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DEPARTMENT OF REGULATORY AFFAIRS

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June 24, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Subject: **Docket No. 2005D-0106**
Comments on Systemic Lupus Erythematosus — Developing Drugs
for Treatment (DRAFT GUIDANCE)

Dear Dockets Management Branch:

Enclosed are comments, provided by Genentech, for the Draft Guidance Systemic Lupus Erythematosus - Developing Drugs for Treatment.

Thank you for providing us the opportunity to comment on this Draft Guidance. We hope that you will find our comments useful and constructive

If you have any questions regarding this submission, please contact Michelle Tallin, Associate Director, Regulatory Affairs at (650) 225-6098.

Sincerely,



for

Robert L. Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality,
and Compliance

2005D-0106

Docket-022 ss

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This submission contains information that constitutes trade secrets and/or is confidential within the meaning of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §331 [j]), the Freedom of Information Act (5 U.S.C. §552[b][4] and 18 U.S.C. Section 1905) and 21 CFR Sections 312.130, 314.430, 601.50, and 601.51 and may not be revealed or disclosed without the prior written authorization of Genentech, Inc.

Draft Guidance for Review and Comment

**Draft Guidance for Industry
Systemic Lupus Erythematosus – Developing Drugs for Treatment**

Docket No. 2005D-0106

**Issued for Comment: March 28th, 2005
Comments due: June 27th, 2005**

**Genentech, Inc.
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Support for this guidance

The following comments are provided by Genentech, Inc. We welcome FDA's efforts to aid sponsors in designing trials and navigating the regulatory pathway. We support the FDA's efforts to describe and discuss issues of disease activity measurement, trial design, and label claims. This should promote clarity in drug development for lupus.

However, we suggest the FDA more precisely define a number of the terms and concepts discussed in the draft guidance, clearly articulate the acceptability and priority (i.e., rank preference) of elements of trial design (e.g., endpoint selection), and provide illustrative examples.

Suggested clarifications and improvements

Some of the terminology used in the guidance is unclear. Thus, a number of terms should be better defined:

- Flare
- Maintenance
- Steroid reduction – The current description provides conceptual aid but not practical guidance (e.g., specifying magnitude of change in immunosuppressive therapy that would support a label claim)
- Remission

Using illustrative examples (historical, theoretical, or contemporary) would clarify guidance terminology. Specifying the important dimensions of these terms would be helpful (e.g., time to flare, frequency of flare, intensity of flare). Developing a glossary of terms would also help. Finally, providing practical advice on how to achieve a claim based on trial metrics, such as flares, maintenance, and steroid reduction, would be helpful.

Providing clearer and more in-depth explanations of expectations, standards, and rationales would help Sponsors engage in effective drug development. Below are a list of issues and questions about specific text or concepts which would benefit from greater clarification:

Endpoints and outcome measures

- What is the implication of a disease activity index that does not delineate important clinical responses in all situations? How does this affect approvability and choice of index? (*Lines 59-60*)

- It would be useful to provide an example of a DAI that could be used in a responder index; how it might categorize mild, moderate, or severe disease; and what would be considered a clinically significant change. (*Line 112*)

- The description of outcome measures could be clearer. We suggest stating each of the outcome measures clearly by separating them out, or laying them out as bullets. (*Line 176*)

- The draft guidance states that “changes in urine protein/creatinine ratio may serve as indicator of need for further assessment with a 24-hour urine collection.” Christopher-Stine et al (2004) note that urine protein to creatinine ratio is highly correlated to 24 hr urine collections. Given that 24 hr urine collections are often inadequate, the ratio should be accepted as an indicator for proteinuria itself as opposed to merely being a trigger for 24 hr collection (*Lines 187-190*)

- On the topic of proteinuria as an outcome measure, we note that data from the Euro-lupus nephritis trial (Houssaiu et al 2004) suggest that achieving proteinuria reduction to < 1g at 6 months is a prognostic factor for good renal outcomes. This would suggest that proteinuria be considered as an efficacy measure in lupus nephritis (*Lines 211-213*)

- Need to define acceptability and non-acceptability of endpoints, as well as priority (e.g., which primary endpoints are acceptable, and which are not). Also need to define requirements for validation of endpoints., e.g., AUC of DAI (*Line 271-72, 292-99, 301-04*)

- Are continuous or landmark assessments preferred for primary endpoint?
 - What is rank order of these potential claims?
 - What kind of claim would this translate into?

Other trial design issues

- In discussing use of the SLICC/ACR Damage Index, FDA refers to the use of organ damaging concomitant treatments not being balanced. This sentence seems to recommend stratification; if this is the case, it should be explicitly stated. Also, an example should be provided. (Line 150)
- It is unclear if the FDA views urinalysis as useful, given difficulty in analyzing. If laboratories are not achieving the accuracy and reproducibility desired, can a trial proceed? What is the acceptable threshold for accuracy here? (Lines 194-200)
- Which assessment tool(s) are acceptable? Which would lead to inclusion of HRQL information in the label? (Line 225, Section E)
- Explain what constitutes adequacy for instruments that assess fatigue. Specifying which fatigue instruments to use would be helpful. Specific examples would be useful here. (Lines 236-37)
- The draft guidance refers to patients with biopsy-proven disease. It is generally accepted that it is unethical to mandate biopsy in all trial subjects. Thus, it would be useful to describe timing and expectations around the biopsy. (Line 325)

Regulatory pathway and requirements

- Draft guidance refers to “full approval.” (Line 183) Does this imply that there is a viable accelerated approval pathway?
- The requirement for trial duration is unclear. (Lines 301-304, 666-667) It appears possible to conduct a 6-month trial in order to support an induction claim (provided there is longer-term follow-up). (Lines 301-304) Yet, it is stated that trials should generally last 12 months (Lines 666-667). What conditions have to be met to qualify for a shorter period than 12 months? These should be described in greater detail.
- The draft guidance refers to an “improved safety profile” (Line 604, Section C). Replace with “superior safety profile.” Is the agency suggesting a co-primary of efficacy and safety?
- Specify which surrogates would be eligible for accelerated approval (Line 702)

We suggest the authors use concrete examples. Hypothetical or historical examples can help illustrate key points.

We suggest the following wording changes to provide greater clarity:

Re-wording some sentences will provide clarity on FDA’s message:

- Lines 45-46 Re-write as: “...it is important to clearly describe acceptable efficacy endpoints, which will facilitate the development of novel therapeutic agents that have the potential to be more effective and/or less toxic.”
- Lines 124-5 is a misplaced sentence. We suggest moving to end of the paragraph
- Line 174 -- Change “not effective” to “fail to be.”

Open questions / comments

The FDA should clarify if it is acceptable to use ISN/RPN classification system instead of WHO system for renal disease. (*Lines 165, 375*)

The FDA may want to consider addressing CNS lupus. The discussion of organ-specific disease in the draft guidance mostly pertains to lupus nephritis. A discussion of the pros and cons of addressing CNS lupus, in terms of therapy development and approval, would be of great value to sponsors designing lupus development programs.

The FDA may want to consider describing key considerations for a Special Protocol Assessment (SPA) in lupus.

Conclusion

The guidance stands to improve lupus drug development. However, clarifying several of the terms and concepts in the draft guidance, indicating level of acceptability of particular trial design elements (e.g., endpoints), and providing rationales for many of the ideas discussed, will help sponsors better understand the regulatory pathway

We applaud the FDA's efforts to clarify the regulatory pathway for lupus therapies.