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Avandia and the Commercial Impact of FDA's Credibility Gap

GlaxoSmithKline's diabetes drug Avandia survived a perilous FDA advisory committee review. The real question is whether the industry can survive the damage to FDA's credibility.

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For GlaxoSmithKline PLC, an FDA advisory committee recommendation that the diabetes drug rosiglitazone (*Avandia*) stay on the market is cause for celebration. There hasn't been a lot of good news for *Avandia* this year, but the overwhelming vote that the drug on the market, albeit with new warnings, was the best outcome possible for the company. "We welcome this decision as positive for patients," GSK chief medical officer Ronald Krall said after the committee vote. "The committee recognized the debilitating nature of this disease and the importance of multiple treatment options."

But the rest of the pharmaceutical industry shouldn't break out the champagne just yet. The committee may have saved *Avandia*, but at the cost of further undermining FDA's already damaged image as a decisive regulator.

A common misconception percolating in drug and biotech companies is that FDA's image problem is strictly an inside-the-Beltway issue. It's not.

FDA's credibility gap ranks as one of the most pressing business problems for drug sponsors for the foreseeable future. The credibility gap creates unprecedented unpredictability in drug development, approval, and marketing. Until it is fixed, that unpredictability will hover over the agency and the industries it regulates. (*See Exhibit 1.*)

That is why the *Avandia* decision may continue to erode the climate for drug development across the board. The joint panel meeting of the Metabolic & Endocrinologic and Drug Safety & Risk Management advisory committees on July 30 undercut FDA's credibility in the eyes of the public in two key ways.

(1) The panel voted almost unanimously in favor of two recommendations that should be mutually exclusive: *Avandia* increases the risk of heart attacks but *Avandia* should remain on the market. The two discordant votes presented FDA with a confusing message to deliver to the public. The experts view Avandia as having a serious safety signal, but they want the drug to remain available for use. For the medical community, that decision can make sense. As a message from an entrusted public regulatory body, it seems almost indefensible.

(2) The meeting showcased the fissure between FDA's Office of New Drugs (the pre-market drug review group) and Office of Surveillance & Epidemiology (the post-marketing safety surveillance group). To the outside observer, and FDA has many now because of the numerous high visibility drug safety issues, it looked like FDA itself has no idea what to do with *Avandia*, since two high level officials essentially contradicted each other about whether the drug should stay on the market. The unprecedented public disagreement also lends support to critics of the agency who claim the new drug group is biased in favor of leaving dangerous drugs on the market too long.

The last thing industry needs right now is more damage to FDA's already battered credibility. But that is precisely what happened in the *Avandia* review.

The "Whipsaw Effect": The Cost of FDA's Loss of Credibility

If you don't think a weak FDA can hurt the drug industry, think again. The cost may be impossible to quantify—or it may be surprisingly easy. How about $13 billion? That is how much value GSK lost from Wall Street's initial reaction to the *Avandia* safety signal.

On May 21, a meta-analysis showing a 43% increased risk of heart attack for *Avandia* patients compared to control was published in an electronic version of the *New England Journal of Medicine*. The analyis was conducted by **Cleveland Clinic** cardiologist Steve Nissen and his colleague Kathy Wolski.

That same day, GSK lost 8% of its market cap, or $13 billion. The stock market was in no mood to wait for FDA to speak on the issue. The market sees, for all practical purposes, that drug safety determinations have been ceded to outside figures with the reputation and ability to generate headlines. Would GSK have lost billions if the investment community trusted FDA as the final word on drug safety? There's little doubt Glaxo's stock price would have taken a hit, but a $13 billion hit in one day?

"No, I think [the hit] would have been less," **MedImmune Inc.** CEO David Mott says. Mott isn't alone. "If there was a stronger FDA, then people wouldn't have been as quick to judge *Avandia* based on what may not be a thorough analysis," agrees Sam Colella, co-founder and managing director of the hedge fund **Versant Ventures**.

And it's not only Wall Street that's not waiting for FDA's response. Physicians fell in line with the safety assessment by Nissen: 40% of GSK's *Avandia* business evaporated in just over three months since the meta-analysis was published at the end of May—a remarkable hit considering the drug has been on the market for eight years.

Maybe most important to the agency itself, Congress isn't waiting for FDA anymore either. The same day the *NEJM* study was published, House Oversight & Government Reform Chairman Henry Waxman (D-Calif.) issued a press release announcing a June 6 hearing on the safety of *Avandia*—hours before FDA was able to get out its own press release about a scheduled media briefing on the study later that day.

As a result, the media and the public knew FDA officials were going to testify before Congress, essentially to defend themselves against negligence, before they knew what FDA had to say about the merit of the findings.

Does What FDA Says Matter Less?

Given the appearance that Congress wasn't interested in FDA's interpretation of the *Avandia* meta-analysis before taking action, there may be a broader implication for pharmaceutical and biotech manufacturers. Outside of outright approval or rejection of a drug, does FDA's opinion matter less? It depends on who you ask.

"I still think what we say matters a lot," Center for Drug Evaluation & Research director Steve Galson, MD, says. "There are a lot more voices and that is, in general, good." Galson acknowledges it is more difficult for FDA to be *the* single voice on drug safety anymore, but he says the challenges FDA faces from outside groups don't diminish FDA's role as a regulator. "I still think that our voice is very important and will continue to be so."

Galson says the public must be able to distinguish between the role of the regulator and everyone else. The role of FDA, he says, is to implement policies and guidelines, provide transparency about sharing information with the public, and stick to the statutory authority given to the agency by Congress. Unlike FDA officials, he notes, "academics are much freer to do whatever they want when it comes to recommendations about drug safety and other public health matters."

But industry executives aren't so sure that FDA has much clout anymore when it comes to drug safety. In the current environment, the agency has not done a convincing job distinguishing itself as the authoritative body on drug safety, according to **Wyeth** EVP for business practices and compliance Bruce Burlington. "All you have to do is look at the *Avandia* scripts," he says. What FDA says "does matter less."

MedImmune's Mott maintains the situation is more complicated than a simple "yes" or "no" answer. "I still think [what FDA says] matters an awful lot to an individual product, to the patients, to the customers and to the company. I think what's happened, though, is there is now another layer of complexity and risk that gets added in, which goes beyond the FDA's position." Companies, Mott explains, now have to worry about outlier positions by individuals outside FDA—individuals like Steve Nissen—while avoiding getting dragged into the political process that has surrounded drug safety. (*See "Shadow FDA? Researchers Are Taking Approval Matters Into Their Own Hands," The RPM Report, December 2005.*)

"Those are just added layers of complexity and risk that didn't used to be as big an element in the drug development process as they have been," he says.

Still, Mott says, the agency's longevity as the gold standard acts as an anchor in a turbulent environment. "The FDA has a reservoir of credibility built over decades. Notwithstanding the recent bashing in the media and political arenas, I think that reservoir still exists."

Mott's right: Not even FDA's strongest critics have come out and said the agency *isn't* the gold standard anymore. But when asked whether FDA's credibility is a real commercial issue for drug and biotech companies, Mott doesn't hesitate.

"Absolutely. Any reductions in either the actual effectiveness or capabilities of the agency—or the *perceived* effectiveness or capabilities and credibility of the agency—increases the already tremendous risks, costs and timelines in the drug development process and hurts the industry and ultimately patients."

"FDA's credibility crisis "does affect our decisions on drug development targets and the risk we're prepared to take on in drug development. Clearly, the safety bar has gone up in the agency over the last few years as we've gone through this cycle of safety questions and credibility assaults on the FDA. That affects how we think about what we're going to develop and how we design and run experiments."

Wall Street and internal R&D programs aren't the only places feeling the negative impact from FDA's credibility gap. The venture capital community is looking at deals through a slightly different lens as well.

"I can think of a deal that I looked at with my partner and one of the factors that led us to turn the deal down was the potential for political, media and FDA risk," Versant's Colella says. The deal involved a company developing a women's health product equivalent to **Pfizer Inc.**'s *Viagra*. One issue, according to Colella, was that the drug treated a "lifestyle" issue and not a life-threatening health condition.

"We looked at it, and I was thinking, this is one where the FDA is going to be sitting there saying 'uh oh, what happens when we approve this and somebody gets hurt?' So we shied away from it." Regulatory risk has always been a critical item on Versant's list of priorities when evaluating a deal, but "it's increased in importance because of the environment now," Colella says.

How Fast is Too Fast and How Slow is Too Slow?

One clear challenge for FDA is deciding how quickly and how publicly to react to new risk information. This is the area where agency officials find themselves in a Catch-22: If FDA officials react too quickly, they may not have an authoritative answer. If they take their time to analyze and validate the data, the agency is vulnerable to attacks for being too slow to act. FDA's Galson thinks the agency can do both without compromising its reputation as the worldwide gold standard.

"We will have to manage information faster; I think that's been very clear to us for some time," Galson says. "We are speeding it up. We are improving our interactions in the Center, and with changes in information technology, there is no question that we have to get information out to the public as soon as possible, and that's good for patients and doctors as well."

In an attempt to upgrade its safety communication efforts, FDA has recently chartered a new advisory group to help specifically on how to explain risks to the public *(See "Not the Usual Suspects: FDA seeks New Advisors for Risk Communication Committee," The RPM Report, July/August 2007.)*

But going public with information much faster isn't always a good idea. In response to the closer attention from Congress and the media on drug safety issues, FDA has gone public with new safety information on several products in recent years that have sent confused messages, messages that probably accomplished very little in terms of changing medical practice—but do contribute to the agency's credibility problems.

So what is FDA to do? On the one hand, the agency has Congress, the media and patients demanding more information and regulatory actions on safety issues sooner. On the other hand, drug and biotech companies are asking the agency to shed what they see to be overly cautious review standards.

One possible solution is for FDA to get more involved with academic journals *before* new safety analyses are published. Galson took particular issue with how quickly *NEJM* published the Nissen analysis, noting that FDA frequently has more information than is available to the public. "I'd be very interested in working more closely with the journals, so that when they are publishing these assessments, we have the opportunity to

comment on them."

"Of course, we don't want to be in the review process, but being given the opportunity to comment based on additional non-public data that may be available to us would be very beneficial for the public and it may reduce the chances of this 'whipsaw effect,'" Galson said.

Within the *Avandia* drug review group there is a strong belief that the Nissen analysis did not merit the urgent treatment it received from the journal publishers. The data, after all, are publicly available already. In the opinion of some current and former FDA officials, the journal is guilty of hyping the safety analysis.

There is a chicken-and-egg quality to that argument, however. Clearly the *New England Journal of Medicine* did not trust FDA to handle the safety issue appropriately—further evidence of the damage done by the agency's credibility problem.

And, whether the journal should or should not have rushed to publication, the impact of the article on medical practice is undeniable: doctors changed their prescribing habits in response to the signal in a way that they hadn't changed them before. If the information in the article wasn't new, clearly it hadn't permeated the physician community yet.

In any event, greater involvement in the external data review process of medical journals is a stopgap at best. Until FDA finds the right balance between speed and rigor when it comes to drug safety, it's only a matter of time before the next *Avandia*.

FDA's Drug Safety Staff Rushes *Actos* Data Into *Avandia* Debate

A key point in the *Avandia* advisory committee meeting illustrates just how difficult it will be for FDA to manage that balance when it comes to drug safety reviews.

During the meeting, OSE director for science and medicine David Graham, MD, presented a meta-analysis of **Takeda Pharmaceutical Co. Ltd.**'s pioglitazone (*Actos*), the other member of the thiazolidinedione class of diabetes treatments. He presented the data even thought it hadn't been "fully reviewed" by FDA officials in the Office of New Drugs.

For Takeda, Graham's involvement must have been terrifying. Graham is the best-known FDA drug safety "whistleblower," a role he has played in more than one congressional hearing: he made a damning presentation during **Merck & Co. Inc.**'s advisory committee meeting for etoricoxib (*Arcoxia*). (*See "The Death of Arcoxia: Drug Regulation in a 'Whistleblower' Climate," The RPM Report, May 2007.*)

But Takeda needn't have worried. The analysis by Graham found that *Actos* had roughly a 25% lower risk of heart attack versus active comparators, including *Avandia*. Graham

emphasized the importance of the Takeda data and noted the study was significantly more robust than the original meta-analysis submitted by GSK for *Avandia*.

To Graham, the apparently superior safety profile of *Actos* argues for pulling *Avandia.* The committee ultimately disagreed.

But the lasting importance of Graham's presentation will not be its impact on the committee deliberations per se, but rather the very public light it cast on the deep fissures within FDA when it comes to responding to drug safety issues. If nothing else, the discussion of the *Actos* data is a compelling case study in what happens when FDA tilts towards acting quickly rather than definitively on a high-profile regulatory issue.

OSE Director Gerald Dal Pan "and I very early in our evaluation on this saw the pioglitazone meta-analysis as the single most important piece of additional data that was needed in preparation for this advisory committee meeting," Graham said.

Graham says he and Dal Pan were promised by OND that the *Actos* analysis would be done in time for the meeting. Subsequently, the OSE officials learned that OND was outsourcing the validation work to Takeda. "FDA said we can't find a statistician—we've got over a hundred statisticians at FDA—to give it a high priority to get the answers," according to Graham

Then, Graham says, OND had trouble finding someone at FDA to oversee Takeda's validation work on the analysis, so a former medical officer was asked to come out of retirement.

Graham's suggestion that OND is somehow dragging its feet clearly rankled other FDA staff at the meeting. Joy Mele, the FDA statistician in the Office of New Drugs who reviewed the rosiglitazone meta-analysis, says the pioglitazone meta-analysis validation was not completed in time because the advisory committee date had been moved up from November to July.

Committee members wondered why the data was presented at all and asked Graham to explain.

"At the end of the day then, I'm sort of faced with a dilemma," Graham told the advisory committee. "Do I present the evidence that we have in-house, that was reviewed by FDA—it's not reviewed the same way as Joy Mele reviewing the rosiglitazone meta-analysis—but keep silent about that and not breathe a word of it, or do I present it? And I presented it."

Dal Pan agreed. "David and I felt that this was a clinically relevant issue, and given what we knew...which has been carefully reviewed by the FDA, we would present some of the early findings from the pioglitazone data with the caveat that these have to undergo

further FDA review."

So given the time restraints in completing the *Actos* review, why didn't FDA keep the original November committee date? Office of Drug Evaluation II Director Robert Meyer, MD, says there were two reasons.

First, there was the pressure for speed again: there was extraordinary public interest in the drug. "It was an issue of transparency—something we've been striving for in other settings," he says. Second, Meyer says the agency wanted to get a process started, anticipating that it might eventually take a long time to get a full picture of the safety risk. It was a more complex decision compared to other cases because of the amount of data coming in to FDA at various times in the review process, Meyer explained.

"As we look at dates, we need to find a balance between having sufficient data for a full discussion...and when waiting another few months is going to give us another piece of critical information." Meyer underscored the importance of the pioglitazone meta-analysis and did not rule out a second advisory panel meeting once the OND review is complete.

A House Divided

The discussion of the pace of the *Actos* meta-analysis review was just the tip of the iceberg when it comes to the differences between the OND and ODS teams on how to handle *Avandia*.

It is not unusual for advisory committees to hear very different interpretations of a data set during a day long meeting. It's just that the differences are usually between a sponsor's analysis and the agency's—not between two different offices within FDA.

But that is what happened with *Avandia*.

FDA OND officials Mele, Karen Mahoney and Kate Gelperin presented their takes on FDA's meta-analysis of the heart attack risk with *Avandia*, the large randomized clinical trials evaluating *Avandia*, and observational studies submitted by Glaxo, respectively. Mele concluded that *Avandia* showed a "nominally" significant increased myocardial ischemic event risk compared to placebo and no evidence of higher risk between the drug and the active controls metformin and sulfonylrea.

As might be expected, ODS' Graham offered a different view. But while in the past, Graham has publicly differed with OND on drug safety issues, it has been while speaking on his own. During the *Avandia* review, Graham's position was explicitly endorsed by his superior in ODS.

"What I present now represents my own view," Graham acknowledged. "But I am

authorized to say the following: my office director, Dr. Gerald Dal Pan, worked closely with me on all of the analyses we'll be showing here. He helped me in putting the talk together, and he fully endorses, supports and agrees with the methods we used; the analyses that I'll be presenting; and ultimately with the recommendations and conclusions that I present."

"This just isn't just 'David Graham, FDA whistleblower and health advocate' talking about a drug safety problem," he said. Rather, Graham's comments carried the weight of the head of the drug safety office at FDA.

With that as a backdrop, Graham went through all the *Avandia* safety data, but the crux of his presentation centered on the meta-analysis of pioglitazone.data on over over 10,000 patients, which indicate a decrease in cardiovascular risk by approximately 25% compared to all comparators, placebo and active drug therapy.

Graham also pointed to a short (24-week) head-to-head study of *Avandia* versus *Actos*, which was submitted to and reviewed by FDA in 2005. *Avandia* demonstrated a 3.5 fold increase in cardiovascular risks compared to *Actos*. The study was designed, however, to assess lipid effects, not CV risk, Graham acknowledged.

But overall, Graham concluded that in the FDA meta-analysis, *Avandia* increased cardiovascular risk by about 40% compared to active control and 70% compared to placebo. And he argued that future studies will not change FDA's "state of knowledge" due to poor design and low statistical power of ongoing studies.

With that, Graham summarized his findings: *Avandia*, he said, increases cardiovascular risk compared to placebo and has no unique benefits related to glycemic control. *Actos* does not increase cardiovascular risk and may decrease that risk. Therefore, he declared, *Avandia* "should be removed from the market."

Showdown over *Avandia*

Graham's presentation set up a public showdown with the Office of New Drugs. Robert Meyer, the head of the Office of Drug Evalution II, was prepared with a written statement countering the drug safety official's interpretation of the data.

"The last talk summarized the opinions of a senior member of the Office of Surveillance & Epidemiology based on his consideration of the various data sets relevant to *Avandia*," Meyer said. "I think it's important the committee understand there's a fundamental disagreement within CDER on the scientific conclusions that should be drawn from the information available."

Meyer argued for a more measured response by FDA. "Speaking for myself, I do not have

a particular opinion at this moment on the correct regulatory action that should be taken with regard to *Avandia*. I do, however, have a profound interest in the FDA making all of its decisions based on good, rigorous, fair evaluation of all the available data that is properly and dispassionately weighed."

Dal Pan immediately followed Meyer: the head of FDA's safety team was steadfast on his position that rosiglitazone should be pulled from the market but open to other interpretations of the vast data presented at the meeting.

"I concur with the overall approach that Dr. Graham has taken to address the issue," Dal Pan stated. "While I may disagree with him on some minor technical issues and the strength of any one given piece of evidence or other, he and I have both concluded that when we look at the data, the balance of benefits and risks of rosiglitazone is not favorable for rosiglitazone."

Dal Pan implied that FDA's *Avandia* meta-analysis and Takeda's *Actos* meta-analysis were the most persuasive in helping him come to his decision. "Pioglitazone appears to be neutral with regard to cardiovascular risk in a way that rosiglitazone does not." He expressed disappointment that none of the completed clinical trials were designed specifically to evaluate risk of myocardial infarction or myocardial ischemia.

"My conclusion is based on an overall public health approach, not a statistical approach," Dal Pan concluded.

Reconciling Contradictory Votes

Given the disagreement within FDA on *Avandia*, it is probably appropriate that the two pivotal votes by the advisory committee went in distinctly opposite directions.

On the one hand, despite raising a number of concerns about the available data—including the short duration of the trials, the low number of cardiac events, a lack of cardiac event adjudication and concerns about the heterogeneity of the study population—the committee still voted 20-3 that *Avandia* increases cardiac ischemic risk in type 2 diabetes.

But when it came to a decisive vote on whether the overall risk-benefit profile for the drug supports its continued marketing, the committee voted almost unanimously in favor of keeping the drug available to patients—with only a consumer representative voting against continued marketing.

It was a surprising moment: two overwhelming votes almost at odds with each other. One of the members who voted against a safety signal wondered at the apparent contradiction. "I'm puzzled how people can vote for both questions," said Thomas

Pickering, MD, Columbia University Medical Center.

"We do have a strong signal in cardiovascular risk from three independent investigative groups," acting committee chair Clifford Rosen, MD, St. Joseph Hospital said. "I'm extremely disappointed that we're not going to get any greater insights from the randomized, placebo-controlled trials. I think there is a signal and I'm quite concerned about that signal."

Committee members attempted to explain the apparently divergent votes. "I would agree that there is a signal," said Morris Schambelan, MD, San Francisco General Hospital. But "I'm very concerned about being asked to throw a class of drugs out...because the TZDs are very valuable drugs."

David Schade, MD, University of New Mexico School of Medicine, agreed: "As a diabetologist, we absolutely need to have a TZD on the market. If we remove rosiglitazone for what I consider a borderline data indication, and in one or two years we find out that pioglitazone causes bladder cancer or something else and we take *it* off the market, we're all going to look back and say, 'why did we do this?'"

Robert Misbin, who was the primary review on *Avandia* when it was approved and is still the primary reviewer assigned to *Actos*, sees the outcome as rational. As a physician, Misbin says, he would not prescribe *Avandia* given the strong indication that *Actos* is the safer choice. But as a regulator, there should be a higher hurdle before the agency decides that no physician can ever prescribe *Avandia*.

Even with those explanations, the two votes are complicated to reconcile. As a result, the meeting did nothing to quell public concern about FDA's handling of the drug. And now the agency has to make up its mind what to do with *Avandia*.

Wrestling Back Control of Drug Safety

GSK avoided disaster during the advisory committee review, but Avandia is a declining treatment at best. (*See "The Race for Avandia's Share: May the Safest Product Win," The RPM Report, July 2007*.) Dal Pan's support of Graham's conclusions—and the availability of Actos as an alternative—effectively applied the coup de grace to the product's commercial future. Avandia may continue to be a treatment option, but one that is sparsely used.

Still, there is a lot at stake for industry when FDA makes a final regulatory decision on the drug. The agency needs to balance the desires of the professional community (reflected in the strong advisory committee vote to retain access to the product) with the analysis of its drug safety staff and its developing reputation as a paper tiger.

The agency has precedents to study: cases where it tried to save a product against a safety signal and then eventually was obligated to remove the drug. One case even esits in the glitazone diabetes class.

Given all that, it may be politically appealing for the agency to step in and take a firmer action than its advisory committee suggested. Certainly no one in industry wants to see another high profile drug withdrawal, but if FDA does opt to pull *Avandia* it would at least have the benefit of bolstering its image with the general public by taking decisive action on a drug safety issue.

Still, most stakeholders think FDA will follow the panel's advice and keep the drug on the market. Former Avandia primary reviewer Saul Malozowski, now a senior advisor on endocrine physiology in NIH's National Institute of Diabetes and Digestive and Kidney Diseases, doesn't think FDA will pull the drug. "They will probably add a warning for a subpopulation of patients and a contraindication for its use with insulin," he predicted.

Tom Garvey, a former FDA reviewer who runs his own drug development consulting business, agrees, citing many of the committee members' concerns that pulling *Avandia* would leave *Actos* as the only TZD on the market. Moreover, "the absolute risk found by Nissen is small, if indeed it exists, and the benefit conferred by Avandia is not inconsequential, especially in certain types of type 2 diabetics."

But then he adds, surprisingly: "All of this having been said, I too get the sense that the drug is probably doomed."

One thing seems clear enough: if the Office of New Drugs has the final say, *Avandia* will stay on the market. The drug is certain to add new warnings about the risks associated with use with nitrates and insulin, but it is highly unlikely OND would end up seeking anything more dramatic—especially given the already dramatic decline in use of the drug.

If FDA does keep *Avandia* on the market with stronger warnings, industry will have to deal with the agency's continued credibility gap as a long-term commercial regulatory hurdle.

Outside of GSK, pharmaceutical and biotech CEOs aren't worried about *Avandia*. After all, it's not their problem. But what they *are* worried about is the reaction to the news that their own superstar drug is the next one being called into question. It's only a matter of time before it's someone else's turn. And the best strategy to guard against panic, down-spiraling stock prices and radioactive script counts is making sure FDA is capable and ready to declare a firm position on the safety of specific products.

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Comments? Email the author at windhover-dc@windhover.com

More Leaks in the Dam: Who's the New Whistleblower on Avandia?

FDA Fast Talk: Health Advisories with Unclear Advice