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Avastin & FDA Were Both On Trial: Dan Explains

By Ed Silverman // [June 30th, 2011](#) // 7:45 am[11 Comments](#)

After months of controversy, an FDA advisory panel yesterday voted unanimously to uphold an earlier agency decision to yank the breast cancer indication for Avastin, a widely used drug sold by Roche and its Genentech unit ([see this](#)). The run-up to the two-day meeting was highly contentious as the drugmaker accused the FDA panel of bias, there were behind-the-scenes debates over potential conflicts of interest among expert speakers, and patients and their families organized protests - online and in person. Clearly, more was at stake than the fate of a best-selling med, which remains available for treating other cancers. The hearing was also a referendum of sorts on the veracity of the FDA accelerated approval program and, by extension, the agency itself. We asked Daniel Carpenter, the Allie S. Freed professor of government at Harvard University and author of "Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA," about the implications...

Pharmalot: This was an extraordinary meeting. What was at stake here for the FDA?

Carpenter: There were several distinctive features to this meeting. First, it comes at an incredibly polarized time in our national politics, where every conceivable issue is getting mapped onto the left-right battles in Washington. With the debate over health care reform, the scientific debate over Avastin has been imbued with the ideological overtones of a debate over rationing and the role of regulation in American society.

Second, the shift in clinical evidence on Avastin - initially, there was a promising set of results in E2100 (a clinical trial) and then a progressively weaker set of results in CONCORD (another clinical trial), including poor safety signals - put the FDA in a more difficult position than it has ever been with an accelerated approval. More than any case before it, Avastin for breast cancer combines a variable evidence base with a disease of almost unparalleled cultural and social proportions, with a large-scale market drug. It was one of the few blockbusters to emerge from the biotech industry.

Third, the company and some patient advocates were much more aggressive in contesting the FDA's recommendation. You could see this in Genentech's brief, which advanced some pretty radical arguments about the kind of values that should apply in these situations. You could also see the hostility of some of the patient advocates, such as when one witness told the committee members that they would be individually responsible for their votes and for the fates of the

women affected.

This meeting exposed a deep division in the advocacy community for breast cancer patients. There were individual patients and their family members who spoke up for keeping the drug's indication. Yet the major breast cancer organizations came out in favor of removing the indication. It isn't the first time that patient representatives have split, but it's perhaps the most vocal one.

So what's at stake for the FDA is trying to preserve the credibility of the accelerated approval process, while maintaining regulatory flexibility in the face of changing scientific evidence. The other aspect of this decision at stake is to try to separate the features of this specific decision from the larger battles over health care and government regulation.

Pharmalot: More specifically, to what extent was accelerated approval really on trial?

Carpenter: By the law of averages alone, you could have predicted 20 years ago that a drug launched under accelerated approval was eventually going to face this kind of controversy. Sooner or later, the second-generation evidence on a drug is not going to turn out as positive as the first-generation evidence. The question is how the FDA reacts to this development when the original approval was accelerated.

The procedural issue at stake concerns the provisional character of accelerated approval. The idea, as I argued recently in the *New England Journal of Medicine* ([look here](#)), is that accelerated approval embeds a contract: quicker market launch and clinical access now in return for confirmatory clinical trials demonstrating efficacy later. Yet if there is no circumstance under which accelerated approval can be reversed, then it isn't provisional anymore and both the meaning and enforceability of the contract vanish.

The methodological issue at stake has to do with the value of progression-free survival as a measure of drug efficacy. It is clear that FDA scientists and other oncologists, not just (Richard) Pazdur (who heads the FDA Office of Oncologic Drugs), but a range of officials and scholars have begun to sour on PFS. I'm not in a position to judge the merits of their stance. But the future looks like one where cancer drugs are going to have to demonstrate meaningful overall survival benefits in order to get approval and keep it.

The limits of progression-free survival point to a deeper issue about accelerated approval - it's dependent on surrogate endpoints. But the difficulty of finding valid surrogate endpoints for a range of therapeutic categories is not just a clinical problem; it is also a regulatory problem. And it's not confined to cancer therapeutics alone. Clinical researchers have become more skeptical towards evidence from biomarker-based surrogate endpoints across a whole range of therapies.

Pharmalot: Such as?

Carpenter: Rosiglitazone (Avandia) and C-reactive protein, for instance, or torcetrapib and HDL.

Pharmed: Should the FDA have chosen panelists who did not previously vote on this matter? If yes, why? If no, why?

Carpenter: I wondered about this myself. One could argue that a fresh new set of panelists would have given a more informative signal, both in the sense that it would have sent a signal of greater credibility to the outside community - a larger set of 'voters' - and in the sense that the advisors on this round would have been potentially less attached to their judgments from the previous round.

Yet to change the membership of an advisory committee midstream would establish a really disturbing precedent. There is normal turnover on these committees all the time, but not a common practice of changing membership whenever someone complains about the committee or whenever there is a contentious issue. The division head would need really persuasive evidence of bias, or some evidence that a critical source of expertise or specialized knowledge is missing, in order to change committee membership substantially during review of the same proposal.

Pharmed: The hearing was set up like a trial and created a circus-like atmosphere. Is there a better way to handle such meetings going forward?

Carpenter: The adversarial nature of testimony at advisory committee hearings is not new. There have been 'pro' and 'con' presenters in many cases, sometimes different FDA staffers themselves presenting a case for and against a drug. What was different here was the vitriol of the public discussion. Some witnesses apparently insulted others testifying, while there was also a great deal of acrimony from the audience.

There is certainly a right and a place for people with vested aspirations and interests in the drug to speak their mind. The question is whether an administrative hearing is the right venue for that airing of views. I'm inclined to think that, for patient advocates and those who are not testifying on the scientific evidence bearing on the case, written testimony in the docket will suffice for future meetings of this kind. The Administrative Procedures Act requires no more than this.

Pharmed: How badly will the FDA be weakened if Hamburg does anything other than yank the indication?

Carpenter: There is a line - sometimes slender, sometimes coarse - between flexibility and capitulation. The ODAC voted strongly to reaffirm its earlier position, essentially 24 to 0, or four separate 6-to-0 votes. These votes leave very little wiggle room for Hamburg. If she keeps the MBC (metastatic breast cancer) label, even temporarily or provisionally while Genentech runs another trial combining Avastin and paclitaxel, she would be openly rejecting the judgment of dozens of specialists in the oncology community. She would also override a supermajority on the agency's relevant advisory committee (10-to-1 on the vote last year, and 6-to-0 on yesterday's vote), and she would rebuke Pazdur, but also the director of her agency's entire New Drugs Division (John Jenkins). She certainly has the authority to do all of these things, but exercising that authority could make her remaining tenure shorter and less

respected in the scientific and public health communities.

It's useful to compare this to the debate over Avandia, even though the drugs and the clinical situations were entirely different. There were various agency opinions with David Graham pushing in one direction and Robert Temple (a deputy director at the FDA's Center for Drug Evaluation and Research) and Janet Woodcock (who heads CDER) pushing in another direction. That diversity of internal opinion left a lot of wiggle room for Hamburg. The advisory committee was also split. But here you have Pazdur and Jenkins saying essentially the same thing, and the advisory committee unanimously supporting them. If Hamburg does not remove the indication, the agency's credibility will be damaged and that the accelerated approval process will itself suffer.

Pharmed: How has the public been served by this whole episode?

Carpenter: This may be something of an educational moment for the public, where we learn something about science and something about the working of our institutions. The larger situation is a tragic one. Like many of your readers, I've lost friends - some of them as young as 35 - to breast cancer. And here we have a drug that looked promising for those patients with an advanced form of the disease. And yet as a society, we have learned in this case that science and technology - despite our attempts to endow them with the mythic promise of producing 'cures' for something so lethal as a metastatic tumor - do not always offer easy and predictable solutions we might wish for.

There is another lesson here about institutions and the meaning of liberty in a republic. Access to medicines and technological advances is an important value, but it's neither a constitutional nor a legal right. Obviously, no such right exists explicitly in the Constitution or at law. But no implicit right to therapy exists either. That point has been decided unanimously by the Supreme Court in the Rutherford decision and it was reaffirmed in the full DC Circuit's decision in the Abigail Alliance case (which was in 2007 - [read about it here](#)).

One final thing should be clear. The FDA we are seeing now is a much more complex organization than the simplistic diatribes from some of its critics would suggest. The rigorous methodological position taken by Pazdur and Jenkins, as well as the unanimous votes taken by the ODAC, show that the FDA is not the subservient handmaiden of Genentech and other biotech companies. But I think the right's broad generalizations about FDA risk-aversion are also mistaken, as the recent Health Affairs article on cancer drug approval times shows ([read this](#)). The FDA is much quicker to approve cancer drug applications than the European Medicines Agency and this flexibility has persisted for decades. The public is witnessing a case in which the contours and outcome, so far, have been shaped by an intricate calculus of scientific, regulatory and legal factors.

Comments

**Merrill
Goozner**

Dan says some of the witnesses (I presume he meant members of the

June 30th, 2011
8:29 am

public who signed up to comment) insulted others. One thing I noticed was that most of the patients and family members who came to testify did not say who paid their way, or say no one paid their way. The FDA advisory committee staff usually asks for such disclosures at the beginning of the public comment period, but failed to do so at this meeting.

dude

June 30th, 2011
12:09 pm

true... and then there are the women who died after taking this toxic drug... who represented them? maybe FDA ??????

Justice in MI

June 30th, 2011
12:33 pm

All of this, including Merrill's comment, evokes the '95 saga of Newt & Co. and FDA. And, of course, the players—WLF, WSJ editorial board, Newt himself—have anything but gone away.

Can we expect to see David Kessler remembering it all on PBS? If so, will anyone be listening?

Pharmfresheggs

June 30th, 2011
12:55 pm

The big issue is that PFS may be a good surrogate for OS with chemotherapy, but not for anti-angiogenics. That's a big question, why do we see PFS with anti-angiogenics and not OS, or not as much OS as we might expect? When we have the answer to this question, then maybe we'll know how to use these drugs optimally. In the meantime, we're spending a lot more on these drugs than we should be. It will be interesting to see what the FDA does with the Avastin ovarian data, which has the same problem, PFS but not OS.

**original
industry insider**

June 30th, 2011
2:16 pm

Agree with Dan. Non scientific testimony from advocacy groups should be submitted in writing and read into the record by the secretary. We need to wring the emotion out of these hearings as anybody present would have seen the histrionics displayed over the past two days. If this were a real trial the judge would have emptied the jury box and the audience chamber.

ovadoc

June 30th, 2011
3:34 pm

Good analysis. Seems that best for the patients would be to discover and validate the molecular biomarker(s) that identify which patients may actually respond to bevacizumab. Certainly hard, complex work, but vital for all these \"niche buster\" targeted medicines to succeed and benefit the proper sub groups of patients for any tumor type. It would seem to be time to redirect the blockbuster discovery and development process and mandate companion diagnostics. Perhaps that is the

unintended benefit to eventually come from these proceedings.

Justice in MI

June 30th, 2011
4:29 pm

Wow, my imagining turned out to be reality. The WSJ editorial folks published their opinion today about what they call the Avastin “medical mugging” (almost straight 1995 rhetoric), and included points like,

“So here we have government-anointed medical patriarchs substituting their own subjective view of Avastin’s risks and costs for the value that doctors and patients recognize.”

Who is “subjective,” again? And who, indeed, are the “patriarchs”?

Presumably, they also get their views on the Founders from Michelle Bachmann. And how to throw toy footballs from Hannity.

Justice in MI

June 30th, 2011
7:29 pm

My bad. The WSJ editorial I googled up is on the same issue, but from August 2010, not today. So the question becomes: What will we hear from them now?

Paul

July 1st, 2011
1:13 am

Fascinating piece...extremely well written. Thanks

Salient point

July 1st, 2011
8:32 am

original industry insider-OK, same kind of hearing, roles reversed. In this case, we have a drug whose indication might be expanded to a rare, difficult-to-treat disease (let’s say ALS). Although this drug has been used effectively by a lot of patients for its current indications, some have experienced very serious side effects, & they or their advocates (survivors, caretakers) are going to the hearing.

But they might as well not, because their only ability to participate is a written submission. Because we’re trying to, you know, “wring the emotion out of these hearings.”

Still OK?

original industry insider

July 1st, 2011
9:25 am

Still ok IMHO. This is a scientific inquiry, not a town hall meeting. The open mike session for patient advocacy groups is strictly a courtesy.

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