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December 15, 2003

Dr. Mark McClellan
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2003P-0274/CP1 – Response to the November 13, 2003 Letter from Ms. Ellen Stovall to Commissioner Mark McClellan ("the Stovall letter")

Dear Commissioner McClellan:

The purpose of this letter is to respond to a submission to the docket from a group of cancer patient advocacy and research groups that identifies Ms. Ellen Stovall as the point of contact ("the Stovall letter"). We would like to have responded to this letter in a more timely manner, but it was not available in the FDA's docket room or on its web site for several weeks after the November 13 date of the letter. Please treat this response as a submittal to the docket for the referenced Citizen's Petition ("the petition").

Introduction

The Stovall letter generally describes certain elements of our petition regarding Tier 1 Initial Approval, and requests that it be rejected. The signatories are supporting the status quo despite the fact that many patients dying from terminal diseases are being denied access to investigational treatments with a potential to help them, solely because they cannot gain access to clinical trials. They also wish to maintain the status quo in a time when the Food and Drug Administration (FDA) should seek increased flexibility in its authority to translate the results of rapidly accelerating medical research to dying Americans with a legitimate need for that access.

Maintaining the status quo is no longer a reasonable or responsible option. The changes underway at the agency are having little effect on investigational drug translation and do not in any material way provide relief for the issues addressed by the Tier 1 Initial Approval proposal. Simply ignoring the problem will not cause it to go away for those

suffering the direct effects of increasingly ineffective FDA regulations and policies governing access to investigational drugs.

We do not question the compassion or interest of the signers of the Stovall letter, nor do we disagree with their three points regarding the importance of research, participation in clinical trials, and third party reimbursement. The proposal in our petition is fully consistent with these concepts, however.

Safety and Efficacy

The Stovall letter appears to raise concerns about the potential for Tier 1 approval of a drug as early as after completion of a Phase I trial. Our petition and subsequent submittals clearly explain the safety and efficacy standards that would apply to gaining Tier 1 approval. It would be possible only with a drug that showed evidence of safety and effectiveness in Phase 1 testing (*e.g.,* high response rates with negligible side effects – for example, Gleevec). Indeed, Tier 1 approval requires meeting a defined standard of safety and efficacy whereas a Treatment IND does not. The early potential for approval was included because the FDA has no regulatory and economically-workable mechanism to allow patients access to a life-saving drug early in the drug development process.

It is likely that most Tier 1 restricted approvals would come later in the clinical trials process when more data is available, but before the point when the sponsor would have enough data to apply for accelerated or regular approval (both of which allow unrestricted marketing). Our petition further explains that Tier 1 Initial Approval is consistent with all provisions of the Food, Drug and Cosmetic Act, including those provisions that call for substantial evidence and well-controlled clinical trials. Given a sufficient quantum of evidence from a phase I trial, such results *are* "substantial evidence" for purposes of the statute, whether or not they meet the FDA's higher, discretionarily-adopted standards for full marketing approval.

In point of fact, the American Society of Clinical Oncology (ASCO), a signatory to the Stovall letter, would surely agree that it is reasonable for patients enrolled in Phase I clinical trials to seek potential therapeutic benefit with tolerable side effects as clearly stated in an ASCO Special Article in 1996, entitled "Critical Role of Phase I Clinical Trials in Cancer Treatment" (attached).[1] In the article, ASCO states:

> Because Phase I studies are unfamiliar to most physicians and patients, there are many popular misconceptions about these trials. It is commonly misstated that such trials are nontherapeutic toxicology studies, that phase I studies pose high risk of extreme toxicity, that cancer patients are too vulnerable to give informed consent, and that the sponsor of the drug covers all costs of such studies.

[1] "Critical Role of Phase I Clinical Trials in Cancer Treatment," *Journal of Clinical Oncology*, vol. 15, no. 2 (1997), pp. 853-59 (adopted Nov. 8, 1996 by the American Society of Clinical Oncology).

ASCO further states:

> Evidence from the literature suggests that, although response rates in phase 1 trials can be low, they very often are helpful in identifying which agents subsequently will be of benefit and in directing subsequent phase II investigations. In fact, it has been suggested that failure to observe responses in phase I trials is predictive of subsequent failure of the agent and should be considered in the decision of moving the agent into phase II development.

And,

> In summary, although the goal of a phase I trial is to determine the toxic effects, pharmacologic behavior, and recommended doses for future study of a new agent, there is a strong preclinical rationale for bringing the drug into the clinic with the expectation of positive clinical outcomes for some patients. In fact, Institutional Review Boards would not permit the administration of potentially toxic treatments to patients unless there was some reasonable prospect of antitumor effect.

These unequivocal statements regarding the potential for benefit even during a phase I clinical trial strongly support our position that administering a drug that has already demonstrated benefit in the form of positive clinical outcomes in a *completed* Phase I clinical trial is reasonable for patients who have no other options and who cannot get the drug in a subsequent clinical trial.

Protection of Clinical Trials

The Stovall letter asserts that Tier 1 Initial Approval would jeopardize clinical trial enrollment, causing patients and their physicians to "avoid randomization and other burdens of clinical trials." But Tier 1 contains specific protections for enrollment of clinical trials that are more prescriptive and more difficult to avoid than those that apply today to Treatment INDs.

We know from the recent success of the Treatment IND conducted for Iressa in non-small cell lung cancer that these programs can be conducted without compromising enrollment in clinical trials. The Abigail Alliance has proposed a model similar to that used for Treatment INDs for Tier 1 drugs in our previously submitted response of October 7, 2003, to the Musa Mayer letter.

The contention in the Stovall letter that physicians will abuse the system by administering ineffective "mild chemotherapy" treatments to intentionally render their patients ineligible for clinical trials is a makeweight argument. No sane physician would play such games with patients' lives or with their own careers. A physician that did practice as

suggested in the Stovall letter would likely face disciplinary action including potential loss of their license to practice medicine, and legal liability in the courts.

In the course of considering the Citizen Petition, to the extent that the FDA determines that there is a realistic danger of such game-playing, the agency could of course adopt more restrictive criteria for access to Tier 1 drugs without rejecting the entire program.

The general concern that Tier 1 will somehow compromise our entire clinical trials system – by allowing access to terminally ill patients who have been denied access to those same trials – is simply unsupported by fact or reason. The provision that allows physicians to make decisions regarding whether a patient should enroll in a specific clinical trial already routinely occurs, for example, when a physician decides not to place a patient with a history of heart disease in a trial for a drug with side-effects that could exacerbate that condition. Today, that patient might be left with no options at all because the clinical trial is an unreasonable course of treatment. If a Tier 1 drug with tolerable side-effects for that patient were available, the physician and patient could reasonably pursue that alternate treatment. The provision of Tier 1 Initial Approval that allows a physician to use his or her skills to map out a reasonable course of treatment for the patient is an essential ethical component of the concept. It is critical for all of us to remember that in our efforts to protect the clinical trials system, the well-being of the patients must come first.

There is general agreement that much needs to be done to improve the design and enrollment of clinical trials. The FDA is well aware that the Abigail Alliance is a strong and active supporter of clinical trial enrollment, having worked consistently to improve sponsor posting of clinical trials information on clinicaltrials.gov. The Abigail Alliance also has proposed a new concept to the National Cancer Institute to increase their communications to the public regarding clinical trials, and is working with them to move that concept forward. The problems with clinical trial enrollment are primarily the result of exclusionary entry criteria, poor communication regarding the existence of trials, and limited geographic availability. These factors will continue to be the primary problems with clinical trial enrollment, with or without Tier 1. In fact, as we have explained in previous submittals to the docket, Tier 1 will likely improve enrollment in clinical trials and could result in broader and more widely available clinical trial programs.

Reimbursement

The Stovall letter expresses concerns regarding third-party reimbursement for Tier 1 drugs and the ability of patients to pay for them. Of course, the cost of health care and the ability of individuals to pay for it, either directly or through insurance plans, is a problem with every available medical treatment, approved or unapproved, in the United States. Tier 1 Initial Approval will not fix the problem, nor will it make it worse. The possibility that some patients would not be able to afford Tier 1 drugs has little relevance if the drug is not available under the status quo in the first place. Under the logic of the Stovall letter,

the FDA should stop approving new drugs altogether, since some Americans lack insurance and thus would not be able to afford them.

It is true, as the Stovall letter notes, that the Centers for Medicare and Medicaid Services (CMS) have instituted national coverage analyses of several FDA-approved anticancer drugs. But as ASCO has noted, these reviews violate CMS's own statutory mandate under 42 U.S.C. § 1395x(t)(2). ASCO correctly observed in its comments to CMS, "The novelty and complexity of a drug is more likely to indicate that it is a breakthrough treatment than that Medicare should deny coverage." Letter of Dr. Paul A. Bunn, Jr., to Thomas A. Scully, Dec. 10, 2002. In any event, if CMS elects to violate the law and embrace bad policy by denying reimbursement for drugs that have received full marketing approval, it is difficult to understand how the FDA's allowance of a new tier of approved drugs would have any effect one way or the other on the CMS's treatment of fully-approved drugs.

In effect, the FDA is being asked to incorporate the cost of drugs to the consumer directly into its approval process by establishing a criterion that will preclude approval of new drug unless everyone can either afford it out-of-pocket, or will receive some form of insurance coverage to pay for the drug. No such consideration is allowed by the FDA's current authority, and in any case, such a position makes no sense from the standpoint of public health.

Bias

We also think it relevant to note that, despite repeated requests from us, the FDA has refused to enter into any form of meaningful dialogue with the Abigail Alliance regarding the issues in the petition, citing advice from counsel related to our lawsuit filed in July 2003 as the rationale. Nonetheless, Dr. Richard Pazdur was scheduled to attend and speak at a recent meeting of cancer patient advocates that included discussion of our petition and lawsuit on the meeting agenda. Some of the advocates that signed the Stovall letter and other letters opposing our proposal were in attendance at that meeting. Well in advance of the scheduled date of the meeting, the Abigail Alliance requested that its President be allowed to attend. The request was flatly denied by Ellen Stovall. Dr. Pazdur is one of the officials at the FDA empowered by statute to rule on our petition, and will certainly provide significant input to that decision even if he does not personally make the ruling.

From this and other incidents, we are concerned that the handling of our petition by the FDA appears to have been biased by active communications and efforts on the part of key FDA staff to elicit the opposition of outside groups. Such activities do not befit the FDA in considering a matter of critical importance to thousands of American's suffering and dying from life-threatening diseases. We consider these practices by the FDA to have been inappropriate, and possibly in violation of proper administrative procedures. We are

concerned that the handling of our petition by the FDA has not been a fair and unbiased process.

We await your decision on our petition.

Sincerely,

Abigail Alliance for Better Access to Developmental Drugs

Steven Walker
Advisor on Regulatory and FDA Issues

Frank Burroughs
President