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Division of Communication and Consumer Affairs, FDA-CBER
Via Email: ocod@fda.hhs.gov

RE: NCT05477524, An Efficacy, Safety, Tolerability, Immunogenicity, and Lot-Consistency Clinical Trial of a 6-Valent OspA-Based Lyme Disease Vaccine (VLA15) (VALOR)

September 21, 2023

To whom it may concern:

TRUTHCURES is a Lyme disease patient advocacy organization committed to ensuring accurate diagnostics and effective treatments for all victims of Lyme disease. As such, our constituency has an interest in the prevention of Lyme disease and specifically, any biologic products being studied for the prevention of Lyme. I am writing to convey my serious concerns about the above-mentioned trial being conducted by Pfizer, Inc. and demand its immediate suspension.

- There is no accurate diagnostic test to determine if subjects in the placebo arm get Lyme disease at a higher rate than subjects in the vaccinated study arm.
- According to public disclosures, well-known Lyme scientists sold biological samples to Pfizer for the purpose of developing a diagnostic test specifically for Pfizer's VALOR trial.
- By seeking to develop their own test, Pfizer acknowledges the inadequacy of commercially available diagnostics while ignoring the scientific reality of decades of failure to improve Lyme tests.
- Pfizer's manipulation of diagnostic protocols mirrors the manipulation of tests carried out for the previous Lyme vaccine, LYMErix.
- These actions constitute a serious breach of ethics and standards of conduct, putting trial participants at significant risk of harm. FDA must act immediately to protect the volunteers.

Evidence Previously Disclosed to FDA

TRUTHCURES previously engaged with FDA via the Office of Criminal Investigation (OCI). Those discussions culminated in a meeting at the FDA New England District Office on Monday, October 18, 2021. Attendees from FDA included LCDR David Sullivan, PhD, John Sciacchitano, Consumer Safety Officer, and Debara Reese, Consumer Safety Officer. There may have been additional FDA attendees who participated virtually but whose names were not disclosed to us.

Backed with federal meeting records, license applications, published literature, and other documentation, our presentation detailed the behind-the-scenes antics carried out by SmithKline and government insiders during trials for the original Lyme disease vaccine, LYMErix, in the 1990s. Publicly available records indicate the disease definition was revised, along with the diagnostic criteria, to limit the number of cases that could be diagnosed with "definite" Lyme disease, thereby inflating the appearance of vaccine efficacy.

The manipulation was done through the identification of a subset of Lyme patient samples that were more likely to produce the abundant antibodies necessary to test positive by serology. Our presentation laid out

in painstaking detail precisely how the scheme was accomplished, some of which will be reviewed here.

Sample Repositories Represent a Narrow Subset of Lyme Cases

Dr. Allen Steere, previously of Yale and Tufts University, and now on the faculty at Harvard, pioneered the research proving a genetic association between a strong immune response and the primary Lyme symptom of arthritis in one or two large joints.[1] These genetically privileged cases test positive on serology in a predictable manner, with reactivity increasing over time. This pattern is borne out in sensitivity studies submitted to FDA in 510(K) applications for Lyme diagnostics. The pattern of increased sensitivity in later stages of disease is frequently misinterpreted as applicable to *all* cases of Lyme, but it only applies to the minority subset identified by Steere.

Samples meeting the manipulated criteria were originally acquired through so-called Academic Reference Centers (ARCS) that were involved with Lyme vaccine development, including Yale, New York Medical College, and SUNY-Stony Brook. ARCS samples were used to develop the diagnostics that were employed in LYMErix clinical trials in the 1990s and then became the foundation of the Lyme Serum Repository (LSR) controlled by the Centers for Disease Control & Prevention's (CDC's) Division of Vector-Borne Infectious Diseases (DVBID). Between 2009 and 2017 the CDC awarded contracts for Lyme patient samples to some of the same Academic Reference Centers and researchers that were involved in the 1990s.

Samples from the LSR are used in validation studies for diagnostic devices, among other purposes. Since the LSR/ARCS samples skew heavily toward the less serious Lyme disease outcome of arthritis in one or two large joints, those with chronic, neurologic manifestations are excluded from diagnosis, treatment, and research. These are the sickest patients, and they fall in the chasm between the number of Lyme disease cases the CDC estimates are infected each year (476,000) and the number *reported* to the CDC each year (about 35,000).[2]

TRUTHCURES' FDA presentation in 2021 provided evidence that all Lyme disease diagnostics should be pulled off the market. They all rely on inappropriately submitted and cleared predicates and a standard that applies to a small subset of immunologically privileged cases.

Pfizer's VALOR Trial

Last February, six months into its Phase III "VALOR" trial, Pfizer made headlines for alleged violations of good clinical practice by its trial site contractor, Care Access. The episode led to disenrollment of half of the enrollees. The initial expectation was that they would be replaced. However, planned enrollment of 18,000 now stands at 6,400 with no apparent intent to increase participation to the original level or a level that would ensure meaningful results.

Therefore, suspicion about Pfizer's methods, practices and motives should already have been heightened. Now we must also question their motive behind developing a proprietary diagnostic test for this trial. Based on the data presented to FDA previously as well as contained herein, it is evident that there is no way for Pfizer to assess the efficacy of its Lyme disease vaccine candidate, VLA-15, accurately and objectively. Pfizer cannot be allowed to continue placing human trial subjects in harm's way under cover of proprietary corporate data.

TRUTHCURES requested information from Pfizer about their diagnostic test, but they refused to answer our questions. We recently discovered through public disclosures that one of the institutions contracted

for ARCS samples at the time of the LYMErix trial, and later for LSR samples managed by the CDC, was paid $156,000 by Pfizer for samples to develop a diagnostic test for its VALOR trial.

TRUTHCURES contacted Dr. Gary Wormser of NYMC for comment prior to publishing an article on TrialSite News last May. Dr. Wormser stated in an email (emphasis his):

> I HAD SOMETHING TOTALLY UNIQUE THAT THEY NEEDED, I HAD CULTURED PATIENT ISOLATES OF BORRELIA BURGDORFERI THAT WE HAVE SAVED AND HAVE BEEN EVALUATING GENETICALLY OVER MANY YEARS.

Given the genetic association of positive serology with the less severe disease outcomes among a minority of Lyme infections, Pfizer's solicitation of genetically evaluated samples warrants serious investigation and the immediate suspension of its VALOR trial.

Compounding the situation, TRUTHCURES also discovered through public disclosures that Pfizer paid $71,019.96 to The General Hospital Corporation, parent company of Massachusetts General Hospital, for similar samples. The principal investigator is listed as Dr. John A. Branda. Notably, he is a colleague of Dr. Allen Steere at Mass General and Harvard. Recall that Dr. Steere was contracted previously for ARCS and LSR samples. The Pfizer work is described as follows:

> LOW INTERVENTIONAL METHODOLOGY STUDY TO OBTAIN BIOLOGICAL SAMPLES FROM PARTICIPANTS WITH SUSPECTED LYME DISEASE FOR THE PURPOSE OF DEVELOPING CLINICAL DIAGNOSTIC ASSAYS

Is Pfizer manipulating the diagnostic criteria for its Lyme disease vaccine trial just as SmithKline did for LYMErix nearly 30 years ago?

We find it appalling that a small, under-resourced patient advocacy organization must point out egregious potential violations of human clinical trial protocols to the FDA. Regulators should be asking some obvious questions:

1. Why is Pfizer developing its own assay rather than using the standards and tests that were developed for the previous, nearly identical, Lyme vaccine, and that have been in use for 29 years?
2. Why are the existing standards, which Wormser and Steere helped develop, "good enough" for the public, but not for this trial?
3. How will the results obtained through Pfizer's own standards and tests correlate with the standards and tests used in clinical practice in the U.S. and internationally?
4. Have the 6,400 current participants been made aware that Pfizer is developing its own test to determine vaccine efficacy, instead of using what everyone else uses?
5. Is Pfizer's diagnostic test a "laboratory developed test" (LDT) which would be subject to certain federal regulations?
6. What were the criteria for the samples provided and how were they validated?
7. Did any other researchers provide samples for the purpose of developing a diagnostic assay or for any other use in this trial?

8. If the diagnostic criteria for this trial differ from the CDC's criteria (https://ndc.services.cdc.gov/case-definitions/lyme-disease-2022/) please describe how they differ, including both clinical and laboratory criteria.

Additionally, TRUTHCURES' constituents would be interested in answers to the following:

1. Who is the Principal Investigator?
2. Who are the Data & Safety Monitoring Board (DSMB) members and who is the DSMB lead?
3. Please help the lay person understand why Pfizer needs to develop diagnostic assays rather than using commercially available tests.

For decades, Lyme experts and authorities have emphasized the need for more accurate tests, yet none have been developed or commercialized. Current initiatives include the LymeX Diagnostic Prize, a public-private partnership led by the Department of Health & Human Services (HHS) to identify an innovative new approach to diagnosing Lyme disease. Are we to believe that Pfizer has suddenly developed an accurate Lyme diagnostic since purchasing some magical samples from prominent Lyme researchers with extensive conflicts of interest?

Let's be clear: The 6,400 trial participants (including children as young as five years old) signed up for this trial on the assumption Pfizer would operate ethically and in good faith. They likely also assumed the FDA would be looking out for their safety. Do the right thing.

The FDA must immediately suspend Clinical Trial NCT05477524 and initiate a full investigation. We expect a response to this letter within 30 days.

Sincerely,

Laura R. Hovind
Executive Director
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References:

1. Kalish RA, Leong JM, Steere AC. Association of treatment-resistant chronic Lyme arthritis with HLA-DR4 and antibody reactivity to OspA and OspB of Borrelia burgdorferi. Infect Immun. 1993;61(7):2774-2779. doi:10.1128/iai.61.7.2774-2779.1993

2. Kugeler KJ, Schwartz AM, Delorey MJ, et al. Estimating the Frequency of Lyme Disease Diagnoses, United States, 2010–2018. Emerging Infectious Diseases. 2021;27(2):616-619. doi:10.3201/eid2702.202731.