



**COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON SYSTEMIC LUPUS
ERYTHEMATOSUS - DEVELOPING DRUGS FOR TREATMENT
(FEDERAL REGISTER, 70 FR 15868)**

LUPUS FOUNDATION OF AMERICA, INC.

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The *Guidance for Industry on Systemic Lupus Erythematosus – Developing Drugs for Treatment* represents a long-awaited document by the lupus treatment development field. Overall, the document is responsive to important unresolved questions in the community; however, the Lupus Foundation of America, Inc. and its Medical/Scientific Advisory Council (MSAC) offer the following comments and points of clarification.

First, we would like to address the issue of claims related to general systemic lupus versus organ-specific outcomes. We believe it would be helpful in the organ-specific sections of the draft guidance document to acknowledge that some serious forms of lupus occur in patients who do not meet criteria for systemic lupus. We refer to patients with life-threatening conditions such as the primary antiphospholipid syndrome and/or disfiguring conditions such as primary cutaneous lupus. The Lupus Foundation of America also serves these groups of people who are seriously ill and would advocate allowing organ-specific clinical trials to lead to organ-specific claims that could reach appropriate primary lupus syndromes as well as systemic lupus. In addition, it will be important to study children and adolescents with lupus either in separate studies, when appropriate, or as part of drug intervention trials. In these studies, activity and damage tools may need to be adjusted to reflect the increased organ system involvement in children.

In Section III., *Measurement of Disease Activity and Clinical Outcomes*, A. *Disease Activity Indices*, Lines 104-106 currently read, “It is important that analyses of disease activity measures be defined prospectively, and they can include comparisons of change in disease activity scores and disease activity.” It is unclear what the difference is between disease activity scores and disease activity.



In this same *Section, B. Flares*, Lines 123-124, it may be more accurate if “followed by” were replaced with “interspersed with,” since it is not just that stable disease is followed by activity but also that activity may later be followed by stable disease. In addition, in Lines 124-125, the draft document suggests that all studies measure disease activity at fixed points. It should be understood that some disease activity indices measure disease activity over a month’s period and that if patients were seen monthly in a study, this would allow full characterization over the course of the study and any intercurrent flares would not be missed.

In *C., Damage*, Lines 136-152 may be overstressing the value of the SLICC Damage Index in clinical trials per se. Although damage may accrue in a six-month period, it has been our experience in many lupus trials to date that not enough damage accrues during a one year or eighteen month follow-up to warrant the use of this instrument. This instrument is much more sensitive and useful for longer term studies lasting a minimum of three to five years.

In *D., Organ-Specific Indices*, Line 158, “measuring if” is incorrect grammar. Lines 172-174 seem to suggest that 80% 10-year renal survival rates in treated nephritis are somewhat acceptable. Since there is an average 10 year lifespan for patients on dialysis, coupled with the fact that most patients with lupus nephritis are younger than 40 years of age, mortality rates for lupus nephritis are not much better than, for example, Stage II breast cancer. We think the term, “however” should be removed from Line 173.

Line 210 seems to minimize the importance and frequency of Class V (membranous) nephritis, despite the fact that prognosis seems better for simple Class V lesions. It is important to recognize, however, that mixed lesions are often present, accounting for variability in reports of frequencies of various WHO Classes of nephritis. Additionally, membranous nephritis is not uncommon, particularly among people of African, Hispanic and Asian descent. For example, in one study of African American patients with nephritis, Class Va and Vb were found in 22/54 patients (*Am J Kidney Disease* 1994 24:159).

Lines 217-219 state, “A variety of outcome measures can be used in clinical trials to assess efficacy of new therapies on skin...” Ongoing work in the cutaneous LE disease area and severity index, CLASI, may allow better scoring of cutaneous lupus as a primary outcome. The community considers this an important initiative and hopes that the FDA will follow its progress closely.

In *F., Serologies*, Lines 248-255 may be misunderstood by the community. It is appreciated that, in general, serologic markers may be imperfect correlates to general disease activity in SLE. However, in severe lupus nephritis, the combined measurement



of C3 and anti-dsDNA have good correlation to disease activity, are probably as sensitive and specific as most accepted global disease activity measures, and seem to be responsive to most effective forms of therapy. If the FDA is to consider these markers insufficient to use as biomarkers, the community might appreciate a more extensive review of the literature that has been published in evaluation of these markers (specifically for nephritis) and a more full formulation of the basis of this reasoning. It is noted that an often-quoted paper in which anti-dsDNA did not correlate with disease activity was not examining nephritis flares per se.

In *Section IV., SLE Claims, Reduction in Disease Activity of SLE*, in response to Lines 274-275, we believe that if confirmation by a second DAI is required when BILAG is not the primary endpoint, it raises some issues that would need to be addressed, including:

- Would the second DAI need to be a co-primary endpoint?
- Would it be acceptable for the second DAI to be a secondary endpoint?
- Would trends in the second DAI be sufficient confirmation?
- Would adjustment for multiple comparisons (and hence increase in sample size) be required when evaluating two DAI's?

Line 424 is in error; the statement should read (increase in the) time to flare.

In *Section V., Disease Activity Trials, Lines 491-508*, we commend the FDA for this sophisticated analysis of strengths and weaknesses of AUC analysis versus dual time point endpoints. We are certain that industry would be grateful for a clarification on whether specifically AUC could be used as a primary endpoint for trials in which an instrument is used that assesses the full spectrum of time between visits, minimizing the chances of missing intercurrent flares.

In the same Section, Lines 536-551, we would caution the use of mild/moderate flare rates as a primary endpoint unless the drug developers are convinced that their agent will be highly effective in the population under study, inducing near remission. Many mild SLE flares are not overly burdensome to the patients and do not require treatment. Thus, there is a risk of failing to appreciate some potentially significant treatments if there is too much reliance on complete remissions (lack of mild flares) at outcomes.

In *Section VI., Surrogate Markers as Endpoints, Lines 675-682*, the community would appreciate a definition of validation for surrogate markers as endpoints. We have variously heard of many such definitions, ranging from, “evidence of community acceptance,” to “complex, multivariate requirements.” We understand the need to use markers which are “reasonably likely” to predict clinical benefit (Line 685). However, it remains unclear how “reasonably likely” is defined or what is meant by “trends toward improvement” in Line 687. This is a critical issue for future development of products for



lupus, since early marketing pathways might be able to ensure the financing required to properly study these agents.

This Section states that early markers of disease activity can be considered for assessment of efficacy in lupus trials (particularly useful in Phase II studies). Later in the Section, the guidance states that accelerated approval may be considered using non-validated surrogate markers that are reasonably likely to predict clinical benefit. We would suggest that the FDA discuss in the guidance its position on the use of shorter-term evaluation of a clinical benefit endpoint, e.g., improvement in disease activity at 6 months, for accelerated approval, with continued follow-up, e.g., 1 year, of the endpoint in the same trial for confirmation of response durability for full approval. This approach is akin to that routinely used in HIV drug development, where HIV viral load at 24 weeks is used for accelerated approval and 48-week data are provided for confirmation of clinical benefit and full approval.

In conclusion, the Lupus Foundation of America and its nationwide network of 267 chapters, branches, and support groups thank the Food and Drug Administration for addressing the challenges of drug development in lupus. We are hopeful that the final document will support and encourage industry to invest in new therapies for the estimated 1.5-2 million Americans with lupus.