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COMMENTARY

Drug Disaster

 By **RICHARD MILLER**
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Cancer patients suffered a serious setback yesterday. The Food and Drug Administration sent back **Dendreon's** Provenge, a development-stage drug for prostate cancer, requesting additional clinical data. The FDA rejected the drug despite an outside advisory panel's overwhelming recommendation to approve it.

Provenge's fate has wider implications. It is the first of a growing number of therapeutic cancer vaccines to go up for approval, and is emblematic of the gap between medicine and statistics that paralyzes the FDA approval process and keeps vital treatments from reaching critically ill patients. The FDA bases its approvals -- for everything from medications for minor ailments to new cancer treatments -- on the rigid application of the same outdated statistical standards. Any new drug or other form of treatment, whether it's a therapeutic treatment for infected hangnails or a cancer vaccine, must meet the FDA's standard of 95% certainty that any positive results claimed for its use are not due to chance.




While hangnail sufferers may be in a position to (uncomfortably) wait for such levels to be achieved, it is difficult to argue that terminally ill patients with only months to live should have to do so -- especially when more than 1,500 Americans die of some form of cancer every day. Given the choice and an understanding of known risk factors, many of these patients would prefer to accept less certainty about a new treatment's

potential to extend or improve quality of life for the time that remains to them, rather than to accept the near certainty of an imminent and often uncomfortable death.

The FDA initially refused to review my own company's Xcytrin, a drug for treating lung cancers that have metastasized to the brain, even though in trials involving nearly 1,000 patients, Xcytrin has been shown to be well-tolerated and to delay for months the onset of impaired brain function associated with this type of cancer. The reason for the FDA's refusal? The positive impact of the

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drug could be shown to be independent of chance at "only" an 88% level of certainty, instead of 95%.

The FDA's initial lack of interest in an evaluation is all the more disturbing because the necessary trials that Pharmacyclics conducted required the use of novel clinical endpoints for which there is no scientific precedent for setting the statistical threshold. In April, Pharmacyclics took the unusual step of filing with the FDA a New Drug Application (NDA) for Xcytrin over protest, a rarely used procedure when an NDA is denied, because we believe in the efficacy of the drug and the rights of patients it might benefit to have access to it. The FDA will complete its review by Dec. 31.

Statistical standards should not, of course, be set aside. That would be absurd. But the current, outdated approach to clinical research and therapeutic assessments has to become more flexible, so that allowances can be made not only for the contexts to which the standards are applied, but also for very real advances in science and medicine.

The deeper problem with the FDA is that its one-size-fits-all method fails to reflect the need to apply different assessment approaches for treatments derived from scientific breakthroughs. Many new treatments are difficult to mold into the existing clinical testing paradigms or the statistics originally designed for measuring them. Like Xcytrin, they may require novel trial designs for which no precedent exists. In such cases, it's unclear how an appropriate threshold should be set. An arbitrary choice might not reflect the way a treatment works, the nature of the disease or the patient base on which it is to be tested.

Fortunately, this is not news to the FDA. In a 2004 white paper, the FDA noted that "not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs."

I agree. But the question is how long should terminally ill patients with a very low quality of life have to wait? Shouldn't the FDA adopt an approval policy that reflects the current reality? We may lack the tools to get the "fundamentally better answers" that the FDA and the rest of us would like, but is that an excuse for staying with a status quo that isn't working?

In testing, Provenge did not meet its goal of slowing the progression of prostate cancer -- but data indicated that patients on Provenge lived an average of more than four months longer than patients treated with standard therapy. Similarly, Xcytrin showed a six-month improvement in the time that lung cancers that had spread to the brain took to grow and seriously impair brain function. Four to six months may not sound like a lot, but it's significant for patients with fatal conditions -- and both Provenge and Xcytrin enable patients to enjoy a better quality of life.

To its credit, the FDA did have an outside advisory panel review Provenge. This panel voted 17-0 that the drug is safe and 13-4 that the clinical data demonstrated substantial evidence of efficacy. At this point, we don't know how long the FDA's decision not to follow these recommendations will delay the opportunity for prostate cancer patients to benefit from the drug.

Biotech companies like Pharmacyclics, Dendreon and a host of others aren't seeking wholesale changes to the FDA regulatory process. What we are looking for is a recognition that context matters. All medical treatments are important, but not all are equally urgent. We need to recognize that terminally ill patients are in no position to wait. They and their doctors need to be able to

choose from among the most promising treatment options available to them *today*.

Millions of healthy Americans willingly face the roughly one-in-a-million chance that they will die from their annual flu shots, because they (rightly) judge that the potential benefits outweigh the potential risks. This risk-benefit analysis changes sharply when you are terminally ill. Shouldn't we give those patients at least a voice in deciding what risks they are willing to take when it comes to treatment options?

If, based on extensive review of all available data, the FDA has determined that a drug is safe and able to benefit some individuals, then patients and their doctors should be given the choice to use it. That will only happen if the FDA changes its one-size-fits-all method and uses a context-based approach to approving new drugs.

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