

# Re: Merck, Schering–Plough Defend Efforts for Vytorin, Zetia

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Vytorin's Missing Fail–Safes  
Matthew Herper, 01.25.08, 6:00 AM ET

For Merck and Schering–Plough, the pile–on over the cholesterol drug Vytorin shows no signs of letting up. The latest: Plaintiffs' lawyers are licking their chops, and Charles Grassley, the powerful Iowa senator, has begun his own inquiry into the companies' handling of a failed clinical trial.

Meanwhile, Michigan Democrats Bart Stupak and John Dingell are asking about everything from the companies' television advertising to insider stock sales to mishandling of data. They're also asking Merck and Schering–Plough some arcane questions about how the failed clinical trial, called ENHANCE, was constructed.

The answers matter to investors, top researchers say. ENHANCE lacked expert committees that might have helped the companies avoid delays in releasing the data. Those committees may also have given them a legitimate way to handle any problems that came up, averting the public relations disaster that has caused share price declines of 15% for Merck and 25% for Schering as investors worry about the future of the companies' \$5 billion cholesterol franchise.

A Jan. 22 letter from the Committee on Energy and Commerce to the chief executives of Merck and Schering–Plough asks essentially the same question, eight different ways: Were there standing committees held to monitor the safety of the trial, or to deal with problems that came up in its progress?

Schering chief medical officer Robert Spiegel provided the answer in an interview with Forbes.com more than a week ago. This study had neither a steering committee, as a group of experts who regularly convened to discuss the trial and its data, nor a data safety monitoring board (DSMB), which carefully watches study information to make sure patients are not harmed.

"You would have thought they would have been more sophisticated in doing trials and would have had all the right checks and balances,"

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says Eric Topol, chief academic officer at the Scripps Health in California. "Every real trial should have both. You need to have the weight of a committee. You can't just have one individual to stand up to the sponsors."

Spiegel said that although steering committees are helpful, that is simply not the structure chosen for this trial. And a safety board wasn't necessary, because all patients were clearly getting "adequate cholesterol therapy."

The 700 patients in the ENHANCE trial, who all had a genetic disease causing their levels of bad cholesterol to spike without treatment, were all on the top dose of the cholesterol–lowering drug Zocor. Half of them also got Zetia, a second cholesterol drug, but there was no additional benefit on artery plaque. Vytorin is a combo pill of Zetia and Zocor. There was no sign Zetia was unsafe.

The lack of a data safety monitoring board is "sub–optimal," says Steven Joffe, a bioethicist and researcher at the Dana Farber Cancer Center. "It's hard to see who is helping to shape these decisions who has a strong level of independence from the company. Who has seen the data who can take public accountability?"

A DSMB might not take direct accountability, he notes, but it provides a mechanism that can reassure the public when problems happen.

Not everyone agrees. "I do not think a DSMB for ENHANCE was necessary," says Steven Nissen, head of cardiology at the Cleveland Clinic. He does, however, think the lack of a steering committee was "irregular."

Here's the rub: Schering–Plough wound up calling an ad hoc group on Nov. 16, 2007, to try to decide how to deal with what the company says were data problems. (See: "Merck and Schering's Secret Panel.") Schering and Merck have blamed the long delay in releasing details of the ENHANCE study on problems the companies saw with the imaging data in the study.

"We did think it was appropriate, as the study was still blinded, to try and get some outside opinions to just validate that the assumptions we made when the study started," said Spiegel.

If that decision had been made by a standing group of experts instead of an ad hoc group, it would have drawn less scrutiny. The same goes for the long delay in the study—if outside experts had been named ahead of time to make decisions about the data, there would be no debate over whether Merck and Schering did the right thing with regard to this trial.

Instead, they must now face a debate in which many top cardiologists argue that their drugs should only be used as second–choice options—

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and a congressional committee that is questioning every step they took—with the benefit of 20/20 hindsight.