

FDA DEFINITIONS OF EMERGENCY/LIFE THREATENING DISEASES AND THEIR APPLICATION TO ALS

A PAPER BY KATHY THOMPSON AND STEPHEN BYER FOR ALSWORLDWIDE.ORG

The FDA has placed a Full Clinical Hold on all ALS Emergency Single Patient Investigational New Drug (IND) applications incorrectly based on FDA guidelines for “Serious Diseases.” Dr Russell Katz has held ALS patients to the “conditions” that the drug must have “Proof of safety *and* efficacy *and* that the IND must not interfere with clinical trials.” These conditions are not required in the guidelines for life threatening disease. Dr. Katz has made the grievous error of applying the wrong FDA guidelines to ALS patient INDs.

There are several places within Congressional records and FDA's own records in which ALS is used as an example of a “life threatening disease” (see examples below). In a powerful acknowledgement of the immediate life threatening nature of ALS, Congress waived the waiting period for Social Security benefits for ALS patients to “zero” months. ALS is also considered an Orphan Disease and is part of NORD.

There is a strong and undeniable case based upon IND guidelines for “immediately life threatening diseases.” There are only one of two conditions required by FDA for this category; ALS clearly qualifies for the second condition as discussed in the link below and in the additional information attached to this memo.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.34>

Subpart B--Investigational New Drug Application (IND)

§ 312.34.

If the drug is to be used for treatment of an “immediately life threatening disease”, section 9 of the regulation provides the following approval standard:

For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) *May* be effective for its intended use in its intended patient population; **or**

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. 21 C.F.R. § 312.34(b)(3)(i).

When used for the circumstances under which a clinical hold may be placed on a treatment IND, the regulation references § 312.42. See 21 C.F.R. § 312.34(d). Section 312.42 in turn provides that clinical holds may be placed on proposed Treatment INDs if they fail to meet the criteria in § 312.34(b) (set forth above) for obtaining a Treatment IND. 21 C.F.R. § 312.42(b)(3)(i)(A). It further provides that clinical holds may be placed on an ongoing Treatment IND for the treatment of an immediately life-threatening disease if:

The evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) *May* be effective for its intended use in its intended population; **or**

(B) Would not expose the patient to whom the drug is administered to an unreasonable and significant additional risk of illness or injury.

That term is defined as “a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.” 21 C.F.R. § 312.34(b)(3)(ii).21 C.F.R. § 312.42(b)(3)(ii)(E).10

One out of the first four IND applicants, whose Iplex IND was rejected by FDA, died within 28 days after the clinical hold was placed on Iplex and one was hospitalized for life threatening issues (combined 50%). At least six additional patients (of the 80 total) seeking Iplex INDs have died between the initial filings with FDA December 16-24, 2008 and the last analysis of patient well-being on February 15, 2009.

FDA must be required to use the correct guidelines and immediately remove the Full Clinical Hold from the IND's for ALS patients seeking Iplex. Further, because FDA, as evidenced by Dr Katz statements, both written and verbal, clearly has apparent extraneous reasons for such denials, it is our contention that Iplex be made available through off-label prescriptions by licensed US physicians as though it was not on a self-imposed (by InSmed, the manufacturer) inactive status.

312.81(a)(1)).

The proposed definition of life threatening illness or disease is intended to include those fatal diseases where death itself may not be imminent, but where treatment is necessary to prevent premature death. For example, an anti-retroviral drug might be found, on the basis of phase 2 studies, to delay progression from the asymptomatic state to the symptomatic state and then to AIDS when used early after infection with HIV. Although this progression ordinarily would take more than 12 months to occur in most patients, this condition would be within the definition of life-threatening. Other examples of life-threatening illnesses include cancer, certain cardiac arrhythmias, intracranial hemorrhage, or amyotrophic lateral sclerosis.

<http://www.fda.gov/ohrms/DOCKETS/DOCKETS/98d0267/c000005.pdf>

The Honorable Kenneth E. Bentsen, Jr.
House of Representatives
Washington, D.C. 20515-4325

Dear Mr. Bentsen:

Thank you for your letter of September 11, 1998 to Dr. Michael A. Friedman, Acting Commissioner of Food and Drugs, commenting on the Food and Drug Modernization Act (FDAMA or the Act) Docket #98N-0339D regarding life threatening diseases and the drug approval process for them. Docket #98N-0339D pertains to the Food and Drug Administration's (FDA or the Agency) Plan for Statutory Compliance (with FDAMA) and Annual Report. Docket #98N-2067 relates to Section 112 of FDA, relating to “fast track” programs to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions. We have submitted your comments to Docket #98N-2067. In addition, on behalf of several constituents who suffer from amyotrophic lateral sclerosis (ALS), you expressed your concern that FDA should give the highest priority to expediting treatments for serious and fatal diseases such as ALS.

[http://thomas.loc.gov/cgi-bin/query/z?c109:S.1217.IS:](http://thomas.loc.gov/cgi-bin/query/z?c109:S.1217.IS)

Section 3 - Congress waives waiting period for Social Security benefits for “life threatening” diseases (ALS).

Sec. 812.36(a) applies the treatment IDE rule to "immediately life threatening" diseases, and defines that as a stage of a disease in which there is a reasonable likelihood that death would occur within a matter of months or in which premature death is likely without early treatment.

What does life threatening mean?

"Life threatening", for the purposes of the above section [21 CFR 56.102(d)] includes the scope of both life-threatening and severely debilitating as defined below:

FDA Definition of Life Threatening: This means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a life threatening situation requiring intervention before review at a convened meeting of the IRB (Institutional Review Board) is feasible.

FDA Definition of Severely Debilitating: This means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Orphan Drug Act, (ODA), P.L. 97-414,