

EXHIBIT F

FEATURE

DRUG REGULATION

FDA official: “clinical trial system is broken”

FDA investigator Thomas Marciniak has spoken out over drug companies and missing or “bad” data, most famously over rosiglitazone. He tells **Deborah Cohen** how he believes the current research and development process is broken

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The clinical trial system is broken and it’s getting worse, according to longstanding Food and Drug Administration investigator, Thomas Marciniak.

For seasoned observers of the drug approval process, Marciniak will be a familiar name and his comments will come as little surprise. In his 11 years at the US federal agency, Marciniak has been embroiled in high profile controversies that have pitted him against his employer—most notably in his assessment of the diabetes drug rosiglitazone (Avandia). This particular battle is one that he may have lost. The FDA has just decided to reverse restrictions placed on the drug that it had introduced in 2010 partly as a result of his assessment of a trial assessing the cardiovascular risks of rosiglitazone (see box).

His public criticism of companies and data integrity have seen him described as a rebel and a “lone wolf”—an epithet that seems to be tagged to those who voice concerns. However, the drug studies that he has reviewed and found problems with seem to have a knack of finding their way into the US Department of Justice’s investigations in-tray.¹

The latest is a trial by UK drug company AstraZeneca of the antiplatelet drug ticagrelor (marketed in the United States as Brilinta and in the European Union as Brilique).²

“Drug companies have turned into marketing machines. They’ve kind of lost sight of the fact that they’re actually doing something which involves your health,” Marciniak says. “You’ve got to take away the key components of the trials from drug companies.”

Seeds of disillusion

The Mayo Clinic trained doctor is based in the FDA’s cardiovascular and renal division, analysing industry data. His career experiences have left him extremely critical of the whole research and development process—from trial design to conduct and statistical analysis of data.

Although Marciniak says he believes that most investigators are honest, there are shortcomings in the trial model to the extent that he doesn’t know what to trust anymore.

His interest in the conduct of trials was piqued early in his FDA career when he reviewed the EPHEBUS trial, a double blind, randomised placebo controlled trial of the aldosterone antagonist eplerenone, used to treat heart failure after myocardial infarction. It was published in the *New England Journal of Medicine* in 2003.³

Before starting the trial, investigators decided the primary endpoint would be death from any cause and set up the trial to measure this accordingly. But halfway through the study, just before a meeting by the data and safety monitoring board—an independent group of experts who monitor safety and efficacy data in an ongoing trial—the study sponsors added a secondary endpoint (death or hospital admission for cardiovascular events).

The board permitted the addition—not that you would know this from the published article—despite the fact that the trial’s code of conduct stipulated that the board must remain as “independent as possible of interactions with persons involved with the conduct of the trial who might in any way influence decisions relating to the study.

The addition of the new endpoints was beneficial to the company. “They actually were winning very strongly on their primary endpoint,” Marciniak says. “The addition of the new endpoints meant that they won on two things.”⁴

Marciniak has no evidence that the company knew what the data were saying at that point, but it worried him that the company could ignore its code of conduct charter.

Missing data crusade

Eleven years on, there are numerous examples that Marciniak cites as evidence to support his concerns about how drug trials are conducted and overseen.

His latest concern revolves around “missing data.” By this he means participants who withdrew their consent to continue participating in the trial or went “missing” from the dataset and were not followed up to see what happened to them. Marciniak says that this has been getting worse in his 13 years as an FDA drug reviewer and is something that he has repeatedly clashed with his bosses about.

“They [his bosses] appear to believe that they can ignore missing and bad data, not mention them in the labels, and interpret the results just as if there was no missing or bad data,” he says, adding: “I have repeatedly asked them how much missing or bad data would lead them to distrust the results and they have consistently refused to answer that question.”

In one FDA presentation, he charted an increase in missing data in trials set up to measure cardiovascular outcomes.

“I actually plotted out what the missing data rates were in the various trials from 2001 on,” he adds. “It’s virtually an exponential curve.”

Marciniak puts this down to two things. “[This is] partly because subjects have become more aware of their rights to discontinue and less trustful of healthcare providers and partly because one can hide a multitude of sins in missing data,” he says.

After his analysis of a study of the antiplatelet drug ticagrelor—the PLATO trial—where he had documented 26 problems with data, he again brought up his concerns over the extent of missing data with the FDA hierarchy. The PLATO study was published in the *New England Journal of Medicine* in September 2009, but the drug wasn’t approved by the FDA until July 2011—a delay caused in part by Marciniak’s probing.⁵

Marciniak says the problems he spotted included misrecording of the dates of adverse events, leading to events not being counted; failure to submit potential adverse events for adjudication; and not counting events because of withdrawal of consent despite the events occurring beforehand.⁶

“In PLATO the missing data for events was about 13%,” he says.

Marciniak says he filed his review with his boss, Norman Stockbridge, director of the FDA’s cardiovascular and renal products division. Stockbridge did not concur with Marciniak’s concerns. He preferred instead to release his own report two months later which criticised Marciniak. “There are six areas in which the decisions that Dr Marciniak makes in his review lack a persuasive rationale and often lack documentation as to their implications,” he wrote.

The *BMJ* put Marciniak’s concerns to AstraZeneca, which holds the licence for ticagrelor. A spokesperson said that the company is “confident in the results of the PLATO trial, and stand behind our data, which is reflected in the 98 regulatory approvals to date for ticagrelor around the world.”

Safety concerns

Marciniak has butted heads with his employers not only over “missing data” but also over drug safety. One recent battle exposed on the pages of the *Wall Street Journal* earlier this year, saw Marciniak complain to bosses that the agency spends longer on the approval of new drugs than it does examining the safety of new drugs after approval.⁷

The class of drugs that ignited that dispute was the angiotensin II receptor antagonists, such as losartan and valsartan, used to treat hypertension.

A 2010 *Lancet Oncology* paper pooled 68 402 patients and found that people taking angiotensin II receptor antagonists had

a 11% greater risk of new cancer (relative risk 1.11, 95% confidence interval 1.04 to 1.18) and a 25% greater risk of new lung cancer, compared with patients who didn’t get the drugs (0.9% versus 0.7%, relative risk 1.25, 1.05 to 1.49). The authors said their findings warranted further investigation.⁸

A year later, regulators on both sides of the Atlantic gave the drugs the all clear. Marciniak, however, was unconvinced. In 2002, while working for the US National Cancer Institute, he had done a drug review of losartan trials in which he had noted there were more lung cancers in the losartan arm.

So Marciniak took it upon himself to plough through the patient level data of the angiotensin receptor II antagonist trials, which led him to dispute his employer’s meta-analysis. His primary hypothesis was that these drugs might increase lung cancer and filed an analysis plan with his boss. He found the drugs increased the risk of lung cancer by 24% compared with placebo or other drugs.

But the FDA did not count lung carcinoma in its cancer tally, and it relied on study level data. “I think that’s completely flabbergasting. Astounding. And it’s been totally washed over. Why?” he says.

The *BMJ* asked the FDA about this apparent omission and if it was planning to publish its meta-analysis. It said that it was available through freedom of information, adding that the omission of a cancer term was an “accident” that conveys “no bias” on the results. Marciniak says the FDA should release their data, so patients and physicians “can make their own informed decisions.” At a meeting on 25 November, attendees urged the agency to release all its safety meta-analyses.

But his bosses were not impressed by his endeavours. When Marciniak had told the director of the office of drug evaluation that he was intending to conduct the review, he responded, “This would represent a lot of man-hours, so I have to assume that there is a paucity of work in the [cardio-renal] division at this point.”

To which Marciniak replied: “You are faced with a serious, unanswered question of whether drugs taken by millions of Americans increase cancer rates and you’re concerned about 62 to 93 man-days for my entire plan?”

Marciniak says he has not dropped the issue despite the FDA’s seeming lack of interest.

While many of Marciniak’s concerns about data integrity have not garnered headlines, that all changed with GlaxoSmithKline’s blockbuster diabetes drug, rosiglitazone (Avandia). It was partly the result of his probing of the raw data in 2010 that led to the drug receiving such a high profile suspension in Europe and severe prescribing restrictions in the US because of concerns over its cardiovascular safety.

The FDA decided to compel GSK to send its data to a third party, in this case Duke Clinical Research Institute in North Carolina. The institute presented its findings at an FDA meeting in June this year (see box).

Before the meeting, Marciniak produced a memo that claimed that the readjudication, undertaken by Duke could not be considered independent, citing financial backing and data that both came from GSK—a point that the institute’s associate director, Kenneth Mahaffey, denies.

Marciniak’s interference wasn’t well received by his employers. A day after he filed his review, the FDA produced a memo offering their view of his analysis of the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) trial that damned his use of “regrettable” and “unprofessional” language and said his

report was unsolicited—points that Marciniak vehemently rebuffs. Indeed, this week the agency decided to lift the restrictions on Avandia that were put in place in 2010 after Marciniak presented his analysis of the RECORD trial to an advisory committee meeting. But Marciniak is unrepentant.

“If I, as a federal employee or simply as an ethical individual, see evidence of a threat to public health, I have an obligation to report it regardless of whether the issue is assigned to me or not,” he says. Marciniak contests that his employers want to discredit him, and his paranoia is perhaps supported by an article in industry trade publication, the *Pink Sheet*.

“The advisory committee’s lukewarm response to Marciniak’s critique of Avandia suggests that his concerns about ARBs [angiotensin-II receptor antagonists] are unlikely to gain broad traction,” an article in June said.⁹

But what can be done to avoid such confusion and antagonism in future? Former editor in chief of the *New England Journal* Marcia Angell has suggested that drug companies should not run their own trials, but Marciniak thinks that would throw up a set of problems of their own. He advocates removing some of the oversight of trials.

To make his point, Marciniak highlights one particular instance in the RECORD trial. An investigator reported that one participant had had a heart attack but later changed his mind.

“Sixteen or eighteen months later he [the investigator] suddenly supposedly woke up and decided it wasn’t a heart attack. I rather doubt it,” he says. “That’s a good example, I think, of something that should never happen.”

“I think what could be done is actually to have all of the data provided from the sites, from electronic clinical study reports directly into the regulatory authority as well as directly to the sponsor,” he says. The FDA would then be able to store them.

“With what the investigator initially sent in I think we would be miles ahead in terms of them being able to verify whether the data are complete or not,” he says. He also says that randomisation should be taken away from the companies and done by the regulator.

But the chances of success are small.

“I’m not terribly hopeful on having it adopted just because I think the drug companies will resist tremendously because right now, 100% true, they control the data.[It’s] very, very difficult to verify whether data are complete or accurate,” he says.

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GSK and the *Fat Duck* challenge

In June this year, GlaxoSmithKline's commitment to data transparency was questioned publicly by Thomas Marciniak, from the FDA's cardiovascular and renal division. He threw down the gauntlet to GSK chief executive Andrew Witty, at a two day hearing to discuss diabetes drug, rosiglitazone, in June this year.

Marciniak, on his government salary, would personally treat Sir Andrew and five staff members to a lavish meal at Heston Blumenthal's three Michelin starred restaurant, the *Fat Duck*, just outside London, if he released all the data from the RECORD trial.

"The CEO of GSK has been making a campaign to say they believe in data transparency and he's going to release all the data. The data, I'm told, is already completely redacted, so it should be trivial for him to in fact send it out and let the public judge whether my complaints are right," he told the hearing.

The RECORD trial—which was published in the *Lancet* in 2009¹⁰—has a long and chequered history. Commissioned by the European Medicines Agency after it licensed rosiglitazone in 2000, the trial was supposed to resolve questions over associated cardiovascular risk. It has done anything but. Its interpretation sparked a bitter feud—the trial design was criticised at the June meeting and there's a dispute whether anyone other than GSK and the US Department of Justice has seen the entire dataset.

The published study found no increased risk of myocardial infarction or stroke in the rosiglitazone arm (hazard ratio 0.99, 95% confidence interval 0.85 to 1.16). The hazard ratio was 0.84 (0.59 to 1.18) for cardiovascular death, 1.14 (0.80 to 1.63) for myocardial infarction, and 0.72 (0.49 to 1.06) for stroke.

But when Marciniak probed the raw data in 2010, he found 11 different conduct problems including failure to refer events to the board for adjudication, missed endpoints, insufficient collection of information, and issues with data handling that could have affected the results of the trial.¹¹

The FDA's resolution was to compel GSK to send its data to a third party, in this case Duke Clinical Research Institute in North Carolina. The institute presented its findings to the meeting in June. The institute's associate director, Kenneth Mahaffey, agreed with the conclusions on risk in the *Lancet* publication,¹² although he also concurred with Marciniak's judgments in three out of the four cases that he'd highlighted as significant events. In the fourth case, Marciniak contests that the data were too sparse. The other seven cases raised by Marciniak were not discussed.

It seems that the FDA has accepted Duke's findings. Earlier this week, the agency released a statement saying it was going to remove certain restrictions on prescribing and use of the drug to reflect "new information regarding the cardiovascular risk of the medicine." It said that there was "no elevated risk of heart attack or death in patients being treated with Avandia when compared to standard-of-care diabetes drugs."

Marciniak is not comforted by this conclusion. He's not convinced that even he as a regulator has had access to all the data. Nor is he convinced that Duke University has seen all the data from the RECORD trial: "Those data are the case report forms for cardiovascular events—the FDA didn't have them all and yet signed off GSK's submission as complete." The forms contain information about any myocardial infarctions or strokes and without them Marciniak says you can't verify whether the events occurred. GSK said that in their original FDA submission of the RECORD data in 2009 that blank entries for cardiovascular outcomes were "not databased"—a term Marciniak has not received an explanation for.

But questions to GSK do not help to clarify. A spokeswoman for GSK said the *BMJ* needs "to ask Dr Marciniak what he means."

In its press release announcing the removal of the restrictions on rosiglitazone, the FDA said it had asked an "independent group of scientists to readjudicate key aspects of RECORD."

But Marciniak has questioned the independence of this evaluation—he says that Duke was neither operationally nor financially independent of GSK. Both Duke and GSK refuted this—and so clearly have senior FDA officials.

At the meeting, Mahaffey said: "We did not perform any systematic investigation of the data to assure that we had every single page of the case report form received."

The *BMJ* asked Mahaffey about this comment. He said that the procedures employed for the re-evaluation effort included that GSK was to provide Duke with all the patient information. "Researchers did not go to the source files at GSK to confirm that what we received was all of the information in the source files," he said.

No one other than GSK stated during the FDA meeting that the data supplied to Duke were complete, Marciniak adds—a point which Mahaffey denied to the *BMJ*.

"Duke refused to verify that they had the complete data," Marciniak contests.

A spokeswoman for GSK said: "We can tell you that the case report forms that were sent to the FDA had all of the required information. We sent all paper and all electronic records to Duke."

She also said that GSK has a process in place by which researchers can apply to see clinical trial data. "Researchers can request access by providing a scientific protocol with a commitment to publish their findings. Their protocol will then be reviewed by an independent review panel."

So the situation has gone full circle. Will Marciniak apply through the GSK system? His answer reflects his lack of faith in the system. "I have no time and no hope for approval of such a request," he said.