanente, is participating in vaccine studies with SmithKline Beecham, manufacturer of Lymerix.^{exciii[193]}

Dixie E. Snider, Jr., M.D., M.P.H, Associate Director for Science, Centers for Disease Control and Prevention, Atlanta, Georgia. Among factors contributing to the potential for the appearance of conflict of interest: Dr. Snider was involved in development of both evaluation for the FDA and recommendations for the CDC. Thus, he was able to influence the process of vaccine approval and then the process of recommendation, activities inherently in conflict according to ethics experts. Dr. Snider is an employee of the CDC, which holds the rights to world patent # WO 99/40200, Recombinant lipidated psaa protein, methods of preparation and use, of potential value for Lyme disease vaccines and diagnostic tests.

Fernando A. Guerra, M.D. , San Antonio Metropolitan Health District, San Antonio, Texas. Among factors contributing to the potential for the appearance of conflict of interest: In October 1999, just a few months after the ACIP meeting, Dr. Guerra and the San Antonio Metropolitan Health District accepted \$87,000 from Lymerix manufacturer SmithKline Beecham to participate in a hepatitis A vaccine clinical trial study.^{exciv[194]} At the time of the ACIP meeting and evaluation, he and his employer were working under a \$102,418.62 grant from MedImmune, Inc., to perform Respiratory Syncytial Virus (RSV) disease surveillance and tracking. This is of great concern because Medimmune, a vaccine manufacturer, is a partner with Aventis Pasteur (SmithKline's competitor in the Lyme vaccine arena) to create a second generation Lyme vaccine under US patent #5,583,038. Aventis Pasteur is using the same adjuvant technology for its RSV vaccine and its second generation Lyme disease vaccine. There is no question that approval of the first generation SmithKline vaccine would clear the way for the second generation Aventis product.

Paul A. Offit, M.D. , The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Among factors contributing to the potential for the appearance of conflict of interest: Dr. Offit told the Committee on Government reform that he is paid by the pharmaceutical industry to travel around the country and teach doctors that vaccines are safe.^{exciv[195]}

Potential for the Appearance of Conflict of Interest, Nonvoting Members Robert F. Breiman, M.D. , Centers for Disease Control and Prevention, Atlanta, Georgia. Potential for the appearance of conflict of interest: Dr. Breiman was present at both FDA and CDC evaluations. Although he did not vote, he had the opportunity to influence both groups, thus creating a conflict of interest.

Appearance of Conflict of Interest Among Liaison Members

The American Academy of Family Physicians has sponsor relationships with a long list of pharmaceutical sponsors. These include the major Lyme disease vaccine manufacturers and large insurance companies with a policy of rejecting Lyme disease claims. For 1999 alone, this organization's sponsors included: Eli Lilly and Company, Schering Laboratories/Key Pharmaceuticals, AstraZeneca, Bayer Corporation, Pharmaceutical Division Boehringer Ingelheim Pharmaceuticals Inc., Bristol-Myers Squibb Company, Ortho-McNeil Pharmaceutical Pharmacia and Upjohn, TAP Pharmaceuticals Inc., Abbott Laboratories, Becton Dickinson, Glaxo Wellcome Inc., Hoechst Marion Roussel, Inc., Janssen Pharmaceutica, Knoll Pharmaceuticals, Novartis Pharmaceutical Corporation, Parke-Davis, Pfizer Inc., The Procter & Gamble Company, Searle, SmithKline Beecham, Wyeth-Ayerst Laboratories, Merck US Human Health, Organon, Inc., Pasteur Merieux Connaught, DuPont Pharma, GE-Marquette Medical Systems, Johnson & Johnson MERCK Consumer, McNeil Consumer Healthcare, Novo Nordisk Pharmaceuticals Inc., Otsuka America Pharmaceutical, Inc., 3M Pharmaceuticals, Ross Products Division, Abbott Labs, Wellpoint Health Networks, Inc., AETNA/US Healthcare, Bayer Corporation, Consumer Care, *American Family Physician*, Clinical Communications Inc., Core Content Review of Family Medicine, *Family Practice Management*, Forest Laboratories, Inc., HealthMatics, Interactive Medical Networks, iScribe, John Deere Healthcare, Inc., Laboratory Corporation of America, Muro Pharmaceutical, Inc., Rhone-Poulenc Rorer Inc., Schwarz Pharma, Scienta Healthcare Education, UCB Pharma, United HealthCare Corporation, Schering Laboratories/Key Pharmaceuticals, Burroughs Wellcome Co., CIBA-GEIGY Corporation, Fisons Pharmaceuticals, Roche Laboratories,

Zeneca Pharmaceuticals, Aetna Health Plans, Boehringer Mannheim Pharmaceuticals Inc., DuPont Pharmaceuticals Company [**Note: as of July 1998, the DuPont bought out Merck's interest and the company is now called DuPont Pharmaceuticals Company**], The Prudential, Wallace Laboratories, Westwood-Squibb Pharmaceuticals, Whitehall-Robins, and Parke-Davis, among many others.

The American Academy of Pediatrics has a financial relationship with all major Lyme disease vaccine manufacturers. Direct sponsors include: Abbott Laboratories (Lyme disease diagnostic test patents,) Astra, Merck & Co., Aventis Pasteur (one of two major Lyme disease manufacturers,) Pfizer, Inc., SmithKline Beecham (one of two major Lyme disease vaccine manufacturers,) Merck Vaccine Division, AstraZeneca LP, Fujisawa Healthcare, Inc., Glaxo Wellcome, Inc., Johnson & Johnson, Pediatrics Insurance Consultants, Inc., Pfizer Pediatric Health, Procter & Gamble Baby Care, Wyeth Lederle Vaccines, Bristol-Myers Squibb Company, MedImmune, Eli Lilly and Company, McNeil Consumer Healthcare, Mead Johnson Nutritionals. Medela, Inc., and Whitehall-Robins Healthcare, among many others.

American College of Obstetricians and Gynecologists. Pharmaceutical sponsors include Berlex Laboratories, Eli Lilly and Company, Novartis, Ortho McNeil Pharmaceutical, Pharmacia, Schering AG, and Wyeth-Ayerst.

American Hospital Association. Sponsors include Abbott Labs, Bristol-Myers Squibb, GlaxoWellcome, Johnson & Johnson, ServiceMaster, and SmithKline Beecham.^{cxvii}

^[196]**American Medical Association.** Sponsors include such major vaccine manufacturers as Aventis, Glaxo Wellcome plc, Merck & Co., Pfizer, and Shering AG.**Infectious Diseases Society of America.** Grants offered by Aventis, Bristol-Myers Squibb Company.^{cxviii[197]}

Section XIII

Treatment Guidelines and Conflict of Interest

Contributors to the Lyme Disease **Treatment Guidelines** from the Infectious Diseases Society of America, published in the year 2000, call for two to four weeks of antibiotic treatment, even in cases that have been long misdiagnosed or are difficult to resolve. Another two to four week course of medicine is suggested if the first course does not resolve symptoms within several months. These guidelines discount the notion that a chronic form of Lyme disease caused by persistent infection may require longer-term treatment. These guidelines are currently accepted as the standard of care across the United States and are endorsed by the American Academy of Pediatrics.

The authors are:

Gary P. Wormser, Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla, New York. Appearance of conflict of interest:

1. Has run clinical trials for Lyme disease vaccines (Pasteur, Merieux, Connaught).
2. Is being sued by patients who claim he negligently handled their adverse reactions during clinical trials. Was subinvestigator for Glaxo in clinical trials of Cefitin.^{excviii[198]}

Robert B. Nadelman, Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla, New York. Appearance of Conflict of Interest:

1. Ran clinical trials for Lyme disease vaccines (Pasteur, Merieux, Connaught).
2. Is being sued by patients who claim he negligently handled their adverse reactions during clinical trials. Was lead investigator for Glaxo in clinical trials of Cefitin.^{excix[199]}

Raymond J. Dattwyler, Division of Allergy, Immunology and Lyme Disease, Department of Medicine, State University of New York at Stony Brook and CEO, Brook Biotechnologies, Stony Brook, New York. Potential for the appearance of conflict of interest:

3. 3. His company, Brook Biotechnologies, manufactures Lyme diagnostic tests in lockstep with vaccines. Currently working under federal grant money to commercialize patent # 5,571,718^{cc[200]}, licensed from Brookhaven Laboratory in New York, to create a series of diagnostic tests, including one that differentiates those vaccinated with the SmithKline Beecham OspA vaccine product from those with infection.
4. 4. Worked with Glaxo on Ceftin and served as consultant and investigator to Roche on Rocephin, one of the recommended drugs.^{cci[201]}

Eugene D. Shapiro, Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. Potential for the appearance of conflict of interest:

1. 1. On the payroll of major insurance companies to formulate Lyme disease policy.^{ccii[202]}
2. 2. His employer, Yale University, invented the OspA vaccine technology in use by SmithKline Beecham and looks to it as a significant revenue source. In the December 2000 issue of *Elle* magazine, Shapiro called Lyme disease a magnet for hypochondriacs, saying, “People would rather say, ‘ I think I have Lyme disease’ than “I’m getting old and tired.’”

Allen C. Steere, Tufts University School of Medicine, New England Medical Center, Boston, Massachusetts. Considered the preeminent expert in Lyme disease by

mainstream medicine, Steere identified a “viral syndrome” he termed “Lyme arthritis” among a group of children in and around Lyme, Connecticut, in 1975. (The disease was later found to be caused by the Lyme disease spirochete, *Borrelia burgdorferi*, by US government scientist William Burgdorfer.) Steere has written virtually every chapter on Lyme disease for medical textbooks, including Harrison’s *Principles of Internal Medicine*, Mandell’s *Infectious Disease* textbook, and Kelley’s *Textbook of Rheumatology*. Potential for the appearance of conflict of interest:

1. 1. Lead researcher for the SmithKline Beecham Lyme disease vaccine, Lymerix, based on the same case definition of Lyme disease put forth in the treatment guidelines.
2. 2. NIH/CDC research grant money to study issues surrounding the vaccine.
3. 3. On consulting the staff on Imugen, a biotechnology company whose product lines hinge, in large part, on success of the OspA vaccine
4. 4. Vested interest in the current case definition by virtue of his prior publications.

Thomas J. Rush, private practice, Briarcliff, New York.

Daniel W. Rahn, Office of Medical Management, Medical College of Georgia, Augusta.

Potential for the appearance of conflict of interest::

1. 1. Dr. Rahn has been an employee of Yale University, which invented the OspA vaccine technology in use by SmithKline Beecham and looks to it as a significant revenue source.
2. 2. Chairman, CHI Board of Directors as well as Director, Center for Health Care Improvement, Professor, Department of Medicine, and Vice Dean for Clinical Affairs, Medical College of Georgia.^{cciii[203]} Established in the spring of 1998, the Center for Health Care Improvement (CHI) was developed as a collaborative venture between Blue Cross/ Blue Shield of Georgia (BCBSGA) and the Medical College of

Georgia (MCG). CHI's mandate is improving efficiencies for managed care, a goal frequently at odds with appropriate treatment of chronic Lyme disease.

David T. Dennis, Office of Medical Management, Medical College of Georgia, Augusta. Potential for the appearance of conflict of interest, defined in sections above.

Patricia K. Coyle, Department of Neurology, and Department of Medicine, Health Sciences Center, State University of New York at Stony Brook. Potential for the appearance of conflict of interest, defined in sections above.

David H. Persing, Diagnostics Development, Corixa Corporation, and Infectious Disease Research Institute, Seattle Life Sciences Center, Seattle, Washington. Potential for the appearance of conflict of interest, defined in sections above.

Durland Fish, Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. Conflict of Interest: Employer holds license to Lyme vaccine patents marketed by SmithKline Beecham, and looks to it as a significant revenue source.

Benjamin J. Luft, Division of Allergy, Immunology and Lyme Disease, Department of Medicine, State University of New York at Stony Brook, and principal, Brook Biotechnologies, Stony Brook, New York. Potential for the appearance of conflict of interest, defined in sections above.

The Infectious Diseases Society of America has a conflict of interest as well, since it counts the Lyme disease vaccine manufacturer, Aventis, among its corporate sponsors.^{cciv}

CONCLUSION

Potential for the appearance of conflict of interest in Lyme disease extends beyond the material covered here. For instance, many of the researchers associated with the patents and products described above are also reviewers for major peer-reviewed journals.

Managed care, meanwhile, has an economic interest in limiting the course of treatment – not just for Lyme disease, but across the board. Individuals on these panels often consult for managed care as well.

The appearance conflict of interest is simply business as usual in the world of medicine. We expect, in the twenty first century, that official and influential committees will be informed by experts, some with financial ties to their fields of expertise. We frequently provide waivers to such individuals because we are willing to trade an appearance of conflict of interest for their superior knowledge. We give them the benefit of the doubt and put faith in their ability to separate financial self-interest from the public interest during the period of time they serve on government panels, including those that set disease definitions and approve new drugs. While we entrust these individuals with our health care future, however, this trust cannot be blind. As a society, we must continue to examine health care decisions in light of the appearance of conflict of interest to make sure that the line between product development and good public policy does not become blurred.

The continuing debate surrounding Lyme disease suggests the need for a closer look where appearance of conflict of interest is concerned. It is not our intent to present every possible conflict of interest, or to claim that we have uncovered a crime. Instead, it is our hope that this report will provide a roadmap for further review by officials charged with examining conflicts of interest and inappropriate bias when they interfere with the public good.

PART FOUR: NOTES AND REFERENCES

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cxli^[141] Interview with Ira Maurer, April 11, 2001

cxlii^[142] http://www.house.gov/reform/staff_report1.doc

cxliii^[143] VRBPAC charter, DHHS, December 21, 1999.

cxliv^[144] 5 C.F.R. ?2640.103(a).

<http://www.afmc.wpafb.af.mil/HQ-AFMC/JA/lo/lojaf/ethics/ogeregs/00-03-29.htm>

cxlv^[145] Waiver Criteria Document 2000, FDA, pg. 2.

cxlvi^[146] Id at 19.

cxlvii^[147] Id. at 23.

cxlviii^[148] Id. at 20. Where the grant or contract relates to the subject matter of the committee discussion, an actual conflict may arise. In situations where the grant or contract is unrelated to the product at issue, an *appearance* problem may arise. In either situation the conflict of interest may be waived and the member allowed to participate.

cxlix^[149] Id. at 25-38.

cl^[150] Id. at 17.

cli^[151] Id. at 25-38.

clii^[152] Id.

cliii^[153] Policy and Guidance, Handbook for FDA Advisory Committees, pg. 12.

cliv^[154] Waiver Criteria Document 2000, FDA, pg. 19.

clv^[155] Id.

clvi^[156] <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3422t1.rtf> at 2-3

clvii^[157] <http://pctgazette.wipo.int/cgi-bin/ifetch5?ENG+PCT+2+1006889-REVERSE+0+5+6871+BASICHTML-ENG-0-0-0+6+22+1+25+110000000000+burgdorferi>
(password: guest, username: guest)
<http://www.cdc.gov/od/ads/techtran/pat/I011970.htm>

clviii^[158] Science Magazine, Vol. 287, #5450, p. 22

clix^[159] <http://fundedresearch.cos.com/cgi-bin/NIH/result>

clx^[160] http://www.aventispasteur.com/us/media/kit_aids5.html

clxi^[161] <http://silk.nih.gov/public/cbz2zoz.@www.all.inst.fy2000.dsnc>

clxii^[162] http://www.iapac.org/vaccines/confvacres99_macd.html

clxiii^[163] <http://www.nih.gov/news/pr/jan98/niaid-14.htm>

clxiv^[164] <http://www.ssharp.org/hvtn/partstr.html>

clxv^[165] <http://www.whale.to/v/staff.html#Section I>

clxvi^[166] <http://www.uchospitals.edu/news/pneumococcus.vaccine.trial.html>

clxvii^[167] <http://www.whale.to/v/staff.html#Section I>

clxviii^[168] <http://fundedresearch.cos.com/cgi-bin/NIH/result>

clxix^[169] <http://fundedresearch.cos.com/cgi-bin/NIH/result>

clxx^[170] <http://www.whale.to/v/prevnar2.html>

clxxi^[171] <http://silk.nih.gov/public/cbz2zoz.@www.all.inst.fy99.dsnc>

clxxii^[172] http://www.aventispasteur.com/us/media/kit_aids5.html

clxxiii^[173] id

clxxiv^[174] <http://www.urmc.rochester.edu/smd/crc/resarea.html>

clxxv^[175] <http://www.medimmune.com/medimmune/press/070699.htm>

clxxvi^[176] <http://164.195.100.11/netacgi/nph-Parser?>

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clxxvii^[177] http://www.aventispasteur.com/us/media/kit_aids5.html

clxxviii^[178] http://biz.yahoo.com/prnews/001019/ma_aquila_.html

clxxix^[179] http://www.house.gov/reform/hearings/healthcare/00.06.15/opening_statement.htm

clxxx^[180] http://biz.yahoo.com/prnews/000911/ca_aviron_.html

clxxxii^[181] <http://biz.yahoo.com/e/000308/avir.html>

clxxxii^[182] 42 C.F.R. §51b.204.

clxxxiii^[183] Section 1928 of the Social Security Act (42 U.S.C. § 1396s), as added by Section 13631 of the Omnibus Budget Reconciliation Act of 1993.

clxxxiv^[184] ACIP Charter, May 3, 1998 as approved by Claire Broome, Acting Director CDC.

clxxxv^[185] *Id.*, pg 3.

clxxxvi^[186] *Id.*, pg 2.

clxxxvii^[187] The Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, Policies and Procedures for Development of Recommendations for Vaccine Use and for the Vaccines for Children, January 2000, pg 4.

clxxxviii^[188] ACIP Charter, May 3, 1998, pg 4.

clxxxix^[189] The Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, Policies and procedures for Development of Recommendations for Vaccine Use and for the Vaccines for Children, January 2000.

exc^[190] Telephone interview of Dr. John Modlin, June 9, 2000.

exci^[191] The Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, Policies and Procedures for Development of Recommendations for Vaccine Use and for the Vaccines for Children, January 2000.

excii^[192] <http://www.whale.to/v/staff.html#Section V>

exciii^[193] <http://www.whale.to/v/staff.html#Section V>

exciv^[194] <http://www.ci.sat.tx.us/atty/1999/ag991014.htm>

excv^[195] http://www.house.gov/reform/hearings/healthcare/00.06.15/opening_statement.htm

excvi^[196] <http://www.aha.org/>

excvii^[197] http://www.idsociety.org/pd/grants_toc.htm

excviii^[198] FDA, CDER Transcripts, July 22-23, 1993. Anti-Infective Drugs. Ceftin for early Lyme disease

excix^[199] FDA, CDER Transcripts, July 22-23, 1993. Anti-Infective Drugs. Ceftin for early Lyme disease

ec^[200] <http://164.195.100.11/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=/netahtml/search-bool.html&r=25&f=G&l=50&co1=OR&d=ft00&s1='Borrelia+burgdorferi'.ABST.&s2='Lyme+disease'.ABST.&OS=ABST/>

eci^[201] FDA, CDER Transcripts, July 22-23, 1993. Anti-Infective Drugs. Ceftin for early Lyme disease

ecii^[202] <http://www.fairfieldweekly.com/articles/lymedisease.html>

cciii^[203] <http://www.mcg.edu/centers/chi/summary.htm>

cciv^[204] http://www.idsociety.org/PD/grants_aventis01.htm