



Robert E. Wittes, MD
Physician-in-Chief

March 13, 2007

Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: 2006N-0062 - Expanded Access of Investigational Drugs for Treatment Use;
Proposed Rule**

Dear Dr. von Eschenbach:

On behalf of Memorial Sloan-Kettering Cancer Center (MSKCC), I am writing to comment on the Food and Drug Administration's proposed rule entitled Expanded Access to Investigational Drugs for Treatment Use, published in the December 14, 2006 Federal Register¹ (the "Proposed Rule"). MSKCC appreciates the opportunity to submit these comments.

Under the Proposed Rule, patients will have increased access to experimental drugs at various stages of investigational testing and, in some cases, long before they are ready for submission to FDA in a new drug application. Many of these drugs are highly likely to prove ineffective on fuller testing and premature use in treatment will expose these patients to significant risk without any reasonably reliable estimates of the chance of benefit or the probability of harm. Moreover, by increasing the availability of these drugs outside of clinical trial protocols, the Proposed Rule may well have the unintended effect of impeding completion of definitive clinical trials, as well as weakening manufacturer and patient incentives to conduct and participate in the trials necessary to establish safety and efficacy. We are, therefore, very concerned that the Proposed Rule does not adequately protect patients or safeguard the process for ensuring that drugs are safe and effective, so that their future, widespread use may be based on firm evidence.

I. The Proposed Rule Does Not Adequately Safeguard Patient Safety

The Proposed Rule would allow an individual patient access to an experimental drug if the patient's physician determines that the probable risk to the patient is not greater than the probable

¹ 71 Fed. Reg. 75147 (Dec. 14, 2006).
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risk from the disease or condition. The very nature of experimental drugs, however, particularly before they are adequately characterized clinically, limits patients' and physicians' abilities to know and fully understand the risks and benefits of a particular drug. The Proposed Rule would allow patients with serious or immediately life-threatening diseases or conditions access to therapies that have not been sufficiently evaluated, which may not improve a patient's condition, and, in some cases, may actually increase patient suffering or hasten death.

II. The Proposed Rule Would Potentially Compromise the Integrity of the Drug Development Process

Despite these serious shortcomings, one might perhaps argue that desperate patients with serious or life-threatening illnesses should be allowed the maximum possible degree of personal autonomy in selecting incompletely characterized therapy. But the consequences of this Rule's application would not be limited to those patients who choose treatment with these drugs. It would extend to future patients as well. Given the indispensable role of clinical research in the development of new cancer treatments, MSKCC is extremely concerned that the Proposed Rule risks paralyzing our ability to define the efficacy and safety profile of cancer drugs, both of which are necessary for evidence-based clinical decision-making.

The Proposed Rule requires the FDA to determine that providing an experimental drug will not interfere with the initiation, conduct, or completion of clinical investigations before the FDA grants patients expanded access to the drugs. This sounds good, but how is the FDA going to do this? Despite the FDA's efforts to minimize the Proposed Rule's interference with the drug development process, allowing this expanded access to experimental drugs outside of clinical trials will likely result in a decreased number of patients enrolled in trials, less stringent clinical trial protocols, and a reduced amount of useful data produced by trials, all of which may limit drug manufacturers' incentives to sponsor trials, particularly when there are willing paying patients requesting the manufacturers' non-FDA approved drugs.

As demonstrated by the legislative histories of the 1938 Food, Drug and Cosmetic Act and the Kefauver-Harris Amendments of 1962, currently accepted protocols for multi-phased clinical trials were developed partly in reaction to incidents that raised concerns about drug safety and efficacy. Multi-phased clinical trials constitute the best means of determining critical information about an experimental drug. The reliability of information obtained through clinical trials provides insight as to whether a drug's expected therapeutic gain justifies the risk entailed by its use. At MSKCC, we have observed quite recently an example of a trial (with bevacizumab and cetuximab in colorectal carcinoma) in which enrollment plummeted following accelerated approval of drugs pursuant to the process outlined in 21 C.F.R. § 314, Subpart H, Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.² It is unreasonable to institute a public policy that rests on the unrealistic assumption that routine access to experimental drugs would not interfere with the conduct or completion of clinical investigations.

Allowing patients access to experimental drugs outside of clinical trials risks undermining the viability of these trials. In order to ensure that they receive the experimental drug, patients are more likely to choose to receive the drug through the expanded access protocol instead of

² Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.500 et seq.

participating in a study in which they may receive a treatment other than the study drug, i.e. the control agent. Although the Proposed Rule stipulates that individual patients would not be permitted to obtain access to these drugs if they are able to participate in a clinical trial of the drug, how will it be determined whether a patient is or is not able to participate? Physicians are likely to be under very considerable pressure to provide drug under expanded access.

The Proposed Rule seems highly likely to decrease the amount of safety and efficacy information available for drugs that the FDA eventually approves. Increased availability of an experimental drug may result in limited enrollment in Phase III of the drug's clinical trials. For drugs approved under Subpart H, there exists at least some sound scientific data on the drug's effectiveness, common short-term side effects, and risks. Access to experimental drugs under the Proposed Rule may even undermine the prospect of obtaining Phase II data, given the likely compromising effect it may well have on trial enrollment. Consequently, the Proposed Rule may potentially lead to less rigorous clinical trial protocols as a consequence of diminished patient participation. Logically, decreased enrollment and less rigorous protocols are likely to yield less useful data, which will mean patients and their physicians will have access to less information regarding a drug's safety and efficacy. Will the FDA really be able to demand that its own customary "gold standard" for clinical trials be met if its own Proposed Rule is the reason trials are failing? We doubt it.

We are also very worried that implementation of the Proposed Rule may be greeted with disapproval by payers and health plans, who may well not agree to reimburse for the routine care of patients receiving these drugs off protocol. The current wording of the Medicare's policies stemming from the National Coverage Decision on reimbursing the routine care costs on certain categories of clinical trials would not apply to this use of investigational drugs. We doubt very much that commercial insurers will react any more permissively to the Proposed Rule.

Finally, the Proposed Rule's interference with the clinical trial process is likely to undermine drug manufacturers' incentives to sponsor clinical trials any more than the bare minimum necessary to attempt initial NDA approval. Such sponsorship is integral to continued innovation in the field of cancer research. Clinical trial research is extremely expensive. The likelihood of decreased patient enrollment in trials which are producing less useful data may cause some manufacturers to limit their sponsorship of clinical research, particularly when they can charge patients not enrolled in a trial for their non-FDA approved products pursuant to the Proposed Rule.³ Why should companies spend large sums for trials that are highly likely to fail?

³ Under the companion rule proposed by the FDA, Charging for Investigational Drugs, 71 Fed. Reg. 75168 (Dec. 14, 2006), trial sponsors may charge patients for investigational drugs provided outside of a trial protocol, so long as the sponsor provides the FDA (i) evidence of sufficient enrollment in any ongoing trials needed for marketing approval to reasonably assure the agency that the trials will be successfully completed as planned, (ii) evidence of adequate progress in the development of the drug for marketing approval, and (iii) information specifying the drug development milestones the sponsor plans to meet in the next year.

III. Conclusion

In sum, we believe this Proposed Rule, if finalized, could place patients at substantial risk and would significantly compromise the integrity of the drug development process. The frequent failure of sponsors to meet their end of the agreement with FDA to sponsor trials in the post-marketing period following Accelerated Approval should make the agency very wary of making investigational drugs widely available for non-investigational uses until safety and effectiveness is shown for at least one indication.

MSKCC appreciates the opportunity to comment on this Proposed Rule. Thank you for your willingness to consider our views. We hope that the FDA will consider these concerns as it prepares the Final Rule.

Sincerely,

A handwritten signature in black ink, appearing to read 'Robert E. Wittes', with a stylized flourish at the end.

Robert E. Wittes, MD