The LYMErix™ Story: FDA Approval to Market Withdrawal ─ Learning from History
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The LYMErix™ vaccine (LV) by Smith Klein Beecham (SKB) was approved by the Food and Drug Administration (FDA) in December 1998 after completing a clinical trial of 10,936 people─ the manufacturer concluding it was to be most effective in preventing the disease in people under age 65. Half the trial participants received an initial injection, then booster shots one month and 12 months after. Uncertainty about the length of vaccine immunity implied that recipients might need more boosters as often as every year to prevent waning immunity. The panel unanimously endorsed the vaccine for use in people ages 15 to 70. Safety and efficacy testing data for young children who were at high risk of developing Lyme disease was not available.

Six months before the vaccine's approval, lead researcher for the LV, Dr. Allan Steere, New England Medical Center, Boston, published results (*Science* 7-31-1998) of his "test tube" study showin*g* that OspA (Outer Surface Protein A of the Lyme bacteria) could cause a "cross-reaction" with a human protein in people positive for the HLA-DR4 gene, 20-30% of the population. The immune system could attack the body's own protein thinking it was an invading bacterium─ not proof of this reaction in humans, but indicating a possible connection. The LV vaccine had an OspA base.

A month before vaccine approval, the Lyme Disease Association, Inc. (LDA) published *LDA's Vaccine Position Paper*. LDA was following the development of the vaccine and was concerned that safety and efficacy had not been fully established. The Steere research pointed to a potential link between OspA and a possible unstoppable immune cascade. LDA suggested that individuals considering vaccination should get answers to the questions posed by the *Paper* before getting vaccinated. Before the LV's approval, it generated so many questions and discussions by FDA panel members that Dr. Patricia Ferrieri of the University of Minnesota, who chaired the FDA advisory panel, chose to summarize the Committee's sentiments: "It's rare that a vaccine be voted on with such ambivalence and a stack of provisos."

As a frequent speaker on Lyme disease nationwide, I was finding the predominant question about Lyme became vaccine safety and efficacy. Many other Lyme groups were reporting the same. The research on the length of protection the vaccine would provide was unclear, and after the trials, people found that the one series of 3 shots they thought they needed might now require several boosters, but even doctors did not know for sure. Information that it did not provide permanent immunity was not widely disseminated. Misinformation abounded─ people came to us and said, we don't have to worry; we can never get Lyme; we got the vaccine. Whether a person with a history of Lyme should get the vaccine was not clear to people, so some got the vaccine and some of them said their symptoms returned. Discussions raged about "healthy" people who said they "acquired" Lyme from the vaccine but perhaps really had had undiagnosed cases and that the shot had "activated" existing subclinical infection. Due to all the uncertainty, many doctors stopped giving the vaccine.

By December 1999, LV safety concerns led the law firm of Sheller, Ludwig & Badey, Philadelphia, and others to file a class action lawsuit against SKB representing all individuals getting the LV vaccine. The purpose was to put people on notice about the dangers of the vaccine and get medical monitoring for any future vaccine use.

Reporter Ridgely Ochs (*NY Newsday* 3-9-2000) quoted Dr. Ronald Schell, University of Wisconsin, who said, "I wouldn't take the vaccine…I recognize that's a prejudice based on my animal research." His published study (*Infection & Immunity* 2-2000) found that hamsters vaccinated with OspA following infection with *B. burgdorferi* developed arthritis. Dr. Schell was a speaker at the now defunct Lyme Disease Foundation's (LDF) March 2000 conference in Hartford. I attended and followed Dr. Schell into the elevator after his presentation to discuss his hamster work, since LDA was so concerned about its relevance to the LV. SKB gave an update of the LV vaccine at the same conference, one which they also supported with a grant to the LDF, which publicly received a large check at the meeting. It appeared that the LDF initially supported the LV vaccine.

By early 2001, the LDA was so concerned with the numbers and severity of adverse events that I testified before the FDA's Vaccines & Related Biological Products Advisory Committee (Bethesda, MD 1-31-01). Scientists, practicing physicians, SKB (by now GlaxoSmithKline), patient advocates, and vaccine recipients who claimed they were harmed by the vaccine, some in motorized wheel chairs, testified. The FDA said the issue "cannot be

resolved with VAERS [Vaccine Adverse Events Reporting System] data alone, although reports of arthritic events to date do not provide clear evidence of a causal association." SKB assured the panel its vaccine was safe and reviewed its Phase IV trial information. Some physicians said they saw reduced Lyme in their practices. Scientists discussed how OspA-related autoimmunity might be relevant in vaccine complications.

My testimony in part, "Today you are hearing about how this vaccine has physically impacted human lives. It appears that little can be done to stop whatever process triggers some of these reactions, or if something can be done, it remains as yet undiscovered. I listen to the despair and bewilderment of those adversely impacted...I do not have any answers, and I do not know who does. This committee has the authority to formulate recommendations that may prevent others from potentially suffering the same fate. You can revisit the original data and research which appears to show a link between OspA and adverse reactions and view it in light of the adverse events you have now heard about. You can recommend further studies. You can find out why many doctors who treat chronic Lyme disease are not giving the vaccine. The Advisory Committee on Immunization Practices recommends under future considerations in their report on the Lyme disease vaccine, June 4, 1999 *MMWR*, 'establish post licensure epidemiological studies of safety, efficacy, prevention effectiveness, cost effectiveness, and patterns of use.' We concur with that recommendation and would like to see a moratorium on vaccine administration until those studies are completed and the results critically analyzed."

After hearing testimonies from all interested parties, the FDA panel concluded that the benefits of LV outweighed its risks and did not change product labeling or indications. FDA did require SKB to provide more vaccine safety and efficacy data by increasing their enrollment in the ongoing Phase IV trial.

The LDA tried to address the vaccine problems privately with the FDA after so many vaccine recipients contacted LDA about serious symptoms such as autoimmune issues they or sometimes their doctors attributed to the vaccine. Vaccinees indicated that their adverse events were often not reported, either by the administering doctor or even by the company when they called directly. The FDA spent considerable time trying to not allow us to bring in experts on the vaccine to a meeting with them, to the point of telling us we could not bring in anyone to the meeting who was not a "consultant" to the LDA, citing a "law" which turned out to be bogus. Finally, with the intervention of Congressman Chris Smith (NJ-4), the meeting was held (Bethesda 1-22-02). We brought in a team of experts including doctors trying to help people who received the vaccine and were now physically debilitated and a researcher integral to the development of the OspA based vaccine, who served as a "volunteer consultant" to LDA. He indicated that differences in trial and post trial rollout in vaccine adverse events issues could be related to the fact that after the trials, people in endemic areas received the vaccine, and that fact could account for events of retriggering latent infections mentioned above. About a month after the meeting, FDA faxed to LDA late on a Friday night (2-22-02) answers to LDA questions prepared for and submitted to that above meeting. A few days later, SKB announced the withdrawal of the vaccine from the market citing poor sales.

The LDA was permitted by the Court to submit a letter (4-02) in support of the proposed LV settlement. In part: [Discussing the FDA hearing on vaccine adverse events]. "The FDA never took further action on the vaccine. SmithKline (now GSK) acted. Citing poor sales of the vaccine, they withdrew it from the market. The class action was instrumental in achieving this result. Its filing caused people to rethink their intent to get the vaccine. SKB agreed not to remarket it without a label change. Consumers are now protected from further harm while the vaccine is not being distributed, and if SKB decides to redistribute, they will have to provide labels which fully inform consumers about the associated risks of the vaccine."

SKB settled the class action suits with Sheller and the other firms who had filed. According to the settlement agreement (6-30-03 Judge Jacqueline Cody, *Judgment, Final Order and Decree Granting Final Approval of the Class Action Settlement*, Chester Co. Court of Common Pleas), legal fees were paid to Seth Lesser (Bernstein, Litowitz, Berger, and Grossman LLP) to distribute to the Plaintiffs' Counsel. It also stated "nothing in the settlement agreement shall be construed as releasing any claim of any Class Member for personal injury arising out of vaccination with Lymerix…." I asked Attorney Steve Sheller in a recent phone interview about subsequent settlement rumors, and he stated, "Numerous claimants who were part of the case and others who came to us afterwards went forward with the Sheller firm, and large numbers were resolved pursuant to required confidentiality agreements, thus settlement terms remain confidential."

Since the suit was designed to warn patients of the drug's potential dangers, the objective of the class action was primarily met with the voluntary withdrawal of the vaccine from the market. A separate proviso would require the manufacturer to go through the FDA process again for relabeling if brought back. The manufacturer never acknowledged that LV caused harm and remained firm that the decision to withdraw was due to poor sales.

Present Day Lyme Vaccine

Fast forward to the present. There is a new vaccine which has just completed Phase I/II trials in Germany and Austria. It is OspA based, uses more than one strain of the bacteria (US plus European) and we have been told that the portion of the OspA which invoked the mimicry which started the arthritis cascade (which SKB has never publicly acknowledged occurred from vaccination) has been modified to prevent that occurrence. The manufacturer is Baxter. According to one of the vaccine's developers, Dr. Benjamin Luft, Stony Brook University "The results of the clinical trial conducted by Baxter are promising because the vaccine generated a potent human immune reaction, covered the complete range of *Borrelia* active in the entire Northern hemisphere and produced no major side effects…We hope that a larger-scale, Phase 3 trial will demonstrate not only a strong immune response but true efficacy in a large population that illustrates protection against Lyme disease."

LDA understands the value of a vaccine for Lyme disease. However, we should and do have concerns related partly to the fact there is no reliable test for Lyme disease yet, almost 40 years into the disease, nor is there one which determines active infection. How can an individual poised to receive the vaccine determine if they have a Lyme infection already, which in light of questions raised from the prior vaccine, could possibly prove dangerous to those individuals. Additionally, there have been published reports of cognitive difficulty and neuropathy including chronic inflammatory demyelinating polyneuropathy (CIDP) in LV patients. This issue also needs addressing in relationship to the new vaccine. (Norman Latov, *Journal of Peripheral Nervous System* 9-9-04; Donald H. Marks, *International Journal of Risk & Safety in Medicine,* 2011)

Questions related to the safety and efficacy of the prior vaccine do not appear to have been fully explored nor answered, but have been met publicly instead with blame being laid at the door of the Lyme community for failure of the first vaccine. In this climate, it is not really a surprise that Lyme patients and the public are concerned about a new rollout. Before that occurs, we recommend the following: 1.All the final reports/studies/research from the past vaccine, LV, need to be made public so concerned individuals can evaluate coverage of issues and corresponding analyses. 2. All of the safety and efficacy issues identified as problematic, unless proven to be false or insignificant rather than not being definitively or clearly established, regarding the past vaccine need to be conclusively addressed in relationship to the new vaccine. Claims of the effectiveness of changes from the previous to the new OspA vaccine in remedying safety concerns need to be scrutinized and verified. 3. More comprehensive and determinative research than was done for the previously approved Lyme vaccine needs to be done prior to approval on safety and efficacy. 4. Coordinated vaccine education programs need to be developed for health care providers and vaccine recipients or legal guardians of recipients. The importance of and mechanisms for adverse event reporting need to be included in education programs, as past LV recipients reported being dismissed by providers and/or the manufacturer and were unaware of the ability to self-report to VAERS. 5. Significant outreach to and education of healthcare providers needs to occur prior to rollout. 6. Listing of adverse events in label contraindications and the VAERS table of reportable events must be seriously protective of vaccine consumers. 7. Safety, immunogenicity and efficacy of the Lyme disease vaccine in children need to be demonstrated if the vaccine is recommended for them. 8. All panels which review the vaccine need to be as free as possible of professional and financial conflicts of interest─ as should always be the case.

Food for Thought

"During the past thirty years, vaccines have experienced a renaissance. Advances in science, business, and distribution have transformed the field to the point where vaccines are recognized as a "best buy" in global health, a driver of pharmaceutical industry growth, and a key instrument of international development." (J. Stéphenne, SKB, *Health Affairs* 6-30-11). While these are all positive outcomes, this statement by an official of the past producer of the only Lyme vaccine ever approved, clearly reinforces the reality that vaccines are big business, and that all stakeholders─ including regulators, advisors, health care providers, consumers, and advocates─ would be derelict if we were not vigilant in ensuring that business objectives do not preempt the goals of public health nor the rights of consumers.