



UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

Jacqueline A. French, M.D. Associate Director

University of Pennsylvania School of Medicine Hospital of the University of Pennsylvania

Penn Epilepsy Center Department of Neurology

0130 04 04 -2 4305

July 30, 2004

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

Re: Docket ID # 2004-N-0181

Dear Ms Meyers,

I understand that epilepsy is being considered for critical path designation within the FDA. I would like to add my support to the selection of epilepsy and antiepileptic drugs. I am an epileptologist whose area of expertise and interest is antiepileptic drug development. I run an international course in alternate years on this topic. We have been fortunate in that a large number of antiepileptic drugs have been approved for use within the last decade. This is primarily as a result of a very active drug screening program run by the National Institutes of Health. Unfortunately, we have not been able to benefit from these additions to the armamentarium to the maximum extent. The newer drugs appear to provide not only benefits in terms of better control of seizures for some individuals, but also gains in terms of tolerability, and decrease in long-term side effects. In addition, drug interactions, formerly a scourge of antiepileptic drug prescription, are markedly reduced with the new compounds. Yet, there has been an enormous difficulty in obtaining approval of these drugs as initial monotherapy. Whereas these same drugs have received regulatory approval for monotherapy outside of the United States, and are currently used as initial monotherapy, only one of eight of the newer antiepileptic drugs has obtained initial monotherapy approval in United States. In Europe, active control equivalence trials meet evidentiary standards for approval, once efficacy has been established in adjunctive therapy. In the US, superiority trials are the only acceptable standard. This is a very difficult standard, in a condition as serious as epilepsy. To date, the only way to demonstrate superiority, has been to compare a new drug to a subtherapeutic dose of the same drug, or another drug. This raises significant ethical issues. I recently submitted a white paper to the FDA suggesting an alternative approach, using a well characterized historical control which was derived from nine randomized trials that used subtherapeutic doses as a control arm. We would very much like for this, or an alternative strategy to be accepted to obtain monotherapy approval. We certainly

2004N-0181

C 45

would hope that critical path designation would be instrumental in reviewing the current situation and arriving at a satisfactory conclusion.

Thank you,

A handwritten signature in black ink, appearing to read 'J. French', written over the printed name.

Jacqueline A. French, M.D.
Professor of Neurology
The Neurological Institute
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, Pa 19104
215-349-5166
Fax: 215-349-5733