

5465 '98 AUG 19 P 4:40

CDER Stakeholder Meeting

Panel A: Presenter -- Hiroshi Mitsumoto, M.D., The ALS Association

The Distinguished Members of the Panel, ladies, and gentlemen:

I am truly honored to be here in the front of this distinguished panel of the FDA and to present our concerns and, if possible, suggestions regarding the implementation of the FDA Modernization Act and how it might change the drug approval process for ALS.

My name is Hiroshi Mitsumoto, the director of Cleveland Clinic ALS Center, Head of the neuromuscular/EMG section, and professor of Neurology at the Cleveland Clinic. I am also a chair of the Medical Advisory Board of the ALS Association. I am a clinical Neurologist, see a large number of patients with ALS, and am actively participating in several ALS clinical trials.

Hat this hearing today, I represent the ALS Association, but I believe I also represent the entire ALS community, which includes: patient voluntary organizations, patients and family, and ALS experts.

First, I would like to briefly describe ALS and its current status in its treatment. ALS is a neurodegenerative disease that leads to death within 3 to 4 years.

Description of Disease:

ALS is called Lou Gehrig's disease by lay people. ALS is described as, "a live body in a glass coffin." It is worse than the majority of cancers and AIDS, because ALS is invariably fatal in 3 to 4 years in the majority of patients.

Epidemiology: 5,000 new patients and 30,000 patients in the United States per year. The impact to patients, families, and the society is gravest.

Treatment:

Only riluzole (the first prescribable drug for ALS but of modest effects) is available. There is no cure and only symptomatic treatment is available.

The current status:

Increasing numbers of novel therapeutic agents are considered based on very plausible hypotheses of pathogenesis in ALS. Some are already in pipe line. FDA is extremely helpful and their commitment in developing ALS therapies is very clear. They participated in the two Airlie House meetings in the past as I explain later.

With this opportunity, I would like to present our concerns about the Guideline for fast-track product and the Scientific Advisory Panel. Our concerns are specifically related to the CDER's Specific Question # 6. Priority -- What should be CDER's highest priorities for action?

98N-0339D

TS7

What changes at CDER would have the most beneficial effects for the American People?

Because almost all neurologists agree that ALS is the most devastating disease in their practice, we in the ALS community believe there is no higher priority for all FDA centers, especially CDER and CBER, than to continue to expedite the development of the review of drugs for treating serious and rapidly fatal disease such as ALS.

Thus, it is imperative that FDA Guidelines be explicit regarding fast-track diseases. The FDA should solicit from both AMA sections and specialty organizations, such as AAN, ANA, or World Federation of Neurology, a recommendation for properties of fast-track diseases. The current Guideline described in the FDA Modernization Act (Section 112) is still not specific and explicit, particularly on ALS. Therefore, we anxiously await the Agency's release for a guidance document for the section, which must be released within one year of enactment of the law (November 21, 1998).

We do not believe that the ALS drug approval process has benefited equally from accelerated approval. We are hopeful that proper implementation of this section of fast-track products will increase and expedite the availability of new therapies for ALS.

As the former FDA commissioner, Dr. Kessler stated some years ago: "when dealing with serious and life-threatening conditions, we cannot wait for all the evidence to come in." For truly life threatening diseases such as ALS, the FDA can expedite the availability of therapies to patients in desperate need, by providing greater authority to approve drugs that strongly suggest effectiveness as stated in the Public Law. By permitting greater use of Phase IV post-approval confirmatory trials, and yet adhering to its own standard, the FDA should be able to acquire substantial evidence of effectiveness. This procedure has worked well in the AIDS and terminal cancer areas, and we believe that fast-track products were intended to expand that procedure to all drugs to treat serious and life threatening conditions, such as ALS. After all, 17 of the 20 Subpart H accelerated approvals since 1992 have been in AIDS and cancer and only 3 have been in other life threatening conditions, according to Drug Information Journal.

A need for controls in the phase I and II studies is obvious. However, for a disease such as ALS, that has no surrogate markers, but is a relentlessly progressive and results in continuously cumulative physical impairments, a need for controls in the phase III study needs to be reassessed, although the placebo-controlled design is still the gold standard for the phase III trial.

In this context, the members of the FDA including by Dr Paul Lieber have been most gracious to attend the WFN meeting and supportive of the effort in ALS clinical researchers and pharmaceutical industries for revising ALS Diagnostic Criteria and ALS Clinical Trial Guidelines. Such meetings already took place twice, in 1995 and this spring at the Airlie House. Therefore, the FDA team understands what issues are involved in ALS clinical trials very well.

The FDA should consider efficacy relative to safety. Large exposure to a drug such as IGF-I which has minimal side effects should weigh heavily even if there is only a small benefit.

In particular, if two studies show safety and only one shows efficacy, in diseases such as ALS where long term exposure is probably not an issue, we need to press ahead. An approval of such safe, yet modestly effective drugs ensures the phase IV studies for long-term efficacy. Many cancer drugs and immunosuppressive drugs for organ transplant are approved based on efficacy relative to safety. Again, ALS has not been treated similarly by the FDA as other life-threatening diseases.

ALS has, at present, no surrogate markers as cancers and AIDS do. Although there is an urgent need for developing surrogate markers for ALS, continuously cumulative physical disability, shown by quantitative muscle strength testing, pulmonary function tests, and a well-validated ALS scale, must be sufficient to evaluate the efficacy of a drug or biological product into the fast track approval process.

Next, I would like to discuss the Scientific Advisory Panel in Section 120 of the Modernization Act.

Only two drugs for ALS, riluzole and IGF-I, have ever come before an FDA Advisory Panel and both were highly controversial and often given contentious reviews. Given the great deference that FDA places on Advisory Panel decision, it is absolutely critical that true experts be represented on these Panels of the actual disease under review.

Public Law Subsection 120 states, "two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated." Undoubtedly the members of the Scientific Advisory Panel are the most capable and reputable members of medical community, however, the ALS community feels that there are no true ALS experts represented within the Panel.

It was apparently difficult to invite experts who have no conflict of interests to pharmaceutical companies. Nevertheless, there are still numbers of senior neurologists and other ALS experts who are not involved with clinical trials or pharmaceutical companies. Again, the participation of ALS experts in Scientific Advisory Panel is imperative.

In this context, the World Federation of Neurology, WFN, and the Committee of Motor Neuron Disease may be able to provide expertise in this review process. There are approximately 100 neurologists world-wide who have formed the International ALS Clinical Trial Consortia. This group has set the ALS Clinical Trials Guidelines and has broad experience with ALS clinical trials.

One solution may be the use of ad hoc reviewers from experts in such diseases. The International ALS Clinical Trial Consortia, again, may be helpful when acting as such an outside ad hoc panel.

I would like to discuss the current forum of a publicly open Scientific Advisory Panel meeting. In this forum, the patients testimonial is allocated and is, in fact, extremely important. However, these testimonials are so powerful and highly emotional that I, personally, wonder how

the panel members can make their judgement based purely on scientific grounds. On other occasions, it appeared the panel had made prior discussions, leaving patient's testimonies to have little influence. This type of forum, although extremely important, may need to be more effectively incorporated in the entire process. The FDA and the Advisory Panel should explore further options.

Next, I would like to point out some confusion I have as regards to CDER and CBER. Obviously, my confusion is derived from the lack of my knowledge and springs from recent experiences with IGF-I. IGF-I is a recombinant biological product; however, this approval process was taken by CDER that requires two independent clinical trials. All other neurotrophic factors, such as CNTF, BDNF, or GDNF, were to be evaluated by CBER that requires only one clinical trial. I do not understand how such a decision is made.

I believe that the FDA should aggressively educate patients' advocacy groups, disease specific organizations, disease experts, and new biotech companies that have never filed their product to the FDA about the FDA's function, process, and scope more than ever, because recent progress in therapeutics will increase drug approval applications even exponentially.

Regarding the future direction of fast-track approval, the FDA should solicit from the disease specific groups information regarding potentially effective drugs in such diseases. The FDA should proactively plan the future drug approval process for fast-track diseases and should then formalize and implement those plans.

Currently, the FDA supports some research in new drug development; however, I propose the FDA should also fund new research for developing surrogate markers in fast-track diseases that have no surrogate markers at present. It is of great urgency to help American people who suffer from this most devastating disease. Since the NIH budget was increased in the past year, I believe the FDA budget should echo such an increase. Without such a Federal budget increase, the FDA will not be able to meet the need of the American people.

Thank you very much for your attention.

Hiroshi Mitsumoto, M.D.
The ALS Association