CITIZEN PETITION
of the
ABIGAIL ALLIANCE
and the
WASHINGTON LEGAL FOUNDATION

to the

FOOD AND DRUG ADMINISTRATION, U.S. DEPT. OF HEALTH AND HUMAN SERVICES

In re Tier 1 Initial Approval Program to Expedite the Availability of Lifesaving Drugs

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June 11, 2003

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Citizen Petition – *In re* Tier 1 Initial Approval Program to Expedite the Availability of Lifesaving Drugs

CITIZEN PETITION

The Washington Legal Foundation (WLF) hereby submits this petition on behalf of itself and the Abigail Alliance for Better Access to Developmental Drugs (Abigail Alliance) under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs amend 21 C.F.R. § 312.

With this petition, WLF and Abigail Alliance seek the creation of a new Food and Drug Administration policy to grant Initial Approval for promising drugs, biologics, and devices ("drugs") intended to treat life-threatening diseases with unmet needs. The Initial Approval authority would become the first tier of a three-tiered approval system consisting of Initial Approval (Tier 1), Accelerated Approval (Tier 2) and Full Approval (Tier 3) designed to provide reasonable treatment options to all Americans. Tiers 2 and 3 are already in place. The petition also seeks regulatory changes to permit expanded availability of developmental lifesaving drugs following phase 1 clinical trials and at all subsequent stages of the trial and review process.

The three approval tiers would create a system that recognizes the need for more effective and timely translation of medical research advances to the public while maintaining the

regulatory oversight and approval authorities necessary to protect and promote the public health. Tier 1 Initial Approval will impose marketing restrictions, unique labeling requirements, informed consent of patients, and continued diligent pursuit of higher tier approval. Tier 2 Accelerated Approval is a well-established approval program and will continue to require Phase 4 testing as a condition of Tier 3 Full Approval. Eventual Tier 3 Full Approval will remain the eventual final goal for all drugs marketed in the United States.

As further detailed in part B below, our analysis of the Food and Drug Administration's statutory authority indicates that Tier 1 Initial Approval would fully comport with the Food, Drug, and Cosmetic Act of 1962, as amended. We believe this measure is needed to deliver medical advances to seriously ill Americans who are effectively abandoned by the present system.

A. ACTION REQUESTED

The FDA has implemented its statutory authority over testing of investigational drugs with the regulatory scheme set out in 21 C.F.R. § 312. The provisions that should be amended, and the text of the requested amendments, are set out below.

Sections 312.34(a) and (b) define the conditions for access to unapproved new drugs outside of a clinical investigation – commonly known as "compassionate use." (The regulation uses the term "treatment use" rather than "compassionate use.") The regulation allows for compassionate use in the case of a serious disease during Phase 3 trials; in the case of an "immediately life-threatening disease," compassionate use may be allowed earlier than Phase 3,

but generally not before Phase 2. These sections should be amended to allow compassionate use before Phase 2, and to take into account the effects of the disease in considering whether to approve compassionate use:

> (a) General. A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3**~~, but ordinarily not earlier than Phase 2~~**. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.
>
> (b) Criteria. (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:
> (i) The drug is intended to treat a serious or immediately life-threatening disease;
> (ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
> (iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
> (iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.
> (2) Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

> (3) Immediately life-threatening disease. (i) 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**, taking into account the risk of illness, injury, or death from the disease in the absence of the drug.**
>
> (ii) For the purpose of this section, an "immediately life-threatening" disease means 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.

Section 312.7 forbids sponsors of a new drug to promote or commercially distribute an investigational new drug, and forbids charging a price higher than cost. This section should be amended to allow charging for drugs provided under Tier 1 Initial Approval:

> (a) Promotion of an investigational new drug. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
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> (b) Commercial distribution of an investigational new drug. A sponsor or investigator shall not commercially distribute or test market an investigational new drug.
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> (c) Prolonging an investigation. A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

> (d) Charging for and commercialization of investigational drugs--(1) Clinical trials under an IND. Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.
>
> (2) Treatment protocol or treatment IND. A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. . . .
>
> (3) Noncommercialization of investigational drug. Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug. **This limitation does not apply to the use of a drug under Tier 1 Initial Approval.**
>
> (4) Withdrawal of authorization. [Omitted]

Finally, a new section 312.37 should be added to implement Tier 1 Initial Approval for limited marketing based on (a) evidence of efficacy from case history data on a modest number of patients, and (b) the results of a Phase 1 trial demonstrating sufficient safety to support the conduct of a Phase 2 or Phase 3 trial:

> **312.37 Tier I Initial Approval.**
>
> **(a) The Commissioner may grant Tier 1 Initial Approval to a sponsor for limited marketing based on the results of a Phase 1 trial demonstrating a safety profile sufficient to support conduct of a Phase 2 or Phase 3 clinical trial intended to further test the safety and/or efficacy of the drug and initial evidence of effectiveness based on case-history data from a small number of patients. Sufficient initial evidence of effectiveness would, for example, consist of documented improvement in a small number of patients with forms of an illness that rarely or never regress spontaneously. Statistically significant support will not be required for Initial Approval. The needed data**

may be generated during a Phase 1 clinical trial and/or from among the initial or later patients enrolled in a Phase 2 and/or 3 clinical trial.

(b) The Commissioner will grant or deny approval within 30 days of a request for Initial Approval, concurrent with review of a Phase 2 or 3 clinical trial protocol. Initial Approval will not be conditioned on an increase in the requirements for approval of a clinical trial protocol.

(c) A sponsor receiving Tier 1 Initial Approval must continue diligent pursuit of clinical trials and other testing required for Tier 2 Accelerated Approval and/or Tier 3 Full Approval.

(d) A sponsor receiving Tier 1 Initial Approval must require informed consent from the patient and adverse event reporting by the prescribing physician. The sponsor shall provide all material information regarding safety and efficacy in informed consent documents and must provide prescribing physicians with any new material information on a timely basis.

(e) A sponsor receiving Tier 1 Initial Approval must provide the drug only to patients who have been found ineligible for or denied participation in a clinical trial for the same drug or who, in the judgment of their physician, are not reasonable candidates for a clinical trial.

(f) Tier 1 Initial Approval shall be withdrawn if the drug receives Accelerated Approval or Full Approval. Initial Approval may be withdrawn if there is no entity pursuing eventual full approval for the drug. Initial Approval may be withdrawn if the drug is found to be ineffective or unacceptably dangerous for the patient populations most likely to be treated, except that any patient receiving the drug under Initial Approval will be allowed to continue receiving the drug subject to updated informed consent. Initial Approval may be withdrawn on the basis of ineffectiveness only if few or no patients can be expected to benefit from the drug. Initial Approval may be withdrawn on the basis of dangerousness only if the risks posed by the drug clearly outweigh the benefits.

Certain technical additions to 21 C.F.R. § 314 will be necessary to define the content and format of a Tier 1 Initial Approval application.

B. STATEMENT OF GROUNDS

Policy rationale. Annually, hundreds of thousands of Americans find themselves suffering from terminal diseases with no approved drugs capable of providing a cure or control of their disease. In most cases, at least one partially proven investigational drug with potential to effectively treat their disease exists, but is generally unobtainable because the drug has not been approved by the FDA for marketing. The current regulatory system has not resulted in clinical trials of sufficient scope and geographic distribution to provide reasonable options for the majority of patients suffering from life-threatening diseases with unmet needs, and is not likely to result in a clinical trials system adequate for this purpose in the foreseeable future. Private-sector participation in compassionate use and expanded access programs, although slowly improving, has been too limited and uncertain to fill the gap. The system that governs the FDA and our nation's drug development and approval process fails to serve hundreds of thousands of Americans each year.

The United States government has a moral and legal obligation to administer its regulation of drugs for life-threatening and terminal diseases in a compassionate manner and in the best interests of all Americans, including those who have exhausted FDA-approved treatment options. It is a civil and human rights issue that adversely impacts Americans from all walks of life. The health-care gap gains hundreds of thousands of new members each year and loses a similar number of existing members as their diseases and conditions, left untreated, take their lives. The existence of this health-care gap is in part the result of a regulatory regime that does

not permit the FDA to act in the best interests of all Americans afflicted with life-threatening and terminal diseases. The changes sought in this amendment, while not a comprehensive solution, will substantially increase the ability of the FDA and new drug sponsors to meet the needs of sick Americans.

The Abigail Alliance and WLF welcome recent encouraging signs of FDA's desire to meet the needs of terminally ill patients, such as the approval of Iressa and Velcade and efforts to define new endpoints for assessment of efficacy. It is important to understand, however, that these salutary activities do not address the concerns that are the focus of this petition: namely, the unavailability of potentially lifesaving therapies during the clinical trial and review process. Clinical trials and existing compassionate use programs are extremely limited in scale compared to the tens of thousands of patients in need.

For example, Iressa entered clinical trials as early as 1998. The sponsor, AstraZenica, sought fast-track review, but was informed by the FDA in late 2001 that more clinical trials would be needed. The FDA agreed in September of 2002 to fast-track review and approved Iressa in May of 2003. By then, Abigail Burroughs had lost her fight for life, despite having actively sought to participate in clinical trials and a compassionate use program. While it is true that Abigail might well have been saved by faster FDA action during the period 1998-2002, it is equally true that thousands of other Abigails would have died while waiting for Iressa's approval.

The situation is similar with regard to other drugs. Erbitux, then known as C225, showed positive results in patients in phase 1 clinical trials as early as 1995. The limited resources of

sponsor ImClone, as a startup, led to delays in subsequent clinical trials. In late 2001, the FDA rejected ImClone's data submission. In early 2002, ImClone was obliged to revise the clinical trial protocol for Erbitux in light of the FDA's approval of Sanofi's drug Eloxatin. It is reasonable to assume the FDA will not approve Erbitux until 2004, if then. Even in the case of the rapidly-approved drug Gleevec (Glivec) from Novartis, in which clinical trials and reviews consumed only around two and a half years, untold thousands of patients were denied access to this medication in the interim despite its early evidence of safety and efficacy.

The proposal for Tier 1 Initial Approval reflects the different risk-benefit tradeoff facing patients who are terminally ill and who have no other treatment options. Extensive marshalling of evidence regarding drug interactions, dose optimization, and the like, as well as studies of sufficient size to yield a high statistical confidence level regarding efficacy, are appropriate for new drugs to treat patients with other alternatives on the market. Yet for patients who are on a fast track to death, these steps may well entail a delay that is fatal. Such patients should have the ability to opt for a new treatment that has met a lower evidentiary hurdle with respect to safety and efficacy (as a very limited number of patients are now able to do if they can win a place in a clinical trial or compassionate use program).

The proposed system would maintain the viability of clinical trials by requiring that any patient obtaining a drug through Tier 1 Initial Approval must have sought and been denied participation in a clinical trial, or that the patient's physician has determined that the patient is not a reasonable candidate for a clinical trial (for example, by reason of geography or prior treatment history).

Statutory authority. The proposed changes to FDA's regulations are within FDA's statutory authority. The FDA's mandate from Congress to regulate drug efficacy is couched in quite general terms. For full marketing approval, the statute simply requires "substantial evidence that the drug will have the effect it purports or is represented to have." Substantial evidence, in turn, is not defined in terms of a specific methodology, but instead as "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have." 21 U.S.C. § 355(d). For investigational use, the statute simply allows the agency to demand "preclinical tests . . . adequate to justify the proposed clinical testing." 21 U.S.C. § 355(i).

Thus, for example, the concept of "phase 1," "phase 2," and "phase 3" trials is not mandated by the statute. The use of double-blind studies is not mandated by the statute. No particular level of statistical power is mandated by the statute. These and many other elements of the approval process are policy decisions within the discretion of the Commissioner.

Under the terms of 21 U.S.C. § 355(i), the Commissioner has the discretion to accept the quantum of evidence specified in the proposed standard for Tier 1 Initial Approval. Section 355(i) provides that the Secretary "may" require "preclinical tests," and does not exclude reliance on case history data. Indeed, case history evidence would be within the statutory grounds for full marketing approval under § 355(d), which requires only "substantial evidence" of efficacy. Even if Tier 1 Initial Approval is considered to be outside the investigational

exemption of § 355(i), then, case history evidence can present a sufficient basis in appropriate cases for limited distribution pursuant to Tier I Initial Approval.

C. ENVIRONMENTAL IMPACT

Petitioners claim a categorical exclusion under 21 C.F.R. § 25.30(h).

D. ECONOMIC IMPACT

Petitioners will submit information upon request of the Commissioner. Petitioners believe that delays in the availability of promising new drugs is raising health care costs and imposing economic harm on patients; adoption of this petition for a Tier 1 Initial Approval policy will have a positive economic impact.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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