VIA ELECTRONIC DELIVERY

September 19, 2025

Martin Makary, M.D., M.P.H.
Commissioner
Food and Drug Administration
5630 Fishers Lane
Attn: Dockets Management Staff (HFA-305)
Room 1061
Rockville, MD 20852

Re: E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials; International Council for Harmonisation; Draft Guidance for Industry; Availability (Docket No. FDA-2025-D-1797)

Dear Dr. Makary,

On behalf of the Lupus Foundation of America (LFA), I am writing to provide comments on the draft guidance for industry entitled "E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials" ("the draft guidance"). This is a critical topic for the lupus community, and we appreciate the opportunity to provide feedback. Given the specific nature of lupus, the affected population, and the high unmet medical need for treatment, including pregnant and breastfeeding women in clinical trials is essential to improve therapy development for the disease.

ABOUT LFA AND LUPUS

The LFA is the largest publicly supported lupus organization devoted to solving the mystery of lupus while giving caring support to those who live with this unpredictable and devastating disease. Through a comprehensive program of research, education, and advocacy, we lead the fight to improve the quality of life for all people affected by lupus. LFA has a strong commitment to advancing lupus research for both adult and pediatric populations and does this through a variety of methods, including funding research, building collaborative research partnerships, and advocating for increased federal research funding.

Lupus is a chronic autoimmune disease that can impact many parts of the body including organs, joints, and skin. Symptoms are heterogeneous both across the overall population with the disease and across individual patients' lifetimes. Common symptoms include extreme fatigue, joint and muscle pain, rashes, photosensitivity, organ inflammation, and, in many advanced stages of the disease, kidney damage or failure. At least 1.5 million Americans have lupus; of particular note for this comment, the majority of people diagnosed with lupus are women, with 80% of new diagnoses made during childbearing years.[i]

COMMENTS ON THE DRAFT GUIDANCE

We appreciate the FDA recognizing the importance of including pregnant and breastfeeding women in clinical trials and developing this draft guidance as a framework to support their responsible inclusion. Below, we offer our specific comments on the guidance.

Including Pregnant Women Early and Appropriately in Product Development

LFA supports including pregnant and breastfeeding women early in clinical trials for products that will be used by women of childbearing age to generate comprehensive data on safety, dosing, and efficacy during pregnancy and breastfeeding. The majority of lupus patients are diagnosed during their childbearing years, so it is vital that pregnant women and women who may become pregnant are included in trials and that women who become pregnant during a trial are able to remain in trials. However, pregnant women are typically excluded from clinical trials. Moreover, women who are planning to have children may elect not to participate in clinical trials either because they are required to take birth control during a trial or because they will be disqualified from a trial if they become pregnant. Collectively, the limitations on including pregnant women and those who may become pregnant in clinical trials – and the incentives that exist for them not to participate - not only can make it more difficult to enroll trials, but also lead to trials that are not representative of the lupus population. As a result, therapies may be less effective or more likely to cause side effects in pregnant or breastfeeding women because limited safety data on the use of medications in pregnancy may lead to medical decisions being made with incomplete data. These limitations also may contribute to a reluctance by the payer community to provide appropriate access to and coverage of therapies because health plans perceive there to be insufficient data on the value of these therapies in specific populations. By having sponsors collect early and comprehensive data that includes pregnant and breastfeeding women, these issues may be mitigated.

Collecting Data for Conditions with High Unmet Medical Need

We also support FDA's specific recommendation that data should be collected in diseases that are likely to cause adverse effects on pregnant women, pregnancy outcomes, and the health of the child. Moreover, we appreciate the agency specifically noting systemic lupus erythematosus (SLE) as one of these diseases. Pregnancy in women with SLE is dangerous for both mother and child. Among complications frequently seen in women with lupus are preeclampsia, preterm birth, growth-restricted fetuses, and pregnancy loss. Preterm births pose substantial risk for cerebral palsy and neurodevelopmental delay. Restriction of fetal growth may also have long-term effects on cognitive development and an increased risk of hypertension and type 2 diabetes in adulthood. Moreover, considering only in-hospital medical costs for the first year of life, the average cost for a premature infant born at 28 weeks is $86,000; at 24 weeks it is more than $200,000. Among survivors, the rate of neurodevelopmental delay and other disabilities is at least 15%. Thus, the long-term financial and medical burden to society is substantial, and the emotional cost to patient and family is immeasurable. Treatments designed to avoid these complications are critically needed. Although we recognize the risk presented by including pregnant women in trials, these lupus patients should have options for therapies they can take during pregnancy. LFA agrees that sponsors must generate robust evidence for populations with high medical need to facilitate the development of these treatments.

Utilizing Patient-Centric RWD and RWE Meaningful to People Living with Lupus

LFA appreciates FDA acknowledging the usefulness of real-world data (RWD) and real-world evidence (RWE) in supplementing limited or difficult-to-obtain clinical trial data and supporting post-marketing assessments of product usage, benefits, and risks in pregnant and breastfeeding women. We also appreciate the agency for mentioning that pharmacovigilance-generated data, electronic health records, medical claims or health insurance databases, medicinal product or disease registries, and digital health technologies – all important types of RWD – can be used to support post-market safety studies. For conditions like lupus that are extremely heterogeneous and affect diverse populations, RWD may offer a way to collect important information that reflects

the broader lupus community. However, information collected outside of a typical clinical trial setting is not inherently patient-centered. Sponsors and the FDA should work to ensure that the RWD generated aligns with the documented needs and priorities of patients. We urge the FDA to address this point when publishing the final guidance document.

Consulting with Patients and Patient Advocacy Groups Early and Often

LFA appreciates the Agency encouraging sponsors to engage with patients and patient advocacy groups prior to recruitment, during the early study design stages, and as part of the recruitment and retention strategies. Given LFA's extensive experience in raising awareness of clinical trials among lupus patients, we believe we are well-positioned to advise sponsors on best practices for designing and recruiting for trials that represent the overall lupus population. Patient organizations like LFA are trusted partners to patients and caregivers across the country. Within the lupus community, we have deep community connections through our support groups and education efforts, which allow us to quickly reach out to patients to engage them on different projects, including opportunities to participate in clinical trials. Additionally, LFA has a long track record of leadership in driving participation in lupus clinical trials. Examples of some of our work on this topic are included below.

- **Research Accelerated by You (RAY®):** A patient-powered data platform of nearly 4,000 lupus patients that captures real-world evidence, including patient experience and preference data, from people with lupus and provides them with information about lupus research and clinical trials.
- **Lupus Research Action Network (LRAN)**: A nationwide peer-to-peer clinical trial education and training program.
- **Center for Clinical Trial Education Program:** A comprehensive program to provide information to people living with lupus nationwide about clinical trials and opportunities to participate in clinical trials.

We also appreciate FDA encouraging sponsors to consult with the Agency early and as needed throughout the product development process. However, FDA should also consider including patient communities and patient advocacy groups like the Lupus Foundation of America in these consultations. As FDA moves towards finalizing this guidance, we encourage the Agency to offer additional direction on how and when patients and patient advocacy groups can be further integrated into the product development process.

Again, the Lupus Foundation of America thanks the FDA for publishing this important draft guidance and appreciates the opportunity to provide feedback. If you have any questions, please do not hesitate to contact me at wildman@lupus.org.

Sincerely,

Patrick Wildman
Senior Vice President, Advocacy & Government Relations

[i] Costner MI, Sontheimer RD. "Lupus erythematosus" In: Wolff K, Goldsmith LA, et al. Fitzpatrick's Dermatology in General Medicine (seventh edition). McGraw Hill Medical, New York, 2008:1515-35.