

Pendergast Consulting

March 20, 2007

Docket No. 2006N-0062 and RIN 0910-AF14

Electronic Submission

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

Dear Sir or Madam,

I am submitting these comments on the proposed rule, "Expanded Access to Investigational Drugs for Treatment Use," published at 71 Federal Register 75147 (December 14, 2006). Although the comment period ended on March 14, 2007, I sought an extension of time in which to file comments until today.

I am writing to express my views related to the challenges that are faced by patients who seek access to an experimental drug when available therapies are no longer providing therapeutic benefit. I worked at the Food and Drug Administration, first as a lawyer and then as Deputy Commissioner, Senior Advisor to the Commissioner. In both capacities I had the opportunity to work with patients, physicians, and pharmaceutical companies who were trying to obtain or offer experimental drugs under compassionate circumstances. While at FDA I also was involved in the creation of the policy of treatment use INDs. Since I left FDA, I have continued my involvement with patients seeking access to experimental agents, first at Elan Pharmaceuticals, Inc. and then in my own consulting firm where I have assisted several patients who sought access to experimental treatments. I have thus had the opportunity to see how well the FDA's regulatory system has worked from three different vantage points, and I am concerned about the changes that FDA proposes.

The views I express are my own, and are not intended to reflect, either directly or indirectly, on any client I have or have had in the past or may have in the future.

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Although the stated aim of the proposed regulation is to improve patient access to investigational therapies, it may not do so because the proposed regulations impose tightened standards for availability. The regulations also impose additional regulatory burdens on companies, thereby decreasing the probability that companies will enter into these expanded access programs. The summary of the preamble states: "The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions, who lack other therapeutic options and who may benefit from such therapies." However, through these proposed regulations FDA will be making the actual access to expanded access programs more difficult.

I. Comments on "Widespread" Expanded Access Programs, Section 561(c) of the Food, Drug, and Cosmetic Act.

(A). The statutory standard for a treatment use IND for a "serious" disease or condition is that there is "sufficient" evidence of safety and effectiveness. Section 561(c)(1) of the Food, Drug, and Cosmetic Act (hereinafter the Act). In the current regulation, 21 CFR § 312.34(a), in the treatment of a serious disease, "in appropriate circumstances, a drug may be made available for treatment use during Phase 2." (Emphasis added.) Under the newly proposed regulation, 21 CFR § 312.320(a)(3)(i), treatment use for a serious disease requires stronger evidence than before, and stronger evidence than is compelled by the Food and Drug Administration Modernization Act of 1997 (hereinafter FDAMA), which added section 561. The proposed regulation states: "Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials... ." (Emphasis added.) Thus in the proposed regulation, the phase 2 trials would have to be completed, not merely ongoing, making the drugs less quickly available to patients than before. In addition, since the data would have to be "compelling," FDA has given itself an additional opportunity to refuse to approve a compassionate use IND. Because of design limitations, many phase 2 trials could be considered not "compelling" so FDA has given itself an opportunity to reject treatment use INDs after completion of phase 2 studies. Thus FDA has chosen to tie its hands which may result in fewer treatment INDs. In the final regulation, FDA should go back to the language in the current regulation.

(B). In the current regulation, 21 CFR § 312.35(a)(ii), a treatment protocol must provide "an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments." (Emphasis added.) In the proposed regulation, FDA drops the word "marketed" so the sponsor has to provide an explanation of why its drug would be preferable to both marketed and unmarketed/investigational products. This expansion of "available therapy"

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is not addressed specifically in the proposed rule, but in the preamble FDA states that "available therapy" includes not just FDA approved products for that indication, but treatments not regulated by FDA (it mentions surgery) and states, "available therapy might mean a treatment ... one that is not labeled for use for the relevant disease or condition, but is supported by compelling literature reference." 71 Federal Register at 75151. FDA expanded the meaning of "available therapy" in a guidance document in 2004, but it has never put that expanded definition into a regulation after notice and comment rulemaking (which it should have). Since under the proposed regulation, a company would now have to show that the product for treatment use is better than both approved and unapproved therapies, thereby making the standard harder to fulfill, FDA should either (a) revert back to the prior, more manageable standard permitting a company to measure its product against other marketed products, (b) use rulemaking to redefine "available therapy," or (c) use its authority to approve the unapproved therapy for the new indication for use so that its use becomes "on label," eligible for wider reimbursement, and less likely to cause liability or other legal exposure for the physician and company involved.

(C). The current regulations do not address the impact of the widespread treatment use IND on other ongoing or planned trials. The requirement that this impact be considered was added by FDAMA after FDA's current regulations were written. FDAMA added § 561(c)(5) of the Act which states the consideration as follows: "the provision of the investigational drug or investigational device will not interfere with the enrollment of patients in ongoing clinical investigations under section 505(i) or 520(g)." (Emphasis added.) In the proposed regulation, FDA expands on the authority it was given in FDAMA to refuse to approve a treatment IND because of a wider variety of impacts on other research. The proposed regulation, 21 CFR § 312.305(a)(3) states: "Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use." (Emphasis added.) This proposed new FDA authority to refuse to approve treatment use INDs is far broader than just stopping enrollment in ongoing trials. FDA should go back to the statutory language for treatment use INDs¹ and not try to impermissibly expand its authority to refuse to approve expanded access protocols.

¹ FDA appears to be taking language from the single patient compassionate use section of the law, section 561(b), and trying to graft it onto the broader "widespread access" treatment investigational use protocols under section 561(c). FDA should not attempt to give itself authority Congress chose not to provide FDA.

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II. Comments on Individual Patient Access to Investigational Products, Section 561(b) of the Act.

(A). Under the law, the physician, not FDA, makes certain determinations for single-patient INDs. The physician, not FDA, decides if there is comparable or satisfactory alternative therapy. FDA has changed the statutory standard imbedded in FDAMA that it is the physician's determination of the patient's therapeutic options that is relevant. For single-patient INDs, the statutory standard in FDAMA, adding § 561(b) of the Act, is that a manufacturer or distributor may provide to a physician an investigational drug, among other conditions,

if – (1) the licensed physician determines that the person has no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved... .

(Emphasis added.) In its proposed regulations, FDA takes away the decision as to whether the patient has a "comparable or satisfactory alternative therapy available" from the physician, and gives that authority to itself. In its proposed regulation, 21 CFR § 312.320(a), FDA states that the criteria in proposed § 312.305(a) must be met. The FDA's proposed criteria in section § 312.305(a) in turn states:

(a) Criteria. FDA must determine that: (1) [...] and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(Emphasis added.) FDA should change its proposed § 312.305(a) to match the statutory standard, which is that the physician is the decision-maker regarding comparable or alternative therapy when the physician seeks a single-patient IND.²

In addition, FDA should strike proposed § 312.210(a)(2), which states that "FDA must determine that the patient cannot obtain the drug under another type of IND or protocol." Again, this is just another way for FDA to substitute its judgment about the availability of comparable or satisfactory alternative therapy for the judgment of the physician, and it should be eliminated from any final regulation.

² This decision is reserved to the Secretary for treatment use INDs that permit widespread access, see § 561(c)(2) of the Act, but not for single patient INDs governed under § 561(b) of the Act.

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(B). The physician, not FDA, must decide whether the risk is worth it. FDA has changed the statutory standard imbedded in FDAMA on who gets to make the risk/benefit decision for the particular patient, taking away the decision from the physician, where Congress put the responsibility, and giving the decision-making authority to itself. The statutory standard in FDAMA, located at § 561(b)(1) reads:

If – (1) the licensed physician determines... that the probable risk to the person from the investigational drug or investigational device is not greater than the probable risk from the disease or condition;

(Emphasis added.) In its proposed regulations, FDA at one point acknowledges that the physician must make this determination, see proposed § 312.310(a)(1) but then in another section FDA again gives the authority to make that risk decision to itself. Proposed § 312.305(a) states:

(a) Criteria. FDA must determine that: ... (2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated;

(Emphasis added.) FDA should eliminate proposed § 312.305(a)(2) to conform to the statutory standard that the physician gets to make the primary risk decision, not FDA.

(C). The physician's risk decision compares the risk of the therapy compared to the disease, not to the benefit of the therapy under the statutory standard, § 561(b)(1) of the Act. In proposed regulation § 312.305, FDA not only changes who gets to make the risk decision as is discussed above, it also changes the standard for making the decision. Congress said the physician should decide, and that the risk of the investigational drug should not be greater than the risk from the disease. In its proposed regulation, FDA revises the standard and says the risks of the investigational drug should be compared to the potential patient benefit from the therapeutic agent– not to the risks of the disease. FDA should revert to the statutory standard in the final regulation.

FDA also changes the standard by adding a new determination – that the risks are not “unreasonable” in the context of the disease or condition. But did Congress invite FDA to make a “reasonableness” determination? It seems not. By placing the responsibility to decide the risks at the physician level, and by creating a standard where the risks of the therapy are measured against the risks of the disease, Congress did not ask FDA to determine whether such a decision would be reasonable. What might seem perfectly reasonable to a dying

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patient might seem unreasonable to a person at FDA who has never met the patient. FDA should eliminate that part of the regulation that permits it to substitute its judgment on what is reasonable for the decision being made by the physician and patient.

Granted Congress gave FDA the right to determine if there was "sufficient" evidence of safety and effectiveness to support the use of the investigational agent, § 506(b)(2) of the Act, but that finding is in a separate section of the law and it does not empower a risk determination.

(D). The physician, not FDA, should decide the duration of treatment. FDA should give more credit to physicians who are treating the patients who have single-patient INDs and not try to micro-manage the individual physician's treatment decisions. In proposed regulation § 312.210(c)(1), FDA states: "Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy." Why? Does FDA think that alternate therapy will suddenly appear? Does FDA want the physician to go through another round of single-patient IND submissions if the patient seems to be tolerating the drug or biologic and wants to stay on it? Does FDA want to substitute its judgment for the physician's about how long the therapy should be given? It is important to remember that these patients have run out of conventional therapy, and they are trying something experimental because they have no other options. Why is FDA imposing this obligation, which does not exist in its current regulations and which usurps the decision-making left by Congress to the treating physician? It also seems quite inconsistent with the FDA's stated goal of improving access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions. FDA should eliminate this requirement.

(E). FDA should not compel sponsors to be closely involved in single-patient INDs. In two sections of the proposed regulations, FDA asks sponsoring companies to be involved, even when the single-patient IND is not held by the sponsor but by an individual physician. The more requirements FDA imposes on companies, the less likely they will permit single-patient INDs for their products, and FDA should drop its efforts to pull the sponsors into single-patient INDs held by individual physicians.

First, FDA states that it may require sponsors to monitor individual patient expanded access if the use is for an extended duration. See proposed § 312.210(c)(3). Basically FDA is taking the position that the individual physician may be incapable of monitoring a patient for an extended duration. On what basis is FDA making that judgment? If an individual physician holds the IND, why should the sponsor be allowed to monitor the patient? What if the patient

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and/or the physician do not want the sponsor to monitor the patient? What if the sponsor wants the patient to travel to the sponsor's offices to be monitored? Would the patient have to agree to travel to be examined in order to stay on the experimental drug? Again, this is interference in a single-patient IND that Congress has said could be held by an individual physician for his/her patient. FDA should drop this requirement.

Second, FDA states that when a significant number of similar individual patient INDs have been submitted, FDA may ask the sponsor to submit an IND or to submit a protocol for use under proposed § 312.315 or § 312.320. While this might speed up access for some patients, it also has the capacity to slow access for individual patients. When the second or third or fourth (or whatever number FDA deems "significant") individual patient IND is submitted by an individual physician, those particular patients and their physicians should not have to wait until FDA asks the sponsor to submit an IND and the FDA decides whether that IND can go forward. Those patients have the right to have their INDs acted on within 30 days, and they should not have to wait until FDA proposes a new scheme for its convenience.

Moreover, if and when FDA would ask a sponsor to submit an expanded access protocol under proposed § 312.315 (intermediate-sized patient populations) or proposed § 312.320 (treatment protocol for widespread use), FDA will also ratchet up the standards under which those treatment INDs might be granted. See, e.g., discussion at 71 Federal Register at 75154 ("There should be more clinical experience for an intermediate-size patient population than for an individual patient...") Pity the poor patient who seeks a single-patient IND through his/her physician only to have the FDA aggregate the request and make it harder to achieve. FDA should not unilaterally decide to convert a single-patient IND into something more. To do so will diminish access for patients.

(F). FDA has no statutory support for its product development criteria. In the case of the single-patient IND, Congress gave FDA authority to authorize a single-patient IND if

[t]he Secretary determines that provision of the investigational drug or investigational device will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.

Section 561(b)(3) of the Act. The proposed regulation tracks that language for single-patient INDs, see proposed § 312.210(a), which in turn refers to proposed § 312.305(a). However FDA adds a new criterion not found in FDAMA. FDA adds the phrase "or otherwise compromise the potential development of the expanded access use." Proposed § 312.305(a)(3). This new, broad, essentially

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limitless standard would permit the FDA to refuse to approve any single-patient IND it wanted to, and it should be removed from the final regulation.

III. FDA Should Take Additional Regulatory Steps To Improve Patient Access

There are additional regulatory steps FDA should take to make it easier for a patient to receive a therapy under a single patient IND, and FDA should revise its proposed rule to include these steps which would meet the proposed regulation's stated goal of improving access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions, who lack other therapeutic options and who may benefit from such therapies.

(A). FDA should take steps to reduce the requirement that there be an Institutional Review Board (hereinafter IRB) review of each single-patient treatment use IND.

When a physician attempts to obtain an investigational drug/biologic on behalf of a patient, the current FDA requirements, and the proposed regulations, would require the physician to obtain IRB approval of the treatment protocol. This is very difficult for two interrelated reasons.

First, if the physician is attached, however tenuously, to a research institution (e.g., the physician has admitting privileges at the hospital attached to the research institution), then the physician may have to obtain approval of the institution's IRB. However some research institutions are unwilling to review single-patient INDs because they see themselves as having liability exposure from the IND while at the same time the IND does not benefit the institution (e.g., the institution is not conducting a study for which there is funding). Therefore, it can be very difficult to obtain institutional IRB approval in some circumstances. Even when an IRB is willing to consider a single-patient IND, it is not always willing to review the single-patient IND quickly, to the possible detriment of the patient.

Second, private, for-profit IRBs are an alternative, but they are expensive and can be too slow for a dying patient. The costs for review of a single-patient IND can run into the thousands of dollars and take weeks to be completed.

FDA should clarify its regulations that a subset of any IRB can review a single-patient IND, and FDA should waive all recordkeeping and other requirements that are not warranted under the circumstances. In the alternative, FDA should waive IRB review for any single-patient IND if the drug has completed any phase I trial. In any event, FDA should take steps to make

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this aspect of a single-patient IND simpler for the physician to accomplish on the patient's behalf.

(B). FDA should explain to sponsors that the adverse events seen in patients with single-patient INDs will not be counted as heavily against the drug or biologic as the adverse events seen in clinical trials.

One of the major reasons more companies do not participate in single-patient IND programs is because they believe that adverse events seen in the single-patient trial will count against the drug or biologic when the company submits a marketing application for the product. The patients who seek single-patient INDs are often sicker than other patients who might take the product once approved: they have run out of available options for their serious illnesses, they likely have intercurrent illnesses, and they may have taken other medications or have other factors that make them particularly susceptible to adverse events. FDA's current practice is to not take these special concerns into account, but rather to require the manufacturer of the experimental agent to include the adverse events from single-patient INDs into the integrated summary of safety when an NDA/BLA is later filed with FDA.

FDA should address the manufacturers' concerns and permit them to report and discuss the adverse events from single-patient INDs in a separate section of the NDA/BLA. While FDA cannot be blind to any adverse events, it could state that it recognizes that single-patient INDs are a special situation and that it will look very carefully and have solid evidence before determining that an adverse event seen in a single-patient IND is chargeable to the investigational product such that the investigational agent might be disapproved or have a severe warning of the adverse event.

IV. FDA Should Take Administrative Steps To Improve Patient Access.

There are several administrative steps FDA could take to improve access to patients who seek investigational products for their serious and life-threatening illnesses.

(A). FDA should streamline and make consistent its internal requirements for physicians when filing single-patient treatment use INDs, and FDA should post those requirements and helpful examples on its web site.

For example:

- o Some Divisions just require a letter from the physician containing all of the needed information. Other Divisions require the physician to file three

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- copies to the Division's main document room and then fax a fourth copy to the Division.
- o Some Divisions require the physician to provide proof from the manufacturer of the investigational product that if the FDA approves the single-patient investigational use IND, then the manufacturer will provide the drug. In other Divisions, the IND can be submitted and approved before the manufacturer commits to providing the investigational product. From the patient's perspective it is often useful to obtain the FDA approval of the treatment use IND before final negotiations with the manufacturer are concluded.
 - o The Divisions vary on how exactly the manufacturer can express its consent to refer to information in the Drug Master File or in another IND. Some Divisions will accept a simple letter from the manufacturer on the patient's behalf. Other Divisions require the company to make a formal amendment to its DMF/IND. The more formal the requirement, the harder it is for the patient to obtain the investigational product.
 - o Some Divisions have more than one system, depending on the type of investigational product. For example, in the Office of Oncology, CDER, there are different submission requirements for chemical drugs and biological drugs.

(B). FDA should also provide streamlined versions of the Forms 1571, etc. for use in single patient circumstances. Much of the information currently required on the forms is not relevant for the single patient IND.

(C). FDA should post the name and contact information of the person or persons responsible in each Division for helping physicians file single-patient INDs. Those contact persons need to be given the resources necessary to do their jobs, and if one person is overloaded with work, additional personnel need to be assigned to assist the contact person. It is not acceptable for patients to have to wait weeks for a phone call from their physician to the FDA to be returned, as happens today.

I support the FDA's stated goal of making it easier for patients to obtain experimental treatments, and hope that the FDA will consider these comments and improve its proposed regulations with that goal in mind.

Respectfully submitted,



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