

Overview of 3 years of research into LYMERix Lyme Vaccine GlaxoSmithKline 2/26/02

This is a shorter easy-read version of the 7 page Testimony given by Karen Vanderhoof-Forschner, BS, MBA, CPCU, CLU to the Food and Drug Administration's Vaccine Advisory Committee Meeting on 11/28/01. This material will be updated in a few days to include the exhibits. This is the result of 3 years of extensive research of many documents.

This vaccine trial is an example of how human research should never be done. Based on information found during a multi-year investigation (especially in the last months of 2001), the trial's integrity as well as that of the manufacturer and investigators is called into question. We are concerned about the people that have been damaged during this time.

Background to Approval

Concerns about autoimmune cross-reactions date back to 1988. In 1991 there was concern that OspA might cross-react with nerve cell axons, joint synovia, and skeletal proteins.

There were indications of problems with the science behind the vaccine very early on. In 1992 the vaccine patent holders at Yale stated that the basic mechanism of action was having the vaccinated person's own immune system kill the bacteria while it was still in the tick, thus preventing transmission. Take a look at the vaccine's package insert and it will cite a 1992 study by Fikrig et al. as showing how the vaccine works. If you read the paper, this just *wasn't* proven. This article, published as an "*Advertisement*", stated the ticks took about *14 days* to become bacteria-free. Unfortunately, Lyme disease transmission occurs in 48 hours or less ... over a week *before* a tick would be "bacteria-free". It makes one wonder who is guarding our public health? Is anyone reading these articles?

In 1994, a Connaught paper on their volunteer's adverse events indicated that some participants appeared to be genetically vulnerable (had a genetic predisposition) to developing arthritic adverse events. Knowing this, why weren't future volunteers screened for these markers? In 1995, with rising adverse events occurring in the trials, Dr. Steere wrote to his Lyme project officer at the National Institutes of Health, "A small percentage of patients have developed joint pain or arthritis following vaccination. I continue to be concerned about this phenomenon." There is no indication anyone alerted the Internal Review Board, Data Safety Monitoring Board, FDA, FDA Vaccine Advisory Committee (VAC), or the volunteers of the problems.

In 1997, SKB touted the monkey vaccine trials as proving the vaccine worked, citing the monkeys negative blood tests and lack of bacteria cultures as proof of complete protection. However, the actual publication clearly stated that monkeys *were not* protected from getting a *low level of infection* that caused tissue damage. When asked about this at the 1998 FDA hearings, SKB representatives shrugged off the findings of infection as lab error.

Right before FDA-approval, the Principal Investigator and others published in Science that they had possibly found the specific mechanism for cross-reaction of OspA with human cells. Accompanying it was an article in Science magazine speculating that the focus by scientists on the cross-reaction in just joints was curious, because "hLFA-1 is found on cells all over the body." Yet, the trial investigators and the SKB private Data Safety Monitoring Board (which included a CDC employee) only focused on arthritis.

SKB OspA Vaccine Trial Details

Following the pattern of the FDA approval process, there were three trials. The Phase 1 trial was conducted in the early 1990's in Europe and in 1994 the Phase 2 trial was initiated. The large scale Phase 3 trial started in 1995, was unblinded in 1996, and was submitted for approval in 1997.

Entry criteria only allowed *healthy* people between ages 15 - 70 to be enrolled. Exclusion criteria specifically stated that people with "active Lyme disease" or those that "had any other illness that might interfere with the assessment of Lyme disease, including those associated with joint swelling or musculoskeletal pain" could not be enrolled. Serious cases and potential vaccine failures were evaluated by the Principal Investigator.

The vaccine contained: *buffered saline* (to maintain the pH); *aluminum hydroxide* (to *boost* the immune system response); 2-phenosxyethanol (to prevent the growth of other bacteria); *sterile water*, and lipidated (boosts the immune system response) OspA (strain 7S7). The placebo had the same contents as the vaccine, minus the lipidated OspA. *Between the*

alum and lipidation, this vaccine now gives a double boost to the immune system.

OspA Vaccine Trial Conclusions

Trials results, reported at FDA meetings and in the scientific literature, showed the vaccine was 76% effective in preventing Lyme disease. Only two cases of neurological Lyme disease were reported and both were in the placebo group. There was no statistical relationship of adverse events and vaccination. While the issue of cross-reactions was still discussed as theory, there was no scientific proof showing this could happen in humans. In June of 1998, the FDA Vaccine Advisory Committee (VAC) reluctantly recommend the vaccine be approved. In December formal FDA approval was given for widespread use.

In 2001, the FDA reconvened the VAC and its expert advisors to evaluate the data on the OspA vaccine because of the dramatically increasing rate of adverse reactions attributed to the vaccine and because of reports of vaccinees having trouble getting their adverse events recorded. Since no additional data was available to indicate that the vaccine was either unsafe or dangerous, no action was taken.

What We Now Know

In the summer of 2001, the LDF received an Freedom of Information (FOI) response from the FDA regarding the vaccine. While most of the material was whited-out, what we found was shocking.

a. Violations of Entry Criteria

About 20% of the volunteers or 2,028 subjects had a known history of musculoskeletal conditions at study entry and an additional 27 subjects had a known neurological condition - a violation to the entry and exclusion criteria.

Preexisting conditions included: osteoarthritis of the hands and spine; hip replacements; depression; knee surgery; arthritic degeneration; pain in joints, elbows, knees; diabetes; connective tissue disease; ankylosing spondylitis; polymyalgia rheumatica; rheumatoid arthritis; malignant fibrohistiocytoma; neurogenic bladder; Lyme disease and bell's palsy; Lyme meningoencephalitis and facial palsy; Parkinson's disease; abnormal movement disorders; inflammatory and toxic neuropathy; multiple sclerosis; disc disorders; and *other* degenerative diseases of the nervous system.

The impact on the vaccine data is clear after reading some of the cases - adverse reactions were linked to preexisting conditions, whenever possible. They were then discounted. Only *healthy* patients had a chance to have their adverse reaction declared "possibly related" to the vaccine.

b. Accuracy of the Reported Data and Failure to meet the Standard of Care

There were serious concerns about the accuracy of the data reported during the trial. Problems ranged from failure of the Data Safety Monitoring Board to perform proper analysis, to patients being treated *below* the standard of care (receiving short-term oral medication for those diagnosed with a Lyme brain infection).

While only two cases of definite neurologic LD were reported during the trial, SKB later stated this was in error and that there were 414 additional patients with facial palsy (bell's palsy) who were not reported because the protocol failed to have a code for this well-known Lyme manifestation.

Another major problem was the failure of the investigators to do testing necessary for patients to qualify as a "Definite" case of neurologic Lyme disease [e.g. a vaccine failure]. Only patients with laboratory evidence of Lyme by a spinal tap or nerve conduction tests could qualify. Nine cases of diagnosed neurologic LD cases were diagnosed, but *not* reported, because *the investigators declined to do the necessary tests*. Three additional patients were diagnosed with *Lyme meningoencephalitis*, but the investigators once again, failed to do spinal taps (which is the standard of care in diagnosis and treatment of the disease). Therefore, they did not meet the case definition for "Definite LD" either. Two vaccinee's experienced 3 cases of paralysis affecting one side of the body. While no one in the placebo group experienced this, it appears these too were not attributed to the vaccine.

The FDA wrote that at least one patient was "*not given the optimal antibiotic regimen.*" This patient should have received intravenous antibiotics for her diagnosed brain infection, but was given a few weeks of pills. When one patient did get a spinal tap during a hospitalization (due to diagnosed Lyme meningitis), *the investigator did not* have the spinal fluid tested for Lyme.

There were numerous other problems including errors in reporting data, split sample blood tests run on the same day producing different results, Western blots being interpreted in a nonuniform manner, and case definitions being changed midstream. There was even a case of a patient who had a positive Lyme culture, positive blood tests and neurologic symptoms (with no test), who was reported as having ehrlichiosis.

So, what did they know from the data? Individuals with a *history of musculoskeletal conditions* as well as those with a *history [self-reported] of LD* had a “**significantly higher incidence** of early and late adverse events.” People who had a *positive test for Lyme disease* at study entry had significantly increased incidence of late adverse events including: skin and appendage disorders, musculoskeletal system disorders, central and peripheral nervous system disorders, autonomic nervous system disorders, psychiatric disorders, gastrointestinal disorders, *white cell and immune system disorders.*” Yikes!!

In March of 2000, Tufts researchers, funded by an NIH grant, patented an OspA vaccine that caused less human autoimmune reaction than the current OspA vaccine. Sometime in the fall of 1999, this highly debated cross-reaction “theory” became a reality. But, from what I can tell, no one but the foreign patent office was made aware of this. The patent states that “*the invention is characterized by a novel modified OspA polypeptide which elicits in treated animals the formation of an immune response, without causing the induction of an autoimmune reaction in certain populations, individuals expressing the HLA-DRB1*0401 allele.*” It explains that the Human leukocyte function-associated antigen 1 (hLFA-1a), which is found on many cells throughout the body, cross-reacts with the piece of the OspA used to make the current vaccine. So, upon vaccination, a genetically vulnerable person’s own OspA-primed antibodies will start an autoimmune war by attacking and binding to its own hLFA-1a.

Tufts modified the OspA sequence so that the resulting human antibodies would not think the vaccinee’s own cells were Lyme bacteria. When Tufts new OspA (“FTK-Osp₁₆₅₋₁₇₃”) was tested on human blood, it was found to cause a less destructive reaction and was safer. The patent repeatedly states that there is a “*continuing urgent need for an improved vaccine*” and “*the use of protective immunogen in vaccines may be associated with the induction of an autoimmune reaction in certain populations*”.

From conversations with FDA officials, Tufts researchers failed to tell the FDA that they knew this very detailed and vital information. I found this patent in late November 2001 and found that Lyme researchers were also unaware of this research. Two weeks later, I presented this material to the FDA asking for a total recall of the vaccine.

In the summer of 2001, SKB had asked the FDA for permission to conduct another 15,000 person Phase 3 trial on another OspA vaccine and was awaiting approval for its pediatric vaccine (which has even more side effects). It is unclear that these have been recalled or pulled.

With the litigation flying and questions about their integrity, I am sure the FDA had a hand in GlaxoSmithKline’s decision to recall the vaccine.

But, we are not yet done with the analysis. We will be continuing to expand on this report and present the results to the public as material becomes available.

More details are in the longer version of this release.

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