United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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For Immediate Release
Tuesday, March 4, 2008

Grassley secures independent review of FDA approvals based on narrow health benefits

WASHINGTON — Senator Chuck Grassley has asked for an independent assessment of how the Food and Drug Administration follows up on the effects of medicines that it approves based on narrowly defined benefits.

"The way things have turned out with drugs like Vytorin and Avandia raise enough questions that a review is warranted," Grassley said. "It's not clear if the FDA's own policies are being enforced internally, where the agency is supposed to require companies to perform follow-up studies. These policies are designed for patient safety."

Grassley's questions stem from a practice of the Food and Drug Administration to use goals called surrogate endpoints to study whether a particular drug achieves a certain benefit, such as lowering blood sugar in diabetics. Grassley said it's critically important that the agency adhere to its complementary policies that require drug-safety reviewers to follow up on drugs that are approved based on surrogate endpoints.

"The public relies on the FDA to keep it safe from dangerous drugs and not just stick to narrow judgments that may not incorporate overall health," Grassley said. The diabetes drug Avandia was approved because it lowered blood sugar but later found to increase the risk of heart attack, even though lower blood sugar is tied to lower heart attack risk.

The Government Accountability Office, which is the investigative arm of Congress, has agreed to conduct the review that Grassley requested in the letter posted below.

February 28, 2008

The Honorable David M. Walker
Comptroller General
U.S. Government Accountability Office
441 G St, NW
Washington, D.C. 20548

Dear Comptroller Walker:

The Food and Drug Administration (FDA) has approved several drugs that appear to have little to no effect in protecting lives and increasing health. For instance, FDA recently approved Genentech's cancer drug, Avastin, to treat breast cancer.[1] Genentech's studies showed that Avastin halted tumor growth, but that breast cancer patients did not live significantly longer than those that did not receive the drug. Surprisingly, FDA's own advisory panel argued against the approval over concerns that Avastin's benefits do not outweigh its toxic side effects.

Further, a study last year found that Avandia, which controls glucose levels, was associated with an increased risk of heart attack. And last month, Schering-Plough and Merck announced that Vytorin, which controls cholesterol levels, provided no benefit to cardiovascular outcomes.

In all three cases, these drugs were approved by FDA because they had an effect on surrogate endpoints (tumor growth for Avastin; glucose levels for Avandia; and cholesterol levels for Vytorin). However, none of these drugs were studied sufficiently to see if they added any benefit to the health and/or lifespan of the patient. Typically, such results can be found through phase IV trials.

Therefore, I request that the Government Accountability Office conduct an inquiry into the FDA's approval of drugs based on surrogate endpoints, including an examination of FDA's process to ensure that drugs approved on surrogate endpoints are both safe and effective. In particular, GAO's inquiry should include an analysis of the following:

- The number of drugs that were approved based on surrogate endpoints;
- The surrogate endpoints that FDA uses to approve drugs;
- For each of these drugs identified, the date each was approved and whether FDA required the companies to complete phase IV trials;
- For each of these phase IV trials, the date they were started and the date they were completed and/or are expected to be completed;
- Describe the tools that FDA has to compel companies to complete phase IV trials;
- Describe any actions that FDA has taken against companies for failing to complete phase IV trials or failing to complete trials in a timely manner; and
- Describe any additional powers that FDA may need to compel companies to complete phase IV trials, in the event the tools that FDA has presently are insufficient.

Thank you for your attention to this important matter.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

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[1] Perrone, Matthew "Cancer Drug Ruling Will Have Wide Impact" Associated Press, February 22, 2008.

AP
FDA's Review Process Under Investigation
Tuesday March 4, 12:53 pm ET
By Matthew Perrone, AP Business Writer
Concerns Over Blockbuster Drugs Vytorin, Avandia Prompt Investigation of FDA Review Process

WASHINGTON (AP) -- The government's watchdog agency is investigating whether the Food and Drug Administration's drug-review process cleared two blockbuster medications without sufficient proof of their safety or effectiveness.

Sen. Charles Grassley said Tuesday the Government Accountability Office has agreed to study a much-debated method for approving drugs used to clear GlaxoSmithKline PLC's diabetes pill Avandia and Merck & Co. Inc. and Schering-Plough's cholesterol drug Vytorin.

The Iowa Republican requested the investigation after recent studies suggested the drugs may not lower the risk of heart attack and artery-clogging plaque, as assumed by millions of patients and doctors.

"There's enough of a pattern of problematic drugs to ask for an independent review of how the FDA follows up on the effects of medicines that it's approved," said Grassley, in a statement.

FDA cleared Avandia because it helped control blood sugar, which many doctors believe decreases diabetics' risk of heart attack. But the agency came under fire last year when an analysis showed Avandia could actually increase heart attack risk.

FDA argued that it has never required diabetes drugs to show lower heart attack risk, and that lowering blood sugar alone is an important benefit.

The agency approved Vytorin, which combines Schering-Plough's Zetia with Merck's older cholesterol drug Zocor, based on its cholesterol-lowering capability. But a study released earlier this year showed Vytorin was no more effective at limiting plaque buildup in neck arteries than Zocor alone, which is now available as a low-cost generic.

At issue now is whether FDA should approve drugs based on biological measures, like cholesterol and blood sugar, without evidence they improve more meaningful measures like survival.

FDA's Director for Medical Policy Robert Temple said the agency has used several alternate study goals, often called surrogate endpoints, to approve drugs for decades.

For example, HIV drugs are cleared based on their virus-lowering power, an effective predictor of survival.

Drug industry advocates favor shorter study goals because they involve smaller, less expensive and faster trials.

Longer trials, they say, may actually jeopardize patients.

"It's probably unethical to do an overall survival study where you're going to have HIV patients taking a placebo for 10 years," said Alan Goldhammer, vice president with the Pharmaceutical Research and Manufacturers of America.

But those who criticize FDA's handling of Avandia and Vytorin say surrogate endpoints aren't the problem. Rather, it's when FDA doesn't demand follow-up studies to prove drugs delivered on the predicted benefits.

"These studies are often never done, so we're left without the knowledge we need to use these drugs wisely," said Dr. Steve Nissen, chairman of cardiovascular medicine at the Cleveland Clinic. "And obviously we've paid the price for that with the safety issues and lack of efficacy issues with Avandia and Vytorin."

Nissen wrote the analysis that showed Avandia raised the risk of heart attack. Last year FDA said the drug's risks were still unclear and asked GlaxoSmithKline to study its effect on the heart. Results from that trial aren't expected until 2014 -- 15 years after the drug was approved.

Schering-Plough and Merck are working on a study to determine if Vytorin extends patients' lives. Results from that study, which FDA did not request or require, are expected in 2011.

When the agency does require follow-up studies of drugs, its track record is poor for making sure companies complete them. A 2006 investigation by the Health and Human Services Department inspector general concluded FDA could not readily identify what progress companies made on the studies.

In its most recent report, FDA said 900 of more than 1,200 studies required of drug makers had not even begun.

Under a law that takes affect next month FDA can fine companies up to $1 million for failing to honor drug study commitments.

Grassley argued for higher fines, and in his request to GAO asked investigators whether FDA needs more authority.

The agency shows no sign of scaling back its use of surrogate endpoints.

Last month FDA cleared Genentech Inc.'s drug Avastin for use in breast cancer patients

who have not taken other drugs. Agency reviewers based their decision on Avastin's ability to slow the spread of cancer. Previously FDA had approved drugs as a first-choice option for cancer patients if they extended, or improved the quality, of patients' lives.

Associated Press
February 21, 2008
Cancer Drug Ruling Will Have Wide Impact
By MATTHEW PERRONE, AP Business Writer

(AP) -- A decision expected Friday on federal approval for Genentech's Avastin cancer drug could have ramifications for all companies developing cancer medicines.

Genentech made its case for Food and Drug Administration approval of Avastin using a widely debated measure of drug effectiveness that focuses on tumor growth, not patient survival.

Industry executives are closely watching the decision to see whether the measure will pass muster with federal regulators.

Approval is far from certain, and many experts say the agency may delay a decision until later this year.

Avastin is already approved for advanced colon and lung cancer and was Genentech's best-selling drug last year, accounting for $2.3 billion in revenue. An additional use for advanced breast cancer patients who have not had chemotherapy would drive new revenue for the company.

In December, a panel of outside FDA advisers voted 5 to 4 against Genentech's application, arguing the drug's benefits did not outweigh dangerous and toxic side effects. FDA is not required to follow the panel's advice, although it often does.

At issue is how the agency judges the effectiveness of cancer treatments. Traditionally, FDA only approved cancer drugs that extended the lifespan of patients. However, in recent years companies have studied alternate measures of a drug's effectiveness. One of the most controversial measures is so-called progression-free survival, or how long the drug halts the spread of cancer.

Genentech's studies of Avastin showed that while the drug halted tumor growth for more than 11 months, breast cancer patients didn't live significantly longer than those who didn't receive the drug.

Genentech has argued that stopping tumor growth benefits patients physically and psychologically, even if it doesn't increase life expectancy. But many experts are skeptical.

"Why would it improve your quality of life to know that you have no disease progression if you still aren't going to live any longer?" asked Dr. Kay Dickersin, Director of the Center for Clinical

Trials at Johns Hopkins University.

Dickersin said that if FDA approves Avastin based only on slowing tumor growth, it could lower the bar for future drug approvals.

American Cancer Society spokesman Dr. Otis Brawley said it's possible Avastin improves quality of life - but the company hasn't shown that.

"Unfortunately, there was no real quality-of-life measurement in this study," said Brawley, who previously served on FDA's panel of cancer experts. "My interpretation of FDA bylaws is that I cannot approve a drug based on disease-free survival unless I have evidence of improved quality of life."

Genentech's Vice President David Schenkein points out that FDA has already approved two drugs for breast cancer based on slowed disease progression: GlaxoSmithKline's Tykerb and Bristol-Myers Squibb's Ixempra.

But those drugs were approved for patients who had already failed to respond to other therapies. Genentech wants Avastin approved as a first-in-line treatment for breast cancer.

Schenkein argues that delayed disease progression has advantages to overall survival as a study goal.

"A trial that has to wait to record overall patient survival will take many more years and be much larger," said Schenkein. He added that companies may be able to bring more medicines to market faster using goals besides survival.

Given the tough medical and ethical questions surrounding Avastin, Stanford Group analyst Gregory Frykman says there is a 40 percent chance FDA will delay a decision to review new data expected from Genentech later this year.

Regardless of when FDA makes a final decision, he writes, "it will provide insight into the agency's tolerance for a non-survival endpoint" for the approval of new cancer drugs.