



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

DRAFT

Patricia V. Smith  
President  
Lyme Disease Association.  
Inc. PO Box 1438  
Jackson, NJ 08527

Dear Ms. Smith (Pat):

On behalf of the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER), I am writing in response to your January 17, 2002, letter and as follow up to our January 22, 2002, meeting. CBER appreciated the opportunity to listen to the concerns of the Lyme Disease Association (LDA), with regard to LYMERix® and related issues.

Because of time constraints at the meeting, you had asked that CBER respond in writing to the list of questions provided by the LDA. CBER's response to those questions is enclosed. Also enclosed is the article from "Vaccine," referenced in CBER's response to Question 2 in your questions list.

At the January meeting, the LDA members had expressed concern regarding physicians' awareness of the use of "booster" doses. Please note that, as specified in the label, LYMERix® is currently approved by FDA for use for only three doses at 0, 1, and 12 months, with resulting efficacy in the Lyme season following the third (12 month) dose; further "booster" doses are not called for in the approved regimen.

The LDA had asked CBER to explore ways to educate health care providers on LYMERix® risk/benefit issues, LYMERix product labeling, and VAERS reporting. This topic is still under consideration.

I hope that the information provided here is helpful to your organization. Please give me a call if you have any questions or wish to discuss anything further.

Sincerely,

Mary T. Meyer  
Director  
Office of Communications, Training and Manufacturers Assistance  
Center for Biologics Evaluation and Research  
Food and Drug Administration

Enclosures

## CBER Response to Questions Submitted by the Lyme Disease Association

1. What does the FDA intend to do about the Lyme vaccine?

### **CYBER Response**

**FDA intends to monitor LYMERix® in accordance with regulations for post-marketing monitoring of vaccines in general. Likewise, FDA monitors studies conducted under IND in accordance with the pertinent regulations. Also, FDA collects reports submitted under the Vaccine Adverse Event Reporting System (VAERS).**

∴ 2. What is the primary endpoint and study design for the on-going telephone survey of a subset of individuals who have reported adverse reactions to VAERS. Specifically, what is the inclusion/exclusion criteria?

### **CBER Response**

**Project Summary: This is a case series follow-up survey using structured, confidential interviews by telephone and requesting medical records from people who have reported arthropathy following Lyme vaccination to VAERS. The survey is designed to collect patient information on demographics, vaccine exposure, risk factor exposure including exposure to other potential causes of arthritis, pertinent medical history, vaccines and vaccine lots administered, detailed information about adverse event symptoms and duration, information regarding time to onset from vaccination, and information regarding the effect of the adverse event on the patient's lifestyle.**

**Objectives: We wish to develop a fuller understanding of the adverse events that have been reported after Lyme vaccine. This information will be used to help evaluate the plausibility that Lyme vaccination may be associated with the development of inflammatory arthritis or other arthropathy. Detailed information as noted above is often absent in VAERS reports, making evaluation of plausibility, and generation of hypotheses about causality, difficult.**

Additionally, this survey will identify cases that are likely to be "new onset" inflammatory arthritis for possible further evaluation and study, such as inclusion in a proposed case-control study for cases evaluated as having "new onset" post-vaccination inflammatory arthritis.

**Inclusion criteria:** The follow-up survey population will consist of patients, at least 18 years of age, identified as the subjects of VAERS reports following Lyme vaccine and received between 12/21/98 and 10/31/00, with at least one of the following COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) terms: "rheumatoid arthritis," "arthritis," "arthrosis," "arthralgia," and "joint disease." These COSTART terms were identified through prior VAERS report analysis as highly likely to be used in coding potential arthropathy reports.

- A. Assuming an inclusion criteria includes arthritis and/or arthralgia, which VAERS codes and/or keywords are used to identify such individuals? And if the inclusion criteria consists of a specific injury and/or disease process, why has the study been so limited instead of addressing the various adverse reactions being reported to VAERS, including non-specific pain syndromes and development of Lyme disease-like symptoms, possibly Constituting exacerbation of previously asymptomatic Lyme disease and neurological conditions such as Bells' Palsy, optic neuritis, and acute transverse myelitis?

**CBER Response**

Please see the response above for the study selection criteria.

This survey was specifically designed to help address the theoretical concern that the OspA Lyme vaccine might serve as a potential trigger for an immune-mediated arthritis because of the specific nature and plausibility of the hypothesis based on the prior published work on treatment resistant Lyme arthritis. Other adverse events reported after Lyme vaccine, in addition to arthritis, are being evaluated in the phase 4 epidemiological study that is currently being conducted. Additionally, a telephone survey of patients from VAERS reports of Bell's palsy after LYMERix® administration was conducted in October-November 2000, a brief summary of which is included in our published report in the journal Vaccine on adverse events reported to VAERS after Lyme vaccine.

- B. Further, what is the FDA's case definition of "definite, probable and possible arthritis for purposes of this study

**CBER Response**

A case is classified as "Definite Inflammatory Arthritis" if the patient has joint swelling and two of the other four symptoms (pain, stiffness, heat, tenderness) present for at least 45 consecutive days; joint swelling (constant

or intermittent) of at least one joint must have been present for at least 45 consecutive days. A case is classified as "Probable Arthritis" if joint swelling and at least one other arthritis symptom have been present for at least 30 days, with joint effusion present for at least 15 of those 30 days. A case is classified as "Possible Arthritis" if at least one of the arthritis symptoms has been present for any period of time. These case classification criteria were developed for this study based on American College of Rheumatology (ACR) diagnostic criteria for rheumatoid arthritis and Lyme arthritis.

The abstract of the "preliminary evaluation" reports completed interviews of 49 patients out of 85 attempted (out of 415 patients with VAERS reports of "arthralgia or possible arthritis following Lyme vaccine") reports 17 cases of "possible arthritis" and 14 cases of "physician-diagnosed definite arthritis". Does this mean that the remaining 18 had "probable arthritis" and, if so, what if anything is being done to evaluate their cases?

#### **CBER Response**

**Medical records were received for 31 of 49 cases for which they had been requested. Of these 31 cases for which we have medical records, there were 14 cases meeting the case definition for "definite arthritis", and 17 cases that were classified as "possible arthritis". No cases met the case definition for "probable arthritis". If medical records have not been received from healthcare providers from whom they have been requested, additional requests for records have been sent.**

- C. How is the FDA dealing with individuals who test positive for Lyme disease after vaccination in terms of distinguishing between a new infection (i.e. vaccine failure) and the exacerbation of a previously asymptomatic or presumably "cured" infection (i.e. an adverse reaction)? It appears from the abstract that 7 of 14 cases of physician-diagnosed arthritis also had what is described as "concomitant exposure or another medical condition, including Lyme disease". What, if anything is the FDA doing to evaluate these individuals, especially in light of the fact that many people who have and who will receive LYMERix reside in Lyme endemic areas and can presumably be easily dismissed as having "concomitant exposure"?

#### **CBER Response**

**Currently we are evaluating the information collected from VAERS reports, the survey, and medical records to look for patterns that might help to identify possible causes of the arthritis. However, VAERS, survey, and medical record data alone are usually not sufficient to determine causality. With regard to Lyme disease, we are evaluating Western blot data, if available in submitted medical records, for evidence of Lyme infection pre and post- vaccination. Unfortunately, we normally cannot determine if somebody had Lyme disease before vaccination unless serology data is**

**available from the time period immediately preceding vaccination.**

**We have proposed a case-control study to evaluate those cases we identify as having "new onset" inflammatory arthritis after-vaccination, and plan to evaluate for evidence of Lyme disease infection in this study. We plan to use newer generation ELISA tests such as the C6 to distinguish cases of Lyme disease infection from cases that solely have a serological response to the vaccine.**

- D. Does the fact that 50% (7 of 14) of cases of physician-diagnosed definite arthritis post vaccination demonstrate the need for a warning and/or contraindication against the vaccination of individuals with "familial history of immune-mediated disease or inflammatory arthritis". "immune-mediated disease", and "prior history of physician-diagnosed Lyme disease"?

**CBER Response**

**Information in VAERS reports and the survey do not provide sufficient evidence that any of these factors is a risk factor for development of arthritis after Lyme vaccine.**

- E. When does the FDA contemplate completion of the interviews of the 415 VAERS reports identified as "arthralgia or possible arthritis"? And what if anything is being done to identify such reports filed subsequent to October 2000?

**CBER Response**

**The survey portion of this study should be completed by the end of 2002 although it is unlikely all 415 cases will be interviewed given limitations in contact information and the voluntary nature of the survey. The study was designed to include cases reported up to 10/31/2000; we continue to monitor reports received after that date however, and these reporters can be contacted if needed to expand the study.**

- F. Given the fact that FDA has now documented 7 case reports of physician-diagnosed definite arthritis which "could not be plausibly explained by concomitant exposure, prior diseases, or familial histories" a number on par with those that triggered regulatory intervention in other pharmaceuticals such as "FenPhen", is the FDA prepared to call for an immediate moratorium and/or withdrawal of LYMERix and, if not, what is the threshold number of case reports needed to trigger such action? It should be noted that 14 cases of physician-diagnosed arthritis post vaccination were identified out of 31 patients whose medical records were reviewed (45.2%) and in 7 of those (22.6%) the arthritis could not plausibly be attributed to any other cause. If these rates hold for the remainder of the 415 VAERS reports identified, the FDA will have documented

187 cases of physician-diagnosed arthritis, nearly 93 of which will not have any other plausible explanation.

**CBER Response**

**For all 14 cases of definite arthritis at least one factor in the familial or medical history that could play a role in the development of arthritis was identified. For 7 of the cases this factor was considered sufficient cause for the arthritis. For the other 7 cases we felt it was important to be conservative in assigning causality, and hence used the phrase noted above. However, this was not intended to imply that these other factors could not explain the arthritis nor that Lyme vaccine was the probable cause in these cases. In addition, arthritis is a very common disorder and many cases of arthritis do not have a specific "plausible" explanation identified. The inability to identify clear-cut explanations for all cases of arthritis does not provide evidence of a causal link to the vaccine.**

G. In terms of determining the rate of adverse reactions, how can the FDA determine how many individuals have been vaccinated?

**CBER Response**

**The FDA cannot determine how many people have received the vaccine. The FDA receives information from the manufacturer on the number of doses of vaccine distributed, but has no specific data on the number of doses actually administered.**

The abstract of the preliminary follow-up study reports "approximately 1.4 million vaccine doses were distributed" between December 1998 and October 2000. Given the fact that this is a multiple-dose vaccination and that most vaccinees have received at least two or three (and sometimes actually more) doses of LYMERix, and the fact that the uptake of LYMERix has been unexpectedly low (as demonstrated by the difficulty in reaching even 25% of the enrollment goals for the Phase IV studies), can the FDA rule out the possibilities that the actual number of vaccinees is in the low six-figures, and possibly as low as 100,000?

**CBER Response**

**The FDA does not know how many individuals received the vaccine, so it is difficult to "rule out" any specific number.**

3. How is the FDA dealing with individuals who participated in the clinical trials but began experiencing adverse reactions (or recognized such reactions) only after the study site was closed? Since VAERS will not accept their reports, and it has been reported that GlaxoSmithKline has been dismissive of such reports, how can the FDA ensure that these reactions are included in the total number of adverse event reports?

**CBER Response**

**Individuals who receive LYMERix® in a clinical trial should report adverse events to the clinical study site or directly to the company, GlaxoSmithKline (GSK), at 1-800-366-8900.**

**Federal regulations require that a company submit reports of adverse experiences to the FDA. Specifically, 21 CFR § 312.32 pertains to investigational products and § 600.80 pertains to licensed products.**

**We request that you provide any available information regarding situations in which GSK has refused to accept reports of adverse events occurring in LYMERix® clinical trial participants.**

**Please be advised that, as stated at the January 31, 2001 meeting of the Vaccines and Related Biologic Products Advisory Committee (VRBPAC), FDA has additionally requested that GSK undertake expedited reporting of adverse events for participants in clinical trials of LYMERix® who reported musculoskeletal or neurologic events with a duration of one month or more, and for individuals vaccinated post-licensure who reported arthritis, arthrosis, arthropathy, rheumatoid arthritis, or any neurologic events including, but not limited to, neuropathy and facial paralysis. FDA requested expedited reporting for these types of adverse events, whether or not the criteria for a serious adverse event were met.**

4. More specifically, how does the FDA deal with study participants who were in the placebo group during the trial (with no adverse reactions) but who received the vaccine after the study was unblinded and went on to experience adverse reactions to the actual vaccine?

**CBER Response**

**Adverse events occurring in individuals after receiving LYMERix® in a clinical trial are to be reported to the sponsor (see #3 above), regardless of whether that study was blinded or unblinded, and regardless of whether or not the subject previously received placebo in a LYMERix® clinical study.**

**Adverse events occurring in individuals after receiving LYMERix® outside of a GSK-sponsored clinical trial should be reported to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967.**

**FDA routinely monitors and reviews adverse event reports for LYMERix®.**

- 5 Given the controversy over the definition of Lyme disease and "sero-negative Lyme disease", how has the FDA distinguished between symptomatic immune

responses and/or exacerbation of pre-existent asymptomatic Lyme disease (an adverse reaction) and a breakthrough case of Lyme disease (a vaccine failure) in the clinical trial data?

### **CBER Response**

The definition of Lyme disease used in the pivotal efficacy trial may be found in the clinical review of the pivotal efficacy trial and in VRBPAC discussions, which are available on FDA's web sites (see <http://www.fda.gov/cbcJ./productsIVJDesmi122198.htm>.; and <http://www.fda.gov/ohrms/ldockets/ac198/transcpt/3422t1.Ddfl>). In brief, definite Lyme disease cases in the clinical trial were required to have an appropriate clinical presentation (e.g., erythema migrans) as well as laboratory confirmation using one of three validated assays (culture of *Borrelia burgdorferi* from skin biopsy, seroconversion by MarDx Western blot, and/or PCR from skin biopsy, synovial fluid, or cerebrospinal fluid). Over 70% of definite cases were confirmed by direct culture of *Borrelia* from a skin biopsy of the erythema migrans lesion; indeed, the majority of definite Lyme disease cases were confirmed by 2 if not 3 different positive laboratory assays. Thus, detection of cases did not rely on serological assays alone. FDA also analyzed the efficacy data by including only Cases that were confirmed by positive *Borrelia* culture; using this method, the estimates of efficacy were essentially unchanged.

FDA is aware of the controversy concerning serological assessment of Lyme disease, and in particular of recent publications suggesting that LYMERix® vaccination may interfere with interpretation of commercial Western blots for diagnosis of Lyme disease. For the pivotal clinical trial, FDA reviewed all primary data and individual Western blots, as is typical for pre-licensure reviews, and was satisfied that the interpretation of the laboratory assays supported the detection of definite cases. Regarding publications on possible interference of Western blot interpretation by vaccination (e.g., Molloy *et al.*, *Clinical Infectious Diseases* 31:42-47, 2000; Fawcett *et al.*, *Clinical and Diagnostic Laboratory Immunology* 8:79-84, 2001), we note the following:

- Neither publication clearly documents individual examples when vaccination resulted in a banding pattern that would be interpreted as positive by the Dearborn criteria;
- Neither publication examines the possible rate at which such positive interpretations might be made in groups of vaccinated individuals.

To date, neither CBER nor CDRH, which is responsible for regulation of the commercial Western blot kits in question, has received data suggesting that revisions to the commercial kits' label or instructions for use should be considered. If you are aware of such data, we would welcome its submission for our review.



6. Why has the FDA not contacted and interviewed physicians who oversaw the study sites for the clinical trials, particularly in light of the fact that some such doctors, ..., have publicly endorsed LYMERix stating that they saw no adverse reactions when the FDA is aware of reports of adverse reactions by several of ...'s study participants?

**CBER Response**

**FDA has a Bioresearch Monitoring (BIMO) program that is responsible for auditing and inspecting clinical trials. FDA conducts bioresearch monitoring of clinical studies according to certain criteria to ensure compliance of good clinical practices. The same approach has been used for studies of LYMERix ® as has been used for clinical studies of other products.**

7. What steps if any has the FDA taken to analyze the data gathered during the clinical trials of the Connaught (now Aventis Pasteur) OspA-based Lyme disease vaccine ImmuLyme for adverse reactions?

**CBER Response**

**FDA can neither acknowledge nor deny the existence of investigational New Drug Applications (IND) or Biologics License Applications (BLA) until any such application is approved, unless it has previously been disclosed or acknowledged. In general, FDA assesses the safety of investigational products by evaluating primary adverse event data submitted to INDs and BLAs.**

8. Why has the FDA failed to invite scientists and physicians not affiliated with, or employed by GlaxoSmithKline, such as Ronald Schell, Ph.D. who has published an article documenting serious adverse reactions to OspA in hamsters, and Carlos Rose, M.D. and Paul Fawcett, Ph.D., who have published an article documenting arthritogenic reactions to LYMERix in adults and the exacerbation of pre-existing asymptomatic Lyme disease in participants in the pediatric trials of LYMERix, to present their findings and opinions to the Advisory Committee or any other body considering the safety and efficacy of LYMERix?

**CBER Response**

**FDA constitutes its advisory committee membership and consultants based on clinical and scientific expertise and screens these individuals for conflict of interest so that they can provide an unbiased assessment. In addition, the public hearings at the advisory committee meetings are provided so that members of the public can participate as well. We would like to assure you that we are familiar with the publications by Croke et al and Rose et al that you refer to above.**

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- Why was LYMERix permitted to include an adjuvant, especially given that the manufacturer used a lipidated version of the OspA protein? Further, since the inclusion of the adjuvant in LYMERix necessitated the inclusion of the adjuvant in the placebo, what if anything was done to adjust for the likelihood that complaints of adverse reactions to the adjuvant among the placebo group were not permitted to improperly "cancel out" adverse reactions to OspA among the vaccinees, and therefore reduce the likelihood of finding a "statistically significant difference" in adverse event rates between the two groups?
- 9.

**CBER Response**

**The clinical design for the LYMERix® pivotal efficacy trial was discussed at a VRBPAC meeting. The VRBPAC endorsed the overall clinical trial design, including the use of adjuvant as a placebo.**

10. What if any steps has the FDA taken to implement the recommendations of members of its Advisory Committee from the January 31, 2001 meeting regarding enhanced warnings and limits on the indicated use of LYMERix (including geographic limits) as well as increased education of both the general public and the medical community of the continued unanswered safety risks associated with LYMERix?

**CBER Response**

**FDA is working with GSK to address the issues raised by the VRBPAC at the January 31, 2001, meeting.**

11. Is the FDA, and/or its Vaccine Advisory Committee aware that the Tufts Laboratory run by Dr. Steere, the principal investigator for the Phase III clinical trials of LYMERix. filed for a patent on March 21, 2000 with the World International Property Organization, which received an International Publication Date of September 27, 2001 (patent # WO 01170252 A1), and that the official patent holders, including Doctors Meyer, Huber and Gross are the scientists who worked along with Dr. Steere on his research documenting the auto-immune responses exhibited by people with certain genetic markers to OspA?

**CBER Response**

**CBER is aware of the patent and that the patent holders are co-authors on a publication that describes a candidate auto-antigen in individuals who have treatment-resistant Lyme arthritis.**

12. Is the FDA aware that "this invention was supported by National Institutes of Health Grant AR45386 and the government of the United States has certain rights thereto?" See Tufts Patent at 1.

**CBER Response**

We are aware of the NIH's involvement.

13. Is the fact that this group of scientists, working under a grant from the government of the United States of America, has demonstrated in this patent that "An additional problem with OspA as a protective immunogen [i.e.: vaccine] is cross-reactivity at the T cell level observed between OspA and LFA-I."Tufts Patent at 4, and "Given the potential cross-reactivity between OspA and LF A-1, the use of OspA as a protective immunogen in vaccines may be associated with the induction of an auto-immune reaction in certain populations. including individuals expressing the HLA-DRB1-0401 allele. Thus it would be highly desirable to generate modified OspA polypeptides with diminished or no binding to the DRB1-0401 allele." Tufts Patent at 5-6.

**CBER Response**

**It is unclear what the question is, and thus we are unable to respond.**

14. How does the FDA reconcile the fact that research conducted and completed by the principal investigator for LYMERix prior to FDA's approval of the vaccine, and largely ignored by the FDA or dismissed as "theoretical" in its review and oversight of LYMERix, nevertheless led the scientists involved to pursue and patent a genetically modified version of OspA aimed specifically at avoiding the risk of auto-immunity from the OspA utilized in LYMERix demonstrated in that research?

**CBER Response**

**FDA has seriously considered the theoretical risk of vaccination with OspA being associated with arthritis at many different stages, including as part of the pre-licensure evaluation and as reflected in the post-licensure commitment for a large Phase 4 study. To date, no causal relationship between vaccination with LYMERix® and arthritis has been established. Nonetheless, theoretical concerns may spur scientists to develop what they believe are theoretically safer products.**

15. Does the FDA believe that the medical community and the public at large should be advised of the fact that scientists and researchers of this caliber consider the risk of auto-immunity from LYMERix so great that they applied for, received, and worked pursuant to, a NIH grant to produce a modified version of OspA to minimize or eliminate the risk? If not, why?

**CBER Response**

**We are aware of the range of opinions among professional Lyme disease researchers and that part of a product's approval process is approving adequate information and instructions for use in the form of the package insert.**

- 16 In light of this documentation, why has the FDA not demanded that GlaxoSmithKline produce in full any and all research which they claim disproves the risk of auto-immunity from LYMERix rather than simply accepting the manufacturer's summary claims without supporting data?

**CBER Response**

**We thoroughly reviewed the data submitted in the license application and concluded that it supported the safety and efficacy of the vaccine, thus leading to licensure. Further, we continue to monitor the safety of the product post-licensure through the Phase 4 study and reporting to VAERS.**

17. In the abstract of the researchers' application for the NIH Grant #1R01AR045386-0, they state that "LFA-1/DR4 double transgenic mice on an MHC class II -/- background will be created and tested for the development of chronic Lyme arthritis after exposure to Bb. This is based on the observation that mouse LFA-1 does not express the OspA cross-reactive epitope." Indeed, the researchers observed an auto-immune arthritic reaction when these mice were exposed to natural OspA, but not when they were exposed to the patented, modified version of OspA.

In this regard, what will the FDA do to determine what if any steps GlaxoSmithKline took to "create and test LFA-1/DR4 double transgenic mice" for its research, as the NIH grantees did, and whether or not the manufacturer did produce such mice and conduct studies which supported the risk of auto-immunity and suppressed those results?

Further, what if any disciplinary or penal steps will the FDA take to sanction GlaxoSmithKline for its apparent attempt to mislead the FDA Advisory Committee on January 31, 2001 by presenting the "results" of a study on mice which it claimed disproved any auto-immune arthritic risk, without revealing the fact, until questioned, that the mice used in their study lacked the cross-reactive epitope, and therefore rendering the study, as one member of the committee stated, "irrelevant"?

**CBER Response**

CBER cannot discuss any intended course of action with regard to a product or a company. We do, however, appreciate interested members of the public bringing their concerns and any new information to us

