FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

EMERGENCY FORMAL DISPUTE RESOLUTION REQUEST

APPEAL FROM IMPOSITION OF CLINICAL HOLD IMPOSED ON IND 104,328, A REQUEST FOR A SINGLE-PATIENT TREATMENT IND FILED ON BEHALF OF A PATIENT SUFFERING FROM AN IMMEDIATELY LIFE-THREATENING DISEASE

Appeal of Mark Smith (Patient)
and Dr. Jacqueline Tran, MD (IND Sponsor)

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Frank M. Torti, Acting Commissioner
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Re: Appeal from Imposition of Clinical Hold on IND 104,328

Dear Dr. Woodcock and Dr. Torti:

This is an appeal from the "Full Clinical Hold" imposed on IND 104,328, a request for a single-patient treatment IND filed by Dr. Jacqueline Tran, as sponsor for Mark Smith. Mark is suffering from ALS, an immediately life-threatening disease. There are no FDA-approved products that, in Dr. Trans's professional opinion, are appropriate to treat Mark's disease.[1] In Dr. Tran's professional opinion, the only product that might effectively treat his condition is Iplex® (mecasermin rinfabate) Injection. The manufacturer of Iplex (Insmed, Inc.) has agreed to supply the drug to Dr. Tran in connection with this IND. But as a result of FDA's clinical hold, Mark is being denied access to the only medical product that might possibly be effective in

[1] FDA has approved one drug, Rilutek, for treatment of ALS; it has been shown to extend the lives of some ALS patients by up to two or three months. Many doctors treating ALS patients are reluctant to prescribe Rilutek because it use risks liver damage.

treating his disease.

The clinical hold was conveyed to Dr. Tran by telephone in mid-January, 2009, with a follow-up letter mailed on January 23, 2009, by Dr. Russell Katz, Director of the Division of Neurology Products. The rejection of the Treatment IND does not appear to be based on any meaningful disagreement between Dr. Tran and Dr. Katz regarding the safety or efficacy of Iplex. Rather, Dr. Katz's actions appear to be based on a misunderstanding of the law governing the approval of Treatment INDs for individuals suffering from immediately life-threatening diseases. We understand that Dr. Katz's decision to reject the Treatment IND (as well as similar Treatment INDs filed on behalf of other ALS patients) was approved by numerous officials within CDER, and that Dr. Katz has said that it would be a "waste of time" to appeal the rejection within regular FDA channels. Accordingly, in light of: (1) the fact that the disagreement between the parties is largely "legal" in nature (*i.e.,* not scientific-based), and (2) we have been advised that an appeal within normal channels would prove futile, we have elected to file this appeal directly with the Director of CDER and with the Acting Commissioner of FDA.

Time is of the essence in this appeal. Mark was diagnosed with ALS two years ago. His physical condition has deteriorated in recent months. Unless he begins treatment with Iplex in the very near future, any chance that it will provide him a benefit will have been eliminated. Accordingly, we ask that you rule on this appeal within 30 days. Your prompt response to this appeal will allow the legal issues we raise to be resolved in federal court in an expeditious

manner, should that become necessary.

There is no legal basis for the denial of this Treatment IND. It is official FDA policy that single-patient Treatment INDs are to be approved in "nearly all" cases involving terminally ill patients who lack alternative treatment options. Indeed, FDA committed itself to that policy in a filing with the U.S. Supreme Court just one year ago. None of the reasons cited by Dr. Katz come anywhere near explaining why this is the exceptional case for which denial of such a Treatment IND would be justified. Iplex is a biologic approved by FDA as safe and effective in the treatment of short growth stature in infants and children. Insmed (the manufacturer of Iplex) is at present conducting clinical trials to ascertain the safety and effectiveness of Iplex in treating myotonic muscular dystrophy (MMD). No well-controlled clinical trials have been conducted regarding use of Iplex to treat ALS; our understanding is that Insmed lacks the funding to initiate such testing in the foreseeable future. However, numerous leading neurologists believe that Iplex shows real promise in treating ALS. It is currently being administered to ALS patients in Italy under an expanded access program sponsored by the Italian Ministry of Health, and anecdotal evidence from that program has been encouraging.

The only safety concern cited by Dr. Katz was based on a 13-year-old study of a different drug, Myotrophin. In fact, those findings were relatively minor and were contradicted by two later studies of Myotrophin.[2] More importantly, Myotrophin (unlike Iplex) is an FDA-approved

[2] Following those three studies, FDA did not approve Myotrophin for treatment of ALS – but only because Myotrophin was not shown to be effective in treating ALS, not because of safety concerns.

product that is readily available to ALS patients on an off-label basis; and large numbers of doctors continue to prescribe Myotrophin to their ALS patients despite studies suggesting a lack of effectiveness, simply because they lack alternative treatment options. Thus, the result of the rejection of the Treatment IND for Mark is to encourage his use of Myotrophin, the very drug whose safety profile caused Dr. Katz to reject the Treatment IND. Nothing cited by Dr. Katz suggests that administering Iplex to Mark would expose him (a man already suffering from an immediately life-threatening disease) to "an unreasonable and significant *additional risk* of illness or injury." 21 C.F.R. § 312.34(b)(3)(i)(B) (emphasis added).

Nor did Dr. Katz contest that Mark has no other treatment options, or provide any basis for concluding that approval of his Treatment IND would interfere with existing or contemplated clinical trials. Only by applying an inappropriate legal standard was Dr. Katz able to conclude that the Treatment IND should be rejected.

I. Mark Smith's Medical History

Dr. Katz's letter rejecting the Treatment IND (attached hereto as Exhibit A) does not purport to base the rejection on any facts regarding Mark Smith's medical history. He did not contest that Mark is suffering from ALS or that it constitutes an immediately life-threatening disease. Thus, the medical history is not an essential element of this appeal. We nonetheless include some basic background information for ease of understanding.

Mark Smith is a 57-year-old man living in Lakewood, Washington with his wife Iwona Smith. He was diagnosed with ALS (Amyotrophic Lateral Sclerosis, or "Lou Gehrig's Disease")

in March 2007 by Dr. Jacqueline Tran of Burien, Washington. The diagnosis was supported in May 2007 by Dr. Michael Weiss of the University of Washington in Seattle, Washington. Dr. Tran currently serve as Mark's primary care physician. Mark's disease symptoms have progressed in severity over the past two years. Due to severe muscle atrophy and weakness, he can no longer walk and is wheel-chair bound. He needs assistance for transfers to and from his wheel chair and can still support some of his weight on his legs during those transfers. He has some use of his right hand and fingers but has no strength in his left arm/hand. He has difficulty in swallowing.

Throughout his illness, Mark and his doctors have been eager for him to enroll in clinical trials for ALS patients, but they have found none for which he qualified and that were willing to admit him. In the absence of FDA-approved treatment options from medical doctors, Mark has been consulting a naturopathic doctor whose treatments have included oral nutrition enhance-ments, chelation therapy, and IV phosphatidylcholine injections coupled with reduced glutathione ("lipid exchange" therapy). Mark has felt subjectively more healthy following chelation treatments, but none of the naturopathic treatments have slowed the progression of his ALS. Dr. Tran has now concluded: (1) there is reason to think that Mark would benefit from taking Iplex; (2) he has no other effective treatment options; and (3) his illness has advanced to the point that it is immediately life-threatening.

II. The Development of Iplex

We do not believe that there is any dispute regarding the status of Iplex as an FDA-

approved medical product, as well as the absence of any well-controlled studies regarding its safety and effectiveness in treating ALS. Accordingly, the undisputed medical evidence is not an essential element of this appeal. We nonetheless include some basic background information to place into proper context the legal issues that separate the parties.

Iplex is an aqueous solution for injection containing a binary protein complex of human insulin-like growth factor-1 (rhIGF-1) and human insulin-like growth factor-binding protein-3 (rhIGFBP-3), both produced by recombinant DNA technology. After extensive clinical testing, Iplex was approved by FDA for treatment of short growth stature in infants and children.

Iplex is not currently being marketed for that indication, however. Genentech holds a patent for IGF-1; along with licensing partners, it markets IGF-1 under the names Increlex and Myotrophin. Genentech filed suit against Insmed, alleging that Iplex infringed its patent. After a federal district court ruled in Genentech's favor, the parties entered into a settlement agreement in March 2007 that effectively ended all marketing of Iplex outside of Italy. While Iplex was still being marketed in the U.S., 14 ALS patients were treated with Iplex on an off-label basis; that treatment ceased after the March 2007 patent settlement. Anecdotal evidence suggests that many of those 14 patients reacted positively to the Iplex treatment.

Dr. Katz is correct: no well-controlled studies have ever been conducted regarding the effectiveness of Iplex in treating ALS patients. But a number of leading doctors and scientists believe that there is evidence to suggest that Iplex may be effective. As noted above,

Myotrophin (often referred to as "free IGF-1") exhibited enough promise in animal studies[3] that three clinical tests were conducted regarding its effectiveness in treating ALS patients. The second of the three studies demonstrated a small advantage over placebo,[4] but the third study showed no benefit – and thus further efforts to win FDA approval of Myotrophin for treatment of ALS patients was abandoned. A number of researchers believe that the structure of Iplex may permit it to succeed where Myotrophin came up short. Myotrophin has been shown to support sensory and motor nerve regeneration, but its dosage requirements and its relatively short half-life may make it unsuitable for treatment of ALS.[5] Some scientists believe it possible that Iplex, by combining free IGF-1 with a binding protein (IGFBP-3), may be more suitable for ALS patients because of its smaller dosing (once daily injection, rather than twice daily) and lengthened half-life.[6]

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[3] *See, e.g.*, www.nature.com/neuro/journal/v9/n11/abs/nn1789.html.

[4] After evaluating the first two clinical studies, the Peripheral and Central Nervous System Drugs Advisory Committee voted 6-3 in May 1997 to recommend against approval of Myotrophin to treat ALS. The vote was based on insufficient evidence of efficacy; according to news accounts, advisory committee members deemed Myotrophin safe for use with ALS patients and did not attach any significance to the increased deaths reported in the first study. *See* Margaret Wahl, "FDA Panel Rejects Myotrophin," THE ALS NEWSLETTER (1997), available at www.als-mda.ora/publications/als/als2-2.html.

[5] We note, however, that FDA continues to grant Orphan Drug Designation status to Myotrophin for treatment of ALS. Myotrophin is FDA-approved for treatment of short stature, and its ready availability means that doctors can (and frequently do) prescribe Myotrophin off-label for ALS patients.

[6] *See, e.g.*, Kelli A. Sullivan, *et al.*, "Insulin-like Growth Factors in the Peripheral Nervous System," 149 ENDOCRINOLOGY 5963 (2008).

There is no clinical evidence to suggest that Iplex is not safe for use by ALS patients. We note initially that Iplex's status as an FDA-approved product at the very least demonstrates that Iplex is safe for use in healthy adults; indeed, Iplex has been clinically tested in various settings in hundreds of patients ages infant to 92-years-old without serious adverse side effects. Anecdotal evidence from the 14 American ALS patients who used Iplex before March 2007, and the several hundred Italian ALS patients who have been using Iplex for the past two years (as part of the expanded access program sponsored by the Italian Ministry of Health) suggests no safety concerns. Dr. Katz raised safety concerns based on the first of the three clinical studies of Myotrophin. That study (the "1202 Study") reported that deaths among those taking Myotrophin exceeded deaths among those taking placebo, but the FDA advisory committee that reviewed the study concluded that the increase was not statistically significant and that Myotrophin was safe.[7] Indeed, FDA thought little enough of Myotrophin's safety risks that it permitted large-scale clinical trials of Myotrophin to go forward among ALS patients – the third study was not completed until 2008. Neither of the other two Myotrophin studies reported the increased deaths identified in the 1202 Study. Moreover, a number of leading researchers have concluded that use of Iplex entails fewer safety risks than does use of Myotrophin.[8]

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[7] Transcript of Meeting of Peripheral and Nervous System Drugs Advisory Committee, June 7, 1996, Vol. II, 60-63, 306, available at www.fda.gov/ohrms/dockets/ac.96/transcpt/3183t2.rtf.

[8] Attached as Exhibit B are letters written by researchers expressing the view that Iplex entails fewer safety risks than Myotrophin in treating a variety of conditions. These letters were written in late 2006 or early 2007 after the researchers became concerned that the Iplex patent

Despite the potential benefits of Iplex for ALS patients, for a long period of time they were blocked by the Insmed-Genentech patent settlement from gaining access to Iplex. That changed on November 8, 2008, when Genentech and its licensing partners entered into an agreement with Insmed that gave Insmed a royalty-free license to supply Iplex to ALS patients world-wide. *See* Exhibit C (November 8, 2008 letter describing the agreement). The letter held out a vague possibility of a future agreement that would permit clinical trials, but only in the indefinite future after extensive analysis of the Italian experience. In the meantime, Insmed recently announced that it has received permission to make Iplex available to ALS patients *throughout Europe*, beginning in the second quarter of 2009.

III. Mark's IND Application

Upon learning of the potential availability of Iplex, Mark and his family quickly put together an IND application. They were assured by the FDA officials with whom they worked that approval of a single-patient Treatment IND would not be a problem.

Exhibit D is a copy of the IND submitted to FDA on December 23, 2008 by Dr. Tran as the IND sponsor for Mark. FDA has not contested the completeness of the IND application, Dr. Tran's qualifications to serve as a sponsor, or the specific treatment protocol she proposed. Rather, FDA's objections relate solely to Iplex itself.

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litigation would lead to the withdrawal of Iplex from the market. The researchers included Profs. Lois Smith and Robert H. Demling of Harvard Medical School, Prof. Morris Schambelan of the University of San Francisco Medical School, and Prof. Richard Moxley of the University of Rochester Medical Center.

IV. FDA's Response.

Dr. Russell Katz, Director of FDA's Division of Neurology Products, informed Dr. Tran during a mid-January telephone conversation that the Treatment IND had been rejected. He said that the rejection was based on FDA's safety concerns and a concern that if too many such Treatment INDs were approved, it would interfere with the development of future clinical trials for Iplex.

Dr. Katz followed that call with a January 23, 2009 letter confirming that the Treatment IND had been rejected and was subject to a "full clinical hold." Exhibit A. The letter cited three reasons for the rejection:

1. Lack of evidence that Iplex is effective. Dr. Katz noted that there have been no "adequately controlled trials" demonstrating Iplex's effectiveness in treating ALS. While noting that the similarity of Iplex to Myotrophin might suggest that Iplex could piggy-back on Myotrophin's effectiveness data, he stated that any such effort would be unavailing because two of the three Myotrophin clinical trials failed to demonstrate effectiveness.

2. "[W]orrisome" signals regarding safety, including – in at least one of the three Myotrophin clinical trials – increased mortality among those taking Myotrophin over those taking placebo. While conceding that the evidence from the Myotrophin study was not a "definitive signal" that Myotrophin was unsafe for treatment of ALS, and that Myotrophin was not the product that Dr. Tran was proposing to use, Dr. Katz concluded, "nonetheless, it is reasonable to be concerned that the potential signal for increased mortality associated with [Myotrophin] may be applicable to Iplex." When combined with the evidence of Myotrophin's ineffectiveness, the "potential increased mortality" of Myotrophin "made it imprudent" to grant the IND, Dr. Katz concluded.

3. Interference with potential clinical trials. Dr. Katz explained, "[G]iven the intense interest in this compound in the ALS community, we believe that granting single-patient INDs to even a few sponsors at this time would result in such widespread use that adequately controlled trials would become virtually impossible."

The letter left the door ever-so-slightly ajar. It said, "As noted, the evidence of the lack of benefit and possible harm of IGF-1 is not definitive. Moreover, Iplex is not identical to IGF-1. We would therefore be willing to discuss with you and/or other sponsors the appropriate development of Iplex as a treatment for patients with ALS."

V. FDA Policy Regarding Treatment INDs for Terminally Ill Patients

In order to demonstrate Dr. Katz's numerous errors of law, we first set out FDA policy regarding the granting of single-patient Treatment INDs for patients suffering from immediately life-threatening illnesses.

Congress has explicitly provided that FDA may authorize individual patient access to investigational products intended to treat serious diseases. *See* 21 U.S.C. § 360bbb(a) & (b). That provision permits such access in emergencies, or when: (1) the treating physician has determined that the patient has no satisfactory alternative therapy, and risks associated with the investigational drug are no greater than the risks associated with the disease; (2) FDA determines that there is "sufficient" evidence of safety and effectiveness; (3) FDA determines that provision of the drug will not interfere with clinical investigations; and (4) the sponsor submits a satisfactory clinical protocol. *Id.*

FDA regulations regarding the issuance of Treatment INDs are set forth at 21 C.F.R. § 312.34. If the drug is to be used for treatment of an "immediately life-threatening disease,"[9]

[9] 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). There can be no argument that Mark's ALS fails

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).

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:

> [T]he 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.

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to qualify as an "immediately life-threatening disease."

21 C.F.R. § 312.42(b)(3)(ii)(E).[10]

Interspersed throughout the regulations are directives that FDA officials are to apply a flexible approach to granting access to Treatment INDs, particularly when the patient to be treated is suffering from an immediately life-threatening disease. In other words, the safety and effectiveness thresholds are to be kept significantly lower in such situations than in more typical IND applications. For example, in Subpart E of the IND regulations (entitled, "Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses"), the regulations explain:

> [W]hile the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that *physicians and patients are generally willing to accept greater risks and side effects from products that treat life-threatening and severely debilitating illnesses*, than they would accept from products that treat less serious illnesses.

21 C.F.R. § 312.80 (emphasis added).

Indeed, FDA has committed itself, in the U.S. Supreme Court and in other federal courts, to a policy of granting "nearly all" single-patient Treatment IND applications for terminally ill patients who lack alternative treatment options. By way of background, we note that the Washington Legal Foundation, the Abigail Alliance for Better Access to Developmental Drugs,

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[10] The regulation also provides that a hold may be placed on a Treatment IND, whether proposed or ongoing, if [t]here is reasonable evidence that the investigation . . .is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug." 21 C.F.R. § 312.42(b)(4)(ii).

and others have raised constitutional challenges to FDA restrictions on patient access to developmental drugs. The U.S. Court of Appeals for the District of Columbia Circuit issued a decision in 2006 (later vacated) that upheld the constitutional right of citizens to obtain access to developmental drugs free from FDA interference under certain limited circumstances. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006). In response, and in order to persuade the federal courts that there was no need for them to step in to protect the constitutional rights of patients, FDA repeatedly assured the courts that, when it comes to terminally ill patients who lack alternative treatment options, FDA interference with access to developmental drugs would be minimal. For example, FDA swore to the U.S. Supreme Court in one recent court filing: "Because the FDA's standards for terminally ill patients who lack alternative treatment options are accommodating, most – indeed nearly all – of the single-patient IND requests submitted to FDA are approved." Brief of FDA Commissioner Andrew von Eschenbach in *Abigail Alliance for Better Access to Developmental Drugs, et al. v. von Eschenbach*, Supreme Court No. 07-444 (December 2007) ("FDA Brief"), at 7.

VI. FDA's Failure to Abide by Its Own Regulations

In his letter denying the Treatment IND for Mark, Dr. Katz failed to abide by the FDA rules and regulations set forth above. To the extent that Dr. Katz cited regulations at all, he cited inapplicable ones. He applied the wrong standards for judging safety and effectiveness. And he failed to provide a plausible explanation regarding how approval of the Treatment IND might interfere with clinical investigations; indeed, there is none. Given that FDA policy is to grant

"nearly all" Treatment INDs under these circumstances, Dr. Katz has failed to explain why this is the exceptional case in which denial is appropriate.

Safety. While FDA takes safety concerns into account when reviewing any IND application, the safety standard is very flexible when the illness to be treated is immediately life-threatening, because "physicians and patients are generally willing to accept greater risks and side effects from products that treat life-threatening and severely debilitating illnesses." 21 C.F.R. § 312.80. A drug to be used for treatment of an "immediately life-threatening disease" meets FDA's safety standard if it "[w]ould 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). Dr. Katz did not cite that standard in his letter,[11] and made no attempt to demonstrate that the risk of taking Iplex would be significantly greater than the risk Mark already faces as a result of having ALS – *i.e.*, the risk of death from a debilitating disease with no proven treatments and that, in the absence of treatment, will lead to certain death in the near term. Instead, Dr. Katz merely found that: (1) there has been a suggestion of an increase in mortality in patients randomized to [Myotrophin] compared to patients randomized to placebo in several studies;[12] (2) this increased mortality, while "not a definitive signal," is "worrisome"; and

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[11] Instead, the letter references 21 C.F.R. § 312.42(b)(1)(i), which has no application to this case. That regulation covers the imposition of clinical holds on Phase 1 clinical trials.

[12] Actually, there was one such study, the 1202 Study; and FDA officials concluded, during a 1996 advisory committee hearing that evaluated the results of that study, that the safety findings in that study were not significant.

(3) although Iplex is not identical to Myotrophin, "it is reasonable to be concerned" that "the potential signal for increased mortality" might also be applicable to Iplex, given the similarities between Iplex and Myotrophin. Even accepting the accuracy of those findings,[13] they come nowhere close to demonstrating that taking Iplex would expose Mark to a *significantly greater* risk to his health than the one he already faces. A finding of a "worrisome" safety profile for a drug that is similar to Iplex is a far cry from a finding that taking Iplex poses "an unreasonable and significant *additional* risk of illness or injury."

Moreover, the ironic result of the rejection of this and similar Treatment INDs is to encourage many ALS patients to take Myotrophin, the very drug whose safety profile caused concern to Dr. Katz. Many doctors treating ALS patients have substantial doubts about the efficacy of Myotrophin in treating ALS. But Myotrophin is an FDA-approved drug that is being marketed for other approved uses, and thus is available to be prescribed to ALS patients on an off-label basis. So in the absence of alternative treatments, many doctors treating ALS patients have ben prescribing Myotrophin in the hopes that it might provide at least a modicum of benefit. Accordingly, it stands to reason that permitting ALS patients to take Iplex instead of Myotrophin would *not* pose "an unreasonable and significant *additional* risk of illness or injury," given that the only reason to believe that Iplex poses any risk at all is that it might have a risk profile similar to Myotrophin's.

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[13] Given the considerable evidence cited above, there is substantial reason to doubt the validity of those findings. However, for purposes of this appeal, we accept their accuracy.

The same could be said of the naturopathic treatments that Mark has sought in the absence of FDA-approved treatments. We are well aware that FDA has significant concerns regarding both the effectiveness and safety of chelation therapy, which Mark is currently undergoing. Dr. Katz has failed to explain why granting Mark access to Iplex would expose him to significantly greater risk than the risk he is already incurring by undergoing chelation therapy.

Effectiveness. Dr. Katz's conclusion that Iplex is not effective in treating ALS was based on his finding that "there is no evidence from adequately controlled trials that Iplex itself is effective in the treatment of patients with ALS." He is correct that there have been no adequate, well-controlled studies to date, but that is not the standard for determining whether a single-patient Treatment IND for treatment of an immediately life-threatening disease meets the efficacy standard; rather, it is enough to show that the drug "*may* be effective for its intended use." 21 C.F.R. § 312.34(b)(3)(i)(A) (emphasis added). Given the evidence cited above, particularly the belief of many top neurologists that Iplex shows significant promise, there can be little doubt that Iplex meets the undemanding "may be effective" standard.[14] FDA regulations make clear that "the benefits of the drug need to be evaluated in light of the severity of the disease being treated." 21 C.F.R. § 312.80. Few, if any, diseases can be said to be more severe

[14] Also telling are the promising results produced by the on-going clinical trial of Iplex for treatment of MMD, a disease with a profile very similar to that of ALS. Based on those promising results, FDA has granted Orphan Drug Designation status to Iplex for treatment of MMD. Indeed, Dr. Katz all but admitted that Iplex meets the undemanding "may be of benefit" standard when he stated in his rejection letter that "the evidence of lack of benefit . . . is not definitive."

than ALS. Accordingly, there can be no justification for Dr. Katz's decision to judge Iplex's effectiveness based on whether there are any well-controlled clinical studies that establish its effectiveness; few, if any, Treatment IND applications could meet that standard.

Interference with Clinical Trials. Dr. Katz also indicated that FDA was rejecting the IND in part because it feared that granting it might interfere with the ability to conduct clinical trials of ALS treatments. He stated, "[G]iven the intense interest in this compound in the ALS community, we believe that granting single-patient INDs to even a few sponsors at this time would result in such widespread use that adequately controlled trials would become virtually impossible."

Dr. Katz cited no evidence to support his conclusion that granting this IND would interfere with clinical trials, and there is none. Granting Mark a Treatment IND could interfere with a clinical trial only if there were a possibility that he would enroll in a clinical trial in the absence of a Treatment IND. But the evidence is uncontested that he would not because he could not. As noted above, Mark has at all times been willing to enroll in clinical trials for developmental ALS drugs; but Dr. Tran was unable to find any for which he qualifies. Tellingly, Dr. Katz himself did not suggest any proposed trials in which Mark should seek to enroll. Nor is there any reason to believe that Mark would qualify if a clinical trial were established for Iplex or any other ALS drug. Mark has been suffering from ALS for two years and thus meets the trial criteria for few if any developmental drugs – those conducting clinical trials do not want to enroll patients whose advanced illness presents too great a risk that they will die during the

course of the trial. Moreover, any ALS trial that is still to be proposed obviously will not begin for another year or more, and Mark cannot wait that long. He is facing a medical emergency with a very poor medical prognosis. His only choices right now are to begin taking Iplex (which may prolong his life and which may pose some risks, which he is willing to accept) or to sit back and wait to die. Denying him the opportunity to pursue the first path will do nothing to increase the pool of trial participants for an as-yet-to-be-proposed clinical trial.

In explaining his concerns about the decreased ability to conduct clinical trials if Mark's Treatment IND were granted, Dr. Katz stated, "The purpose of an IND is primarily to permit the evaluation of an investigational drug, and it is not intended to be a mechanism to permit the treatments of patients with investigational drugs outside a formal developmental program." It is disappointing that FDA personnel have such an inaccurate understanding of the purpose of Treatment IND programs, but it goes a long way to explain what may have motivated Dr. Katz to deny the IND. As we suspect you are well aware, Treatment INDs *are* intended to as a mechanism to permit, in appropriate situations, the treatment of patients with an investigational drug, even though few Treatment INDs will provide useful evidence that can be used in determining whether the drug should later be approved for marketing. Both Congress and FDA have determined that Treatment INDs are to be granted based on a sense of compassion for the patients involved, not primarily for their scientific value. *See* 21 U.S.C. § 360bbb(a) & (b); 21 C.F.R. § 312.34(b)(3). Indeed, it is announced FDA policy that it will grant "nearly all" single-patient Treatment IND requests filed on behalf of terminally ill patients who lack alternative

treatment options. FDA Brief at 7. While FDA is justifiable concerned that Treatment INDs not be permitted to interfere with the clinical trial process, FDA statutes and regulations do not permit FDA to invoke such generalized concerns as a basis for denying a specific Treatment IND in the absence of any evidence that the IND would, in fact, have an impact on the clinical trial process. Indeed, any attempt to deny Mark access to Iplex under these circumstances would deny him his Fifth Amendment rights to due process of law.

CONCLUSION

Dr. Tran and Mark Smith respectfully request that FDA lift the Full Clinical Hold imposed by Dr. Katz and grant Treatment IND #104,328. The patient, the doctor, and the manufacturer of Iplex all agree that it is an appropriate medical decision to administer Iplex to Mark on a controlled basis, pursuant to the protocol set forth in the IND. Adequate safeguards have been adopted to minimize any risks to Mark's safety. Denial of the Treatment IND is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. Because time is of the essence for Mark, we request that you respond to this appeal within 30 days.

Respectfully submitted,

/s/ Daniel J. Popeo
Daniel J. Popeo
General Counsel

/s/ Richard A. Samp
Richard A. Samp
Chief Counsel

cc: Dr. Douglas Throckmorton, Deputy Director, CDER
Dr. Robert Temple, Director, Office of Medical Policy
Dr. Russell Katz, Director, Division of Neurology Products
Jeffrey M. Senger, Acting Chief Counsel, FDA
Division of Neurology Products