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Mark McClellan, MD, PhD
Commissioner
Food and Drug Administration

Via e-mail and fax

Dear Dr. McClellan,

Cancer is a deadly disease. With an annual US mortality rate in excess of 500,000 people, it would take only five weeks to fill the Vietnam War Memorial with the names of those who have lost their personal war against cancer. In addition, treatments for cancer – even treatments with great success rates such as those for childhood leukemia – generally carry significant side effects and risks associated with use. At the same time, clinical research seems to progress in tiny increments. Survival improvements are frequently miniscule and require years of testing in hundreds of patients to confirm benefit. Thus, the cancer community – FDA, NCI, institutions, researchers, clinicians, patients, advocacy organizations, industry – continues to search for ways to improve the drug development process. These discussions are proceeding in a variety of forums and involve topics such as surrogate endpoints, central institutional review boards and new paradigms of research.

We are in full agreement with the goals of those who are seeking to improve the drug development process and patient access to promising treatments. At the same time, we – the cancer community – must ensure that improvements to the process don't result in throwing the baby out with the bath water, so to speak. For example, a recent proposal (the Conceptual New Early Conditional Approval for Drugs, Biologics and Devices Intended to Treat Life-Threatening Diseases with Unmet Needs from the Abigail Alliance for Better Access to Developmental Drugs, also known as the Tier 1 proposal) urges FDA to conditionally approve drugs for marketing very early in the drug development process. We have several grave concerns around this proposal and others like it, and wish to lay them out for your consideration.

Safety

The concept – that drugs treating deadly diseases which have no effective treatment options should be conditionally approved after showing promise in phase 1 trials – raises both safety and efficacy concerns. Such an approval might well involve only about 30 patients total exposed and about 6 exposed at the intended dose. In such cases, it is quite possible that a drug could cause serious and fatal acute adverse events at high incidence (say 30%) without

having been observed, due to chance. Drug interactions, dose optimization, subacute toxicity, and many other aspects of safety assessment would not have been completed prior to "early conditional approval." Minimal compelling evidence of efficacy would be apparent, especially if the benefit increment was small.

Manufacturing quality standards

Other safety concerns involve manufacturing checks and the risk of infectious disease to contacts and the broader community. The sale of serum from cancer survivors (popular in the Bahamas) can spread infections through a community. So can many of the biological therapies, if they are not manufactured to rigorous quality standards. Use of animal organs and tissues raises issues regarding creation or introduction of new pathogens. The notion that such products might be broadly used prior to extensive manufacturing review and control followed by inspection programs is concerning – especially during the early development process, when sponsors may not have fully characterized their product or controlled their process. The potential exists for sponsors, either inadvertently or even intentionally, to produce for marketing a drug that differs substantially from that for which safety and efficacy data were submitted to and reviewed by the FDA. The potential for fraud is high, especially when dealing with people in a desperate quest to save a life.

Impact on development of effective treatments

All drugs have risks, and drugs for deadly diseases such as cancer tend to have significant toxicities. At the same time, patients use these drugs because the risk is presumably outweighed by the hoped-for benefit. If marketing is permitted with initial safety data and without compelling evidence of efficacy, the financial incentives for companies to take the risks and expend the time and resources necessary to demonstrate efficacy will be diminished. Ultimately, development and identification of safe and effective products will be delayed and impaired.

In addition, the treatment landscape is littered with examples of treatment options that looked promising in early stages of development only to prove ineffective in phase 2 or phase 3 trials. One classic example of such a treatment is the use of bone marrow transplantation in breast cancer, a therapy that did not require demonstration of efficacy to the FDA prior to widespread use. Many of these treatments have not reached the public eye due to commercial confidentiality. We have seen over and over that the only way to truly show efficacy in the current technological and scientific environment is through controlled trials. This is particularly true if the benefit increment is small.

Impact on clinical research

In addition to safety and efficacy, another concern involves the public perception of FDA approval. Any form of FDA approval represents a "gold star endorsement" in the minds of most consumers, and perhaps some physicians, as was clearly documented in the March Oncology Drug Advisory Committee (ODAC) meeting on accelerated approval. The ODAC panel noted that accelerated approval works best for drugs such as Gleevec and Eloxatin which show clear and substantial patient benefit. Other drugs, such as DepoCyte and Doxil, have less clear benefits; however, confirmatory research proceeds slowly once a drug is perceived as being “FDA-approved.”

These points were aptly summarized in a Wall Street Journal article on March 13, 2003:

> “After drugs get early approval to be sold in the U.S., pharmaceutical companies have little incentive to finish required research on them, a federal panel of cancer experts said Thursday.
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> “Further, doctors and patients are confused by the government's early approval of drugs that treat life-threatening conditions, these experts said, and wrongly think that drugs that get early approval are better treatments.”

Thus, this form of early conditional approval is likely to markedly impair the progress of clinical trials. By allowing sale for profit of unproven drugs, the proposal substantially diminishes the sponsor’s incentive to conduct and complete trials. This phenomenon would be most worrisome for a drug whose risk benefit did not look very good since completing the trial would likely lead to a loss of marketing approval. Even if the sponsor diligently tries to enroll such trials, the availability of the drug through the market would make enrollment difficult, as was also shown at the March ODAC meeting. Eligible patients frequently prefer to be treated with the “new and improved” treatment rather than entering a controlled trial. Physicians may prefer to treat their patients with an “FDA-approved” but actually unproven remedy over referring them to a regional center for a trial. The end result is an impairment of development of new treatments.

Conclusion

Ultimately, this type of proposal – that sponsors should be allowed to sell almost anything to patients with terminal disease as long as the patients consent – is built upon the false premise that only the patients stand to be harmed. As we see it, such proposals have the potential to harm patients, slow research (and thus harm both current and future cancer patients) and result in a number of treatment options which may “look good” but actually have no beneficial effect for the majority of patients, thus harming an already over-burdened health care system.

Unfortunately, the development of cancer-fighting treatments is complex, and there are few simple and easy answers to questions about how to speed effective treatments to patients. We believe that the Improving Innovation in Medical Technology: Beyond 2002 initiative lays out an effective roadmap for improving FDA's processes, including those involved with:

- **Expanded Access Programs** – We have been involved with the development and implementation of several EAP programs, and are actively working with sponsors to explore the development of incentives for additional EAPs. Additionally, we've had initial discussions with FDA regarding the potential of using EAPs to answer important questions about a treatment before the treatment is approved for marketing.

- **Accelerated Approval** – The March 2003 ODAC meeting showed that accelerated approval, while successful in many ways, needs fine-tuning especially in treatments that don't show a significant benefit to existing therapy.

- **Orphan Drugs** – The Orphan Drug program, designed for diseases with limited mortality, can and does help move treatments move through the approval process.

We fully support these FDA efforts.

Finally, earlier access to promising treatments might be possible through changes to the clinical trial process. We believe that collaboration between the scientific, corporate, advocacy and regulatory communities – such as the National Dialogue on Cancer, the Clinical Trials Summit, the recent Georgetown Center for Drug Development meeting and ongoing discussions between FDA, ASCO and ODAC regarding surrogate endpoints – is the way to move this process forward.

We are always available to FDA on these important topics, and look forward to continuing our productive working relationship. We urge FDA to proceed very carefully when considering revision of its legislative or regulatory standards of approval, to ensure that the FDA truly serves the public good.

Thank you very much for your consideration of our concerns,

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