

## FDA chief looks to speed diabetes, obesity drugs

By Christopher Rowland, Globe Staff, 6/4/2003

Mark McClellan, commissioner of the Food and Drug Administration, said he wants to apply a fast-track review process normally reserved for drugs for terminal cancer and AIDS patients to drugs for diabetes and obesity.

McClellan's initiative is unprecedented because it would expand the accelerated review for treatments to a much larger group of people with health problems that generally are not immediately life-threatening. His approach also puts the agency in a position of calling on the drug industry, doctors, and researchers to come to the agency with fast-track ideas; ordinarily, pharmaceutical companies approach the FDA seeking fast-track status.

"We have an awful lot of premature death and huge morbidity associated with diabetes," McClellan said in a telephone interview. "While we've made some progress in treating obesity, this is one of the leading causes of death and disability in this country."

FDA guidelines say "accelerated approval," the fastest form of agency review, is for drugs that treat "life-threatening diseases" and should be undertaken on behalf of patients with low survival expectations and no other treatment options. Since the provision for accelerated approval was adopted 10 years ago, it has typically involved drugs for diseases such as AIDS, late-stage lung cancer, and leukemia.

Although millions of Americans live long and productive lives with obesity and diabetes, McClellan said that large numbers of deaths associated with those conditions justify use of the accelerated approach. The accelerated process can trim a year or more off the clinical trial phase of drug development, and then reduce the final FDA review period to as little as four months instead of 10 months. The agency can largely decide to make changes in the process on its own.

The FDA has been under fire for several years from drug companies, patients groups, and physicians over a drug approval process they felt was slow and cumbersome. The FDA under the Bush administration is "leaning toward making it faster," said Robert Blendon, a health policy professor at the Harvard School of Public Health.

"It is an administration that in general is trying to ease the regulatory burden on industry," Blendon said. "At the same time, I think they are arguing that they are trying to maintain protections in public health," said Blendon, who added that he thinks the administration is striking an appropriate balance.

Some health advocates said that speeding up the approval process could result in needless risks to public safety by putting drugs on the market with side effects that only become clear years later. Peter Lurie, deputy director of the healthcare team at Public Citizen in Washington, D.C., the advocacy group founded by Ralph Nader, said McClellan is more concerned with assisting drug companies. "It's more finding ways to use the accelerated approval track to favor industry. It's a new twist on an old theme," Lurie said.

When it comes to diabetes and obesity drugs, the FDA has had troubles in recent years. In 1997, the FDA ordered the recall of fen-phen, a widely used obesity drug that was approved using standard reviews, after patients developed heart problems. In 2000, in another highly publicized recall, the agency ordered the withdrawal of the diabetes drug Rezulin, which was linked to scores of deaths. Rezulin had been given "priority" status when it was approved by the FDA in 1998, one tier down from

"accelerated approval."

In a statement, Democratic Senator Edward M. Kennedy of Massachusetts, a leading member of Congress on FDA issues, said that "given the questionable track record on assuring the safety of drugs for obesity and similar conditions, caution is warranted."

McClellan's plan to further expand use of the accelerated approval mechanism, still in its earliest phases, would allow drug companies to win licenses for new therapies based on preliminary indicators -- in the case of diabetes drugs, measures such as weight loss or lower blood sugar -- instead of waiting for completion of lengthy phase III clinical trials that show long-term effectiveness. A phase II trial is designed to show signs of efficacy, while a phase III trial attempts to prove effectiveness by studying hundreds or thousands of patients and comparing their outcomes to patients taking traditional therapies or a placebo.

"Are there valid biomarkers, valid indicators, that we could observe early on, that are highly predictive of clinical benefits that could take years to observe," McClellan said.

The plan does not mean the FDA would relax its vigilance, McClellan said. Once experimental drugs reach the market, drug makers will be required to continue clinical trials to prove their long-term effectiveness and closely monitor side effects. Although the FDA's track record in forcing industry compliance on these so-called "post-market" trials has been mixed, with a 49 percent compliance rate in a study released last month, McClellan said \$75 million in new funding over the next five years will be put toward post-market reviews.

"The whole integrity of the accelerated approval process depends on completion of these studies," McClellan said.

In January, the FDA announced a broad initiative to "enhance efficiency" of its drug reviews for obesity and diabetes, but without providing many details. FDA spokeswoman Kathleen Quinn said the agency is now ready to open talks with the industry to develop guidelines and goals that could be used as milestones in a faster approval regimen.

"It really has been applied to the cancer and AIDS area the most, and it is something novel to be looking at other areas of disease to see how it could apply," Quinn said. "We are open to meeting with companies that want to develop drugs in those areas."

The Bush administration also is looking to speed approval of new cancer drugs, encouraging the FDA and National Cancer Institute to collaborate on development of new therapies by developing guidelines for clinical trials and developing ways to streamline reviews.

Markets have responded favorably, with investors flocking to biotech stocks recently with new discoveries. In the last few months, the FDA announced accelerated approval of AstraZeneca PLC's Iressa, a drug used to fight lung cancer; a new use for Gleevec, produced by Novartis AG to treat leukemia and now available to treat children as well as adults; and Fabrazyme, Cambridge-based Genzyme Corp.'s drug for Fabry's disease.

In a case being held up by McClellan as a model of the new approach, the government last month approved Cambridge-based Millennium Pharmaceuticals Inc.'s application for Velcade, a new drug to treat patients with multiple myeloma, a devastating cancer of the bone marrow. The FDA approved Millennium's Velcade application in less than four months, based on results of a phase II trial that showed positive changes in 28 percent of 202 patients studied. Phase III studies are still underway.

"Velcade went from lab studies, to animal models, to clinical trials in a period somewhat under three years. That is remarkable," said Dr. Ken Anderson, a Harvard Medical School professor who led Velcade's preclinical trials at Dana-Farber Cancer Institute.

At her home in Marshfield, Nancy Touhey, 42, a multiple myeloma patient and mother of two daughters, 10 and 8, followed Velcade's development closely and is now waiting for her doctors to decide whether she should receive it. Since she was diagnosed with the disease in 1992, she has been on a slew of chemotherapy agents and steroid drugs, she has received a bone marrow transplant and been treated with total body

radiation. She is part of a clinical trial at Dana-Farber for another cancer treatment, Revamid, but was removed from the drug because her blood platelet count was too low. Velcade may be her next option.

"You're always hoping for that next therapy," she said.

These decisions are difficult. A New York breast cancer survivor and author who is a patient representative on the FDA's Oncology Division Advisory Committee, Musa Mayer said patients clamor for approval of experimental drugs that may or may not be effective. Experimental drugs "will be used more and more without a solid foundation of evidence," Mayer said. "I don't want to see anybody die because they can't get access to a drug, but I don't really believe the simplistic claims that are made by some advocates that these are miracles."

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