

March 13, 2007

Re: Docket No. 2006N-0062

NBCCF Comments on Expanded Access to Investigational Drugs for Treatment Use

The National Breast Cancer Coalition Fund (NBCCF) believes that access to investigational interventions outside of clinical trials undermines the clinical trials system and the principle of evidence-based medicine. Furthermore, it has the potential to seriously harm individuals, and raises important issues of fairness. For these reasons, we believe that access to investigational interventions outside of clinical trials should be allowed only in very limited circumstances. We have attached our Position Statement on Access to Investigational Drugs Outside Clinical Trials, which develops the rationale for this position and should be included as part our comments on the proposed rule.

NBCCF does not agree that public policy should aim to make investigational drugs more widely available and is concerned about the likely consequences of this rule: harm to patients and erosion of the system of rigorous clinical research necessary to test interventions to improve survival and save lives.

The proposed rule presents three ways expanded access to treatment use (EAU) of investigational drugs would be available. We believe that of the three, only the Expanded Access under IND or Treatment Protocol has the potential to adequately balance the plight of patients with a “serious and immediately life-threatening disease or condition” with the goals of public health. However, we have concerns about the proposed rule even under this scenario.

While not in support of most proposed ways for expanded access use (EAU) under the proposed rule, we will offer comments on each of them:

1. Expanded Access for Individual Patients

NBCCF does not support a process for single patient access to investigational new drugs (INDs). Furthermore, we are very concerned that the FDA would consider permitting “low-little if any clinical evidence to suggest potential benefit or possibly only animal data to support the safety of the use” on patients with an immediately life threatening condition outside of a controlled research setting. It is wrong to permit use in the absence of evidence in humans and to present this scenario as “treatment” even for desperately ill patients.

2. Expanded Access for Intermediate-Size Patient Populations

NBCCF has significant concerns about the proposed regulations for intermediate-size populations. The situations presented for the proposed intermediate-size patient populations are too diverse to belong to one category, raising questions and concerns, including:

- a. Drug not being developed: How would FDA determine that the drug is the only promising therapy for the people with a rare condition in the absence of

clinical data to support this use? The proposed rule would further erode the possibility of conducting a controlled clinical trial in this situation.

- b. Drug is being developed, but patients requesting it are unable to participate in the trial. Scenarios under this situation include: patients with a different disease from the one being studied; not eligible for a clinical trial; trial enrollment closed and others. These scenarios are too disparate to belong in one category. We see no justification to allow expanded use for a disease different from the one being studied outside a research setting. For the other situations, the Expanded Access Treatment IND would be the appropriate way for expanded access.
 - c. Drug is no longer marketed for safety reasons but there may be a subset of patients for whom the benefits of treatment are believed to outweigh the risks: It is unclear why access would be offered as part of EAU in this circumstance. Given known safety concerns under this scenario, the burden of proof for potential benefit must be quite high in order to expand access. On what basis would the FDA make the determination of benefit/risk balance for an approved drug that is no longer marketed due to safety reasons? We believe a clinical trial is the appropriate setting to make this determination.
 - d. Allow uninterrupted therapy when drug is approved but not being manufactured (therefore not marketed) in a manner consistent with approval (GMP): Is it necessary or even appropriate to offer continuing access under the Expanded Access rule? Since the drug is not investigational, access should be handled under a different mechanism. More importantly, there needs to be assurance of close oversight of the manufacturer to minimize harms to patients.
 - e. Drug shortage: It is very possible that the numbers of patients needing access under this scenario will be higher than 100. Also, it is not clear that the Expanded Access rule will be the right mechanism for access.
3. Expanded Access Treatment IND or Treatment Protocol
As per NBCCF's position statement, "expanded access should be allowed only in very limited circumstances. These are:
- a. The patient has no treatment options left;
 - b. The patient is not eligible for any open clinical trial investigating the therapy in question;
 - c. The therapy has shown some effectiveness and a low risk of serious harm in a phase II trial

Off-trial access should be in the context of an expanded access protocol in which distribution of the investigational therapy is fairly and blindly allocated, and data are captured that will add to the scientific knowledge about the intervention. To capture meaningful information, all individuals who apply to the program must be followed, and that data must be reported to the trial sponsor."

We believe that application of the submission requirements as described under 312.23 (b)(2) to the Access Treatment IND is closest to NBCCF's position.

However, we are concerned about language in the proposed rule that under a Treatment IND “evidence would ordinarily consist of data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence”. We believe this is inappropriate.

4. Open-Label Safety Studies

NBCCF favors FDA’s proposal to evaluate whether proposed open-label safety studies should be considered more accurately as a treatment IND or treatment protocol. NBCCF agrees that, compared to open-label safety studies, the formal review process of the treatment IND or treatment protocol offers more assurance for patient safety, integrity of the clinical trials process and an efficient drug development system.

5. Continuation Phase of a clinical trial: NBCCF is concerned about clinical trial designs that allow crossover before adequate analysis of efficacy and safety, particularly at interim analysis. This practice limits the generation of robust evidence of efficacy and safety.