
# ROSIGLITAZONE WHAT WENT WRONG

Over 10 years after the diabetes drug rosiglitazone was approved by regulators, and despite studies on tens of thousands of people, questions remain about its cardiovascular safety. An investigation by **Deborah Cohen** looks at why this happened.

It was, as one Food and Drug Administration (FDA) adviser put it, a "perfect regulatory storm"—a combination of problematic data, uncertain clinical need, politics, and poor drug company behaviour.

Now, 10 years after its approval by regulators in the United States and Europe, the widely prescribed blockbuster diabetes drug rosiglitazone may be about to fold. Two months ago, in July 2010, the FDA convened a 33 member expert advisory panel to decide whether it should be withdrawn from the market in the light of evidence that it may increase the risk of myocardial infarction. Earlier this year a US Senate finance committee report had detailed concerns about the paucity of evidence to support the use of rosiglitazone and about the way in which the drug was evaluated and licensed.[1]

At the advisory meeting, members of the public heard a damning analysis of the RECORD trial, commissioned by the European Medicines Agency (EMA) when it approved the drug in 2000 in order to determine its safety. Millions of prescriptions later and with the drug still on the market around the world, this trial and other post-marketing surveillance have failed to resolve the concerns.

To date, the FDA and the EMA have decided that the drug is safe enough to stay on the market. But the story reflects badly on almost everyone involved: the regulators, the manufacturer, GlaxoSmithKline, and the clinical community. It has also raised a host of questions. Why did the regulators accept such poor evidence on benefit and safety for rosiglitazone? Did GlaxoSmithKline mislead the regulators? Should the drug have been licensed in the first place and should it now be withdrawn? Why haven't patients in the UK and Europe been made aware of the concerns about rosiglitazone's effects? And is the current drug regulatory system up to the job?

The FDA meeting was held in the open, in front of a packed audience including the world's media. Ahead of the meeting, the FDA published the 765 page report circulated to panel members.

This is far removed from the secrecy shrouding proceedings at Europe's regulator, the EMA. The *BMJ* has talked to a range of experts close to the European regulatory process and submitted a series of Freedom of Information requests to the EMA, but we still have no clear picture of why, after initial rejection in October 1999, the EMA gave market authorisation to rosiglitazone in July 2000 in the absence of new evidence. Neither have doctors and patients been told that in July the UK's Commission on Human Medicines— in an unanimous vote— advised the Medicines and Healthcare products Regulatory Agency (MHRA) to withdraw the drug. In a statement, the MHRA has confirmed that the evidence now suggests that the risks associated with rosiglitazone outweigh the benefits and "that it no longer has a place on the UK market." But a "dear doctor" letter sent to UK doctors in July advised doctors to "consider alternative treatments where appropriate."[2] The MHRA said that it used the information provided by the Commission on Human Medicines to push for a UK withdrawal as part of the Europe-wide review by the European Medicines Agency.

Rosiglitazone is one of two available glitazones known to reduce blood sugar and was heralded as a much needed new approach to improving outcomes and long term complications, including cardiovascular disease, for people with type 2 diabetes. Of the other glitazones, troglitazone was withdrawn in 1997 in the UK and in 2000 in the USA because of hepatotoxicity; pioglitazone remains on the market as a competitor to rosiglitazone.[3]

### A paucity of evidence

Concerns were expressed early on about the paucity of evidence to support rosiglitazone's use. According to documents obtained under the Freedom of Information Act, advisers to the EMA noted the lack of good evidence during its approval process.

In comments sent to the EMA approval meeting in 1999, one expert adviser noted that without a long term study with hard primary endpoints it was not clear whether rosiglitazone would have any beneficial impact on cardiovascular disease. This adviser also questioned whether you could put a drug on the market without these long term data and was unconvinced that rosiglitazone in combination therapy offered any advantages over what was already available—metformin and sulphonylurea combined, or insulin.

Another adviser pointed out that safety problems were evident in the data presented by GlaxoSmithKline (then SmithKline Beecham) and asked the panel whether they should postpone approval until better data were available.

Silvio Garattini, a member of the EMA panel in 2000 that approved the drug and director of the Mario Negri Institute for Pharmacological Research, told the *BMJ* that the documentation presented for approval was initially poor and that the studies were of a relatively short duration. The initial decision to reject the drug was overturned despite there being no new evidence, he says.

When rosiglitazone was approved, even clinicians who were nominally supportive of the drug remarked about the poor evidence base and lack of long term clinical trials.[4]

After approval, three EMA panel members—whose names were redacted from the minutes

**CLINICAL IMPLICATIONS**

According to John Yudkin, emeritus professor of medicine at University College London and endocrinologist; "No new patients should be started on rosiglitazone, and patients already taking it should be reviewed and alternative treatments considered. Those at higher risk of heart disease should be advised to stop taking the drug."

Rosiglitazone was approved by the FDA in 1999. The same year it was rejected by the EMA, but was later approved upon appeal

Silvio Garattini was on the EMA committee which approved the drug. He was concerned that the long term risk/benefit was unknown

Steven Nissen, a cardiologist at the Cleveland Clinic, published a meta-analysis in the *NEJM*. This drew public attention to the increased risk of heart attacks

Janet Woodcock, head of the FDA's Center for Drug Evaluation and Research admitted there were divisions within the FDA about withdrawal

The Commission for Human Medicines, which advises the MHRA, voted unanimously to withdraw the drug in July this year saying the risks outweigh the benefits

sent to the *BMJ*—remained concerned that "the long term risk/benefit of rosiglitazone is still unknown and that there are several safety concerns."

The EMA told the *BMJ* that the principal safety concerns at the time were that rosiglitazone induced weight gain, with possible serious cardiovascular effects; the induction of anaemia; and that rosiglitazone raises blood lipids, although this effect was of unknown clinical relevance.

### Why did the EMA let it through?

Given these concerns and the lack of good evidence, why did the EMA approve rosiglitazone?

Garattini said that rosiglitazone is "an example of what happens for drugs that have large commercial interest such as the antidiabetic drugs."

When appealing against a decision not to approve their drug, Garattini says pharmaceutical companies bring forward opinion leaders who are obviously favourable. These paid advisers give presentations to the regulators and companies turn to them whenever an oral presentation is required.

On receiving the negative opinion Jan Leschly, chief executive officer of SmithKline Beecham, told the press it was "a temporary setback," adding that "in the coming months we will be working with the committee to address their concerns. We are confident that by the end of March we will have demonstrated Avandia's unique benefits in the treatment of type 2 diabetes to the CPMP [Committee for Proprietary Medicinal Products]."[5]

According to Edwin Gale, a diabetologist and adviser to European regulators, in the years before rosiglitazone's approval diabetologists were also putting pressure on the regulators and clamouring to use this new class of drug. Some of this clamour was fuelled by pharmaceutical analysts touting its blockbuster potential, which at the time they said was crucial to SmithKline Beecham's future growth.[6 7]

"There were tremendous expectations about Avandia—partly because scientifically it was extremely interesting. It was a whole new model of the way a drug could act. It affected the body and its energy metabolism in totally new ways that were very interesting and fascinating," said Gale.

One anonymous member of the EMA committee that approved rosiglitazone in 2000 told the *BMJ* that he had been contacted by respected members of the diabetes community to urge him to approve the "wonder" drug, something he had not experienced before.

Speaking at the European Association for the Study of Diabetes (EASD) annual conference in September 1999, diabetologists urged the use of rosiglitazone as a first line treatment for type 2 diabetes.

"Unlike most traditional drugs for type 2 diabetes, rosiglitazone works in a novel way to reduce insulin resistance, helping the body's own insulin work more effectively and offering patients improved glycaemic control, as measured by fasting plasma glucose. The hope is that this will slow long-term deterioration," Dr David Matthews of the Oxford Diabetes and Endocrinology Centre told the meeting.

But it was this new way of working—the stimulation of genes that acted on more than blood glucose—that would account for its adverse effects. This should have led to greater caution in the regulatory process, says Gale.

In 1999 in the United States, pressure was on the regulators to fast track rosiglitazone to provide a safer alternative in the same class of drugs as troglitazone.[8]

For example, in the weeks leading up to the FDA's initial approval meeting in 1999, the American Diabetic Association affirmed the importance of glitazones on its website. "These drugs have mechanisms of action—working directly on insulin resistance—that are not shared by other drugs in other classes for treating type 2 diabetes. These drugs offer new options to health care professionals who treat people with type 2 diabetes and represent important advances in drug therapy," it said.[9]

### Was there a need?

Before the final approval, the EMA committee discussed whether there was an unmet need among the treatment options currently available for diabetes and whether a niche indication could be appropriate. Minutes of the meetings show that this suggestion won out. The committee decided that rosiglitazone could be used in combination with other oral antidiabetics as a second line treatment in certain circumstances.

However, Garattini, who was on the panel, was not convinced. "There was no need for another antidiabetic drug—there are so many already that are more or less the same," he told the *BMJ*. And as one adviser from the FDA said at an advisory meeting, it's for the regulators to protect public health and not to equip physicians with a broader array of medicines for clinical choice.

### The RECORD trial

Confronted with weak evidence and an appeal from GlaxoSmithKline to reconsider its decision to reject the drug, the EMA's committee discussed whether additional clinical trials should be required before or after marketing authorisation. In the event the committee approved the drug with the requirement for two additional studies once the drug was on the market. The first was study 211, a double blind trial of the effect of rosiglitazone on cardiovascular structure and function in patients with type 2 diabetes and chronic heart failure. And the second was a randomised trial of six years' duration with the composite outcomes of cardiovascular hospitalisation and cardiovascular mortality—the RECORD trial.[10 11]

## TIMELINE

**1999**
APRIL: American Diabetes Association declares that the drug's properties are not shared by any others, offering new options to healthcare professionals
MAY: Rosiglitazone approved as monotherapy by FDA with label precautions for use in patients with heart failure
OCTOBER: Rosiglitazone turned down by EMA by 14 of 25 votes

**2000**
JULY: Rosiglitazone given market authorisation in Europe with restrictions and with warnings on heart failure. GlaxoSmithKline (GSK, then SmithKline Beecham) is asked to conduct two post-marketing trials: one study to look at effect on cardiovascular structure; the other to assess cardiovascular safety—the RECORD trial.
OCTOBER: Pioglitazone approved in Europe

**2001**
FEBRUARY: FDA approve new warnings on potential for heart failure

**2004**
With an increasing number of people taking rosiglitazone, World Health Organization picks up safety signals and alerts GSK
June: GSK ordered to publish summaries of results of all its clinical trials on its website once a product has been launched in a settlement in New York


**2005**
SEPTEMBER: Internal GSK meta-analysis finds 29% non-significant increased risk of ischaemic cardiovascular events

**2006**
APRIL: FDA approves new warnings on risks of cardiovascular events
MAY: Internal GSK meta-analysis finds 31% increase in ischaemic events

According to Bo Odlind, EMA rapporteur at the time of the SmithKline Beecham's first attempt to get Avandia approved in 1999, the EMA committee believed it was important to do a cardiovascular outcome study rather than one looking only at surrogate endpoints such as haemoglobin A1c—although he is critical of the RECORD trial's open label unblinded design.

And Odlind isn't the only person to be critical. In an internal memo, Thomas Marciniak, a drug approver for the FDA, wrote: "We did not review the protocol [of the RECORD trial] prior to study implementation. If we had, we would have judged it to be unacceptable"[11]

It seems GlaxoSmithKline knew this. A company slide show cited in a US Senate finance committee report noted that the RECORD trial did not provide sufficient data to test for cardiovascular safety. It also noted that GlaxoSmithKline was trying to create studies to counter the PROactive study on rival drug, pioglitazone (Actos) that Takeda planned to release.[1]

In a statement to the *BMJ*, GlaxoSmithKline said that this was not the case. RECORD met its primary endpoint. "The study confirmed its primary hypothesis. It showed that cardiovascular hospitalisation or cardiovascular death (which includes heart attack, congestive heart failure, and stroke) was not statistically different between the two groups after an average of 5.5 years of therapy."

However, the EMA told the *BMJ* that it acknowledged weaknesses in the trial, including a low event rate in a high risk population of patients with diabetes, a high loss to follow-up, and the open label design of the study.

"The RECORD study was designed some 10 years ago. Since then the design of post marketing studies has evolved," a spokesperson for the EMA said.

### Problems with post-marketing surveillance

But even without the flawed design, was commissioning a trial after approval to resolve safety concerns the right approach? Garattini says that regulators request additional trials after approval to overcome a stalemate when concerns about toxicity exist. "It is not the best way because you need a long time to do the study and meanwhile the drug remains on the market. By the time the study is finished the drug patent is finished so there is no inconvenience to the company. This is what happened with sibutramine as well, which was eventually withdrawn," he says.

Garattini is concerned more broadly about the current reliance on drug companies to perform post-marketing surveillance. "The EMA has never produced a document indicating the percentage of fulfilment of such commitments," he says. "For the FDA, it's about 30%." The *BMJ* has asked the EMA to say how many companies carry out their post-marketing surveillance commitments to be told that it has never published a comprehensive report on post-marketing commitments. But a study on the number, type, and status of post-authorisation studies requested by the CPMP or centrally authorised products in the year 2007 until 2010 is pending.

### Agencies swamped

Another flaw in post-marketing surveillance is that regulators sometimes fail to act on safety information appropriately when they are given it. In 2004, with increasing numbers of people taking rosiglitazone, signals of adverse events were picked up by WHO. They sent GlaxoSmithKline an alert about cardiac disease. GlaxoSmithKline conducted a meta-analysis and confirmed an increase in cardiac events to the FDA and the EMA in 2006.

The FDA has been accused of sitting on the reports and not sufficiently alerting the public.[12]

"These data were kept from the public because of acceptance of the proprietary nature of companies' trial results, even when they concern the safety of marketed drugs—a proposition that badly needs public debate and reconsideration," Jerry Avorn, professor of medicine at Harvard University, told the *BMJ*.

Labelling in Europe by the EMA was updated shortly afterwards to reflect the results of the GlaxoSmithKline meta-analysis, with cautions about cardiovascular risk.[13]

### Sales still booming

Safety concerns didn't seem to hit sales of the drug, and in early 2006 GlaxoSmithKline won approval for a combined product of rosiglitazone and glimepiride in both the US and Europe.[14] Rosiglitazone remained in wide clinical use. At the end of 2006 and beginning of 2007, the sales of Avandia were up.[15 16] It was GlaxoSmithKline's second biggest drug, making an estimated $3billion per year.[17] And it was outselling its rival, pioglitazone.[18]

### Beginning of the end?

But in 2007, the fortunes of rosiglitazone began to change with the publication of a meta-analysis of GlaxoSmithKline's study reports by Steve Nissen and Kathy Wolski in the *New England Journal of Medicine*.[19] It claimed that rosiglitazone was "associated with a significant increase in the risk of myocardial infarction" compared with placebo or other antidiabetic regimens. When the adverse effects of the drug became widely known in the wider medical community, sales halved.[17 20]

Nissen's ability to access study reports arose out of a court case in New York. As part of a settlement with the state over GlaxoSmithKline's non-disclosure of possible heightened suicide risk among teenagers taking antidepressant paroxetine (Paxil) the company had to put all its recent clinical studies on a website.

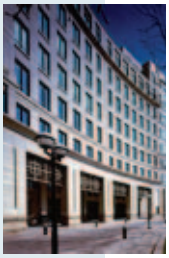
Whatever the criticisms of this particular meta-analysis were, it allowed academics to scrutinise the study summaries.

**2007**
MAY: *New England Journal of Medicine* publishes meta-analysis reporting 43% increased risk of myocardial *infarction*
JUNE: NEJM publishes interim analysis of the RECORD trial
JULY: FDA advisory committee finds increased cardiac ischaemic risk but votes to keep drug on market
OCTOBER: European Medicines Evaluation Agency asserts positive benefit-risk profile, recommends new warnings for patients with ischaemic heart disease
NOVEMBER: FDA approves new boxed warnings that drug may increase myocardial ischaemic events, including myocardial infarction, though evidence "inconclusive"
DECEMBER: UK Medicine and Healthcare products Regulatory Agency warns drug might be associated with small increased risk of cardiac ischaemia

**2008**
Updated internal GSK analysis finds no risk of myocardial infarction or other major cardiovascular events

**2009**
MARCH: *International Journal of Cardiology* meta-analysis finds no risk of myocardial infarction
JUNE: RECORD trial published in the *Lancet*. EMA adds a statement to its scientific information document saying there was no difference in the number of adjudicated primary endpoints between the arms of the study

**2010**
FEBRUARY: US Senate finance committee releases report that includes internal FDA safety report calling for drug to be withdrawn
JUNE: David Graham's study leaked to the Pharmalot blog. It is published in *JAMA* regardless. At the same time, another *JAMA* journal, *Archives of Internal Medicine*, publishes an updated meta-analysis by Steve Nissen
13-14 JULY: FDA advisory committee meeting held. FDA drug approver gives damning verdict on the RECORD trial. Majority of committee vote either to withdraw the drug or restrict it severely
15 JULY MHRA meet. Commission on Human Medicines vote to withdraw rosiglitazone
TIDE trial suspended by the FDA
19-22 JULY: EMA (left) meet to discuss rosiglitazone
26 JULY: the MHRA send out "dear doctor" letter advising doctors to consider alternative treatments where appropriate
SEPTEMBER: EMA will finalise its review



"It's important to realise what an important role publicly available trial results data played in the rosiglitazone story. Having this information posted on the GlaxoSmithKline website made it possible for Steve Nissen to perform his critical meta-analysis published in *NEJM* in May 2007, which really 'broke the case wide open' on this matter," says Jerry Avorn, professor of medicine at Harvard Medical School.

"Requiring the posting of clinical trial results on clinicaltrials.gov should help provide a warning system for other drug risk issues in the future, as will the growth of FDA's new Sentinel system for post-marketing surveillance. The Avandia case provides compelling evidence of the vital necessity and importance of both of these developments," he added.

### FDA rules allowed greater scrutiny

For those with access only to the medical literature, unpicking the evidence behind rosiglitazone has not been easy. Bristol University diabetologist, Edwin Gale—who was chair of the EMA's scientific advisory group on diabetes—complained in 2001 in the *Lancet* how little data on rosiglitazone had been placed in the public domain. Company documentation at that time cited five confidential files, 13 abstracts, and four papers (two of which were clinical) for rosiglitazone.[3]

The regulators have access to more information. Since the 1950s, FDA rules have required drug companies to turn over all individual patient case reports from their clinical studies, not just the statistical summaries but the reports that permit re-analysis of how each case was coded.

It was the availability of these case reports that allowed Thomas Marciniak, an FDA medical officer, to scrutinise the RECORD trial. He was asked in October 2009 to review the cardiovascular events in the trial.

GlaxoSmithKline's own analysis showed that 321 (14.5%) patients treated with rosiglitazone compared with 323 (14.5%) controls experienced either cardiovascular death or hospitalisation. In essence, rosiglitazone did not cause more cardiovascular problems than metformin or sulphonylureas.

The EMA accepted these findings when it received the findings of the completed trial in 2009. "No difference in the number of adjudicated primary endpoint events for rosiglitazone (321/2220) versus active control (323/2227) (HR 0.99, CI 0.85-1.16) was observed" the EMA's scientific summary said.[13] It took the FDA to thoroughly analyse the trial, which raises questions about the EMA's ability to oversee post-marketing trials.

The FDA had the individual case reports to do a more thorough job, but not the resources. In house statisticians could not wade through the voluminous RECORD trial dataset—running to 1438 pages for one patient, and several hundred pages for most of the other 4500 patients. But Marciniak analysed 549 patient case report forms, including 278 from the rosiglitazone group and 271 controls. Of these 549, 100 were a random sample and the rest had been the subject of adjudication disputes.

Marciniak found problems that cast doubt on GlaxoSmithKline's analysis, which he detailed in his damning report for the July FDA advisory committee.

His concerns were over study design, confounding variables that could have biased the overall findings, and the conduct of the study. He considered that these limit "any reassurances that RECORD can provide regarding the CV safety of rosiglitazone."[1]

Much of his concern hinged on data ascertainment in patients who stopped the trial or were lost to follow-up. Marciniak detailed 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.

Specifically, he detailed eight failures to refer patients for adjudication—all in those taking rosiglitazone. "The eight cases weren't the only problem cases I found. I classified the problem cases into categories and the eight were ones of 'failure to refer for adjudication.' Of 549 patient case report forms reviewed I found 70 serious problems, four to one favouring rosiglitazone," he said in an interview.

GlaxoSmithKline says there was no wrongdoing. In a statement to the *BMJ*, a GlaxoSmithKline spokesperson said "An inspection of the RECORD study by the FDA concluded that there was no evidence of systemic or pervasive findings that would undermine the reliability of the RECORD data."

Nevertheless, in his report Marciniak said: "While these numbers may seem small compared to the size of the trial, note that about 15 more [myocardial infarctions, MI] in the rosiglitazone arms are needed to change the GlaxoSmithKline MI results to a relative risk of 1.4 and a p value of 0.042"—which would make an increase in myocardial infarction statistically significant.

Marciniak said it was "a huge challenge to try to find those few needles in the haystack," and it's certainly too much for the under-resourced European regulator. But it's a job that's needed, he says. According to Odlind, unlike the FDA, the EMA takes a top down approach—it takes the study summaries and asks the drug companies for more data if it sees fit.

Marciniak is a keen advocate of accessing raw data: "You will not find the truth in drug review unless you dig," he told the *BMJ*. "I believe the FDA approach is better or potentially more thorough than the EMA's, but it also needs more complete implementation. One public suggestion has been to release the raw data to academic

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- Analysis: Patients and the public deserve big changes in evaluation of drugs (*BMJ* 2009; 338:b1025)
- Research: Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone (*BMJ* 2009;339:b2942)
- Editorial: Rosiglitazone or pioglitazone in type 2 diabetes? (*BMJ* 2009;339:b3076)
- Research: Association between industry affiliation and position on cardiovascular risk with rosiglitazone (*BMJ* 2010;340:c1344)
- Feature: Rosiglitazone, marketing, and medical science (*BMJ* 2010;340:c1848)

organisations. That would be an advance, but I believe that most of the academic organisations don't realise that you need not only raw computer data files but also the case report forms and a variety of other source documents to understand completely a study," he said.

GlaxoSmithKline had employed an independent statistician, as is a prerequisite for the publication of pharmaceutical sponsored trials in some medical journals, notably *JAMA*. Marciniak does not blame the statisticians for not picking up the flaws in the case reports, as they can work only with what is given to them.

### Shining a spotlight on GlaxoSmithKline

Neither the Nissen meta-analysis nor Marciniak's digging show GlaxoSmithKline in the best light. In a Senate committee finance report published in February 2010, GlaxoSmithKline executives stood accused of focusing "on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk." Internal documents show that GlaxoSmithKline quickly published an interim report of the RECORD trial to counter the negative effect of Nissen's meta-analysis.[1]

The company, however, said in a statement that the interim analysis of the RECORD study was conducted urgently to "gather additional information about the potential risk for patients."[21]

To add to the company's woes, on the day of the committee meeting this year the *New York Times* splashed with allegations that GlaxoSmithKline—then known as SmithKline Beecham—had started a secret trial to see if rosiglitazone was safer for the heart than pioglitazone.[22] "Not only was Avandia no better than Actos, but the study also provided clear signs that it was riskier to the heart. The company did not post the results on its Web site or submit them to federal drug regulators, as is required in most cases by law," the article alleged.

To date, there are no head to head trials of the two drugs in the public domain—companies do not have to demonstrate added therapeutic value under European Union or United States law.

The news story went on to quote from an internal company memo: "'Per Sr. Mgmt request, these data should not see the light of day to anyone outside of GSK,' the corporate successor to SmithKline."

GlaxoSmithKline, however, say that the emails were "selectively disclosed by lawyers seeking damages" and that "other documents [were] taken out of context, which therefore are incomplete and misleading." They also said that the "assertion that this study informed GSK's views about heart attacks and Avandia is completely unfounded."

### Decision time

As Gerald Van Belle, director of the Clinical Trials Center at Washington University and FDA advisory panel member, put it—it was a "perfect regulatory storm."

At the hearing in July, the FDA panel voted that the available data supported a conclusion that rosiglitazone increases cardiac ischaemic risk in type 2 diabetes patients.

**Will regulators, industry, and the clinical community do a better job for patients next time?**

But the question of what to do raised mixed answers. There were five options to choose from, ranging from the removal of the black box warning to withdrawal—and the breakdown of the votes would mean that it could be subject to interpretation. A majority of votes recommended keeping the drug on the market, but with more warnings or restrictions. But viewed in a different way, a majority recommended either removal or severely restricting access to rosiglitazone. However, they voted to continue the TIDE trial—a study commissioned by the FDA to assess rosiglitazone's cardiovascular safety—which some argue the FDA should have asked for at the outset. This trial has since been put on "clinical hold" by the FDA.

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, admitted the advisory meeting featured conflicting opinions between two branches of the FDA.

Marciniak agrees: "The Avandia advisory committee meeting was a battle between the "diggers" [Marciniak and a few others] and the "deliberators," [meaning] the rest of the FDA and most of the committee and, I believe, the EMA."

Trying to gain an overall perspective of deliberations within the EMA has been far trickier. The *BMJ* attempted to speak to people who had sat on panels for the MHRA and the EMA. But they were bound by confidentiality clauses. The EMA would not release the names of the members of the scientific advisory group discussing rosiglitazone under the Freedom of Information Act. Secrecy also shrouds the UK's regulatory agency.

### Where next for diabetes drugs?

While the focus has been firmly on rosiglitazone, what about pioglitazone? Its manufacturer Takeda had benefited from the controversy of rosiglitazone. But like rosiglitazone, pioglitazone is associated with an increased risk of oedema, heart failure, and bone fracture.[23]

As Professor Van Belle said, he doesn't want to be sitting at an FDA advisory meeting in three years' time discussing pioglitazone. Professor Gale is also concerned. In a letter to the UK regulator in 2008 seen by the *BMJ*, he wrote that "there is an urgent need to determine the safety of pioglitazone".

"Pioglitazone may or may not prove to be safer than rosiglitazone. There is an urgent need for more and better data addressing this issue. On present evidence, its safety cannot and should not be assumed," he wrote. Takeda say that they continuously monitor the safety and efficacy of their compounds.

Meanwhile other anti-diabetes drugs using a similar pathway are in development: the chequered history of the glitazones not having deterred manufacturers. According to reports, Dr Reddy's Laboratories and Nordic Bioscience's partial PPAR-gamma agonist balaglitazone met its primary endpoint in its first phase III trial in patients with type 2 diabetes (reduction in glycated haemoglobin). It was claimed to be "non-inferior" to pioglitazone. The companies are currently in discussions with regulators and hope to eventually file the drug in the European Union and the United States.[24] And both Roche and Metabolex have drugs in phase two trials.[25]

Will regulators, industry, and the clinical community do a better job for patients next time?

Deborah Cohen is investigations editor, *BMJ*
dcohen@bmj.com

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**See EDITORIAL, p 513; LETTERS, 519**

COMMENTARY NICK FREEMANTLE

# What can we learn from the continuing regulatory focus on the thiazolidinediones?

Should rosiglitazone be withdrawn from use? An answer is hampered by the inadequacies of the data collected to date. In particular, regulators have tolerated loss to follow-up in trials designed to examine the effects of rosiglitazone on surrogate outcomes (haemoglobin A1c) despite relying on these same trials to provide evidence on safety (mortality and morbidity). The more robust regulatory approach required for new diabetes drugs introduced in late 2008 should prevent this situation recurring in diabetes, but if we are to avoid similar problems in other clinical areas, we need a far more widespread overhaul in the standards of regulatory trials.

Few would disagree that large scale randomised trials provide the most reliable evidence on the safety of interventions.[1] Through randomisation, both known and unknown biases are distributed between the experimental groups by the play of chance.[2] Because of random allocation of participants, any observed difference between groups on an outcome of interest may be attributed either to the play of chance or to the random treatment allocation. If chance is unlikely (for example, if the confidence intervals are relatively narrow and the corresponding P value small) the only plausible alternative is that the randomised treatment is responsible for the difference.

When there are few or no good randomised trials, we have to look at other sources of evidence, but this should not have been necessary with rosiglitazone. More than 30 000 participants have been randomised in trials of rosiglitazone.[3 4] This should allow us to estimate small differences in event rates attributable to rosiglitazone. However, not all trials are alike and, sadly, in the case of rosiglitazone, sponsors, investigators, regulators, and journal editors seem to have been content to accept truly dreadful standards of methodological quality. Until the recent RECORD study,[5] trials have used symptoms and surrogates rather than major morbidity and mortality as the outcomes of interest and were sabotaged by unacceptably high and sometimes hidden losses to follow-up.

## Loss to follow-up

Loss to follow-up can undermine randomisation and introduce bias, reducing the reliability of the trial.[6] If patients leave a trial because of health reasons, and if there is a risk that the reasons for loss to follow-up may differ between the randomised groups, then the results of that trial may no longer be explained simply by chance or the treatment allocation but may be due in whole or in part to selection bias. In the ADOPT trial, which examined rosiglitazone, metformin, and glyburide, 40% of participants did not complete the one year follow-up.[4] The article describing the main results of the trial states that safety data are based on all randomised patients, and yet 5% of patients had disappeared before the first follow-up visit.

**In the case of rosiglitazone, sponsors, investigators, regulators, and journal editors seem to have been content to accept truly dreadful standards of methodological quality**

Regulators are well aware that loss to follow-up is a big problem in clinical trials examining serious morbidity and mortality and that very low losses can be achieved. For example, when comparing the 30 day outcome in a trial of tenecteplase versus alteplase, the ASSENT-2 investigators knew the vital status of all but six of the 16 949 participants randomised to that comparison.[7] But for reasons that are unclear, regulators have been less critical with trials that use surrogate endpoints.

This acceptance of higher rates of loss to follow-up in trials where outcomes are symptoms or surrogates makes no sense. This ill conceived distinction is highlighted when we use those same trials of symptoms and surrogates to assess safety, since adverse events will include serious morbidity and mortality. Even when trials examine serious morbidity and mortality, loss to follow-up remains a problem. The RECORD trial, conducted to examine the safety of rosiglitazone and sponsored by GlaxoSmithKline in the UK,[5] failed to follow up survival in 127 participants (2.9%). In the context of an observed mortality of 6.6% this failure is challenging and requires a series of exploratory analyses examining the possible implications. These result in the conclusion that rosiglitazone could be associated with either an increase or a decrease in mortality given different assumptions on the fate of those lost to follow-up. As for the non-mortality outcomes, the 11.7% rate of loss to follow-up in RECORD makes interpretation very difficult, although the FDA has rightly long emphasised the importance of all cause mortality as an outcome measure.[8]

## Wider change

In the US, the FDA has made changes to improve the quality of data on the safety of new drugs for diabetes.[9] Requiring a predefined upper boundary to exclude the possibility of excess cardiovascular risk will lead to substantial increases in the size and length of follow-up in diabetes trials, and should ensure that high rates of loss to follow-up are no longer considered acceptable. But what about other clinical areas? It would make sense to have better quality trials in all contexts, rather than waiting until safety concerns arise and reacting, at which point trials will be harder to run as the experience of RECORD shows.[5]

In order to learn from our mistakes, we must improve the quality of safety data from clinical trials on all new healthcare interventions. Sponsors should not be content to design and undertake poor quality trials. Regulators should insist on high quality trials with low loss to follow-up, and adequate examination of potential safety challenges early in the development of new pharmaceutical agents across all clinical areas. Investigators should seek to keep participants in trials, and journals should be more critical of the trials that they are offered for publication. A trial like RECORD is clearly of legitimate public interest and should be published and available for scrutiny,[5] but the limitations of such a study should be described more carefully in order to achieve a balanced portrayal of the facts and their interpretation.

Nick Freemantle professor of clinical epidemiology and biostatistics, School of Health and Population Sciences, University of Birmingham, Birmingham
N.Freemantle@bham.ac.uk

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# Commissioners doing it for themselves

All general practitioners in England will soon be expected to commission the majority of health care services for their patients. **Jane Cassidy** talks to two groups already fulfilling this role

When a group of Northamptonshire general practitioners started commissioning patient services, little did they know that three years later they would find themselves in the media spotlight.

The publication of the government's health white paper in July kick started a stream of requests from journalists to the Nene Commissioning office in Northampton.[1] An interview with Nene's chairman, Darin Seiger, on BBC Radio 4's *Today* programme sparked 12 000 hits to the organisation's website in one day.[2]

Now media interest is being replaced by calls from doctors keen to shadow the GPs' work. They want to find out more about a role all family practitioners are expected to take on by 2013.

## Making it work

The Nene group is the largest of its kind, representing 76 practices, more than 350 GPs, and a patient population over 650 000—94% of the county. A not for profit social enterprise set up in 2007, it is run by a board of nine elected GPs supported by a small management team.

Ideas for new and improved services, along with concerns, are aired at monthly meetings in four locations countywide. Progress reports are fed back regularly. The group's website is bulging with examples of how its innovative ideas are winning awards and transforming patient care. It is easy to see the benefits for patients, but what's in it for clinicians?

How about greater job satisfaction, less frustration, and lower stress levels? The move away from primary care trust (PCT) control has resulted in all of these, say three of Nene's GP directors.

Nene deputy chair, Raffaella Poggi, explains her involvement evolved from dissatisfaction about a PCT merger four years ago that led to a series of "blunt cuts."

"Managers stopped services without thinking about the implication for patients," she said. This led to meetings between like minded GPs, which led to Nene Commissioning.

She is now able to save time and stress for herself and patients by helping design streamlined projects such as the county's end of life service. There is now a link nurse at the local hospital to ensure whenever possible that patients die in the setting they choose. This means Dr Poggi has only one person to liaise with instead of many. It's one instance of how Nene tries to provide a more seamless service.

Dr Seiger had similar motivations. In 2006 he was the medical director of a local GP cooperative and, along with clinical colleagues, had to explain to patients the effect of the PCT cuts. Telling couples that NHS funding for in vitro fertilisation had stopped was particularly painful, he recalls.

Practice based commissioning, introduced by the last government, gave GPs some power to design care for patients through commissioning. The Nene group wanted to operate independently from the local PCT as a GP led organisation. To do this, they formed a community interest company.

A support team deals with the administrative side of the commissioning process, so GPs can get on with the task of making clinically sensitive decisions. They say the PCT is now supportive.

GP director Matthew Davies believes commissioning can lead to a feeling of empowerment and increased morale in the profession.

But what about clinicians anxious that they will be expected to become hybrid doctor-managers?

"People get hung up on technical skills. I don't think there is a need for these. It's leadership skills that are important," he said. Softer skills are crucial to commissioning success. Winning hearts and minds when redesigning services and the ability to negotiate and influence to ensure quality is maintained are paramount. "It's not about accountancy and contracting. Other people will do that better than you," he said.

Providing education to support those involved in change helps smooth the way. Nene provides several training programmes.

Behaviour change from some medical professionals is also vital, say the Nene doctors. GPs will need to ask themselves: "How does my behaviour affect relationships with other practices in the locality and in the consortium?"

They will no longer be able to say: "I do it this way because I've always done it this way."

The Nene GPs are used to sharing best practice, scrutinising activity such as referral patterns to identify variations and to improve quality. Though they stress this is done in a supportive rather than finger pointing way.

### TIPS FROM THE COMMISSIONING GPs

- Don't get hung up on the technical side of things—accountancy, contracts. The most important thing at the moment is to talk about forming relationships
- Ask yourself, "What will this mean for me as a GP, for my practice, my locality?"
- Learn the lessons of GPs who have already set up commissioning organisations
- Don't let your PCT bounce you into making decisions too soon. You've got to sit back, talk to each other, and reflect on where you want to go
- Read the white paper. It's not going to go away

## Answering concerns

What do they think of the concern that hospitals that fail to compete with other providers in the market will be starved of cash under the new commissioning arrangements?

Over the years, a wedge has been driven between GPs and secondary care and these relationships need to be rebuilt, they say. "There have previously been perverse incentives in the system whereby managers see collaboration across a pathway, between primary and secondary care, as a threat to their income. While some of these incentives will still be present, I believe that clinically led commissioning can identify and break them down," said Dr Davies.

But acute trusts will need to adapt too. The white paper challenges everybody in the system to work differently.

The Nene doctors are obviously highly motivated. Dr Seiger lists endurance triathlons among his hobbies. Dr Poggi has an MBA. Dr Davies has been involved in commissioning for several years. But how will others manage such thorny issues as conflicts of interest, performance related pay, and anxiety over bankruptcy?

The doctors point to some troubleshooting solutions. Performance can be managed using agreed standards everyone can be supported to achieve. A group decision can be made about how to share

**Darin Seiger: Commissioning gives GPs power to design care**

**Matthew Davies, GP: Commissioning increases morale**

**Dr Raffaella Poggi: Commissioning has saved time and stress**

**Laurence Buckman: Commissioning more an opportunity than a threat**

quality money. Clear governance rules and transparency will prevent conflicts of interest, they say.

If a practice is overspending, there needs to be a peer supported process in place to support commissioners working alongside the local medical committee.

The accusation of a privatisation agenda underpinning the government plan is also rejected by the Nene doctors, who say their organisation is entirely committed to the NHS.

What about concerns over time management? How do you encourage good clinical directors to come forward?

The answer, they say, lies in paying well and offering a professional management structure that allows focus on areas in which GPs have clinical flair. They shouldn't be expected to put in extra hours on a goodwill basis or get bogged down by tasks that can best be done by administrators.

In Redbridge, north east London, Anil Mehta is no less enthusiastic about commissioning, although he admits to putting in extra hours.

"Initially, I thought it would be a one day a week job. I've ended up doing a lot more in between and after hours."

He does eight clinics a week and is also clinical director of Fairlop Polysystem, one of five advanced practice based commissioners run by GP boards. Each supports 40 000 to 70 000 patients in one geographical area. They are on course to control 80% of the commissioning budget by the end of the year.

He is currently using his weekends to get to grips with population management software that allows him to scrutinise patient data in detail.

Each polysystem is charged with redesigning services to meet the specific needs of its immediate community. Set up to allow GPs to have real control over health services in their area, the polysystems work collaboratively with a community panel and share local knowledge.

In contrast to the Northamptonshire model, the local PCT worked closely with GPs to create and roll out the programme last year.

"We have a good relationship with the PCT and our monthly meetings are extremely useful. We're learning the ropes from an excellent management team," said Dr Mehta.

It is, however, a steep learning curve, he says, which makes it essential that GPs get support from managers who have already done the job.

A doctor in the area for 13 years, he believes GPs are in an ideal position to influence health care. One example of a service reshaped under the new system was a costly specialist GP service for diabetes where patients were failing to turn up for appointments. Non-attendance was picked up from conversations with patients and from clinic staff.

**"People get hung up on technical skills. I don't think there is a need for these. It's leadership skills that are important."**

Diabetic specialist nurses now run the clinics, spending up to an hour with patients, talking to them about a range of issues such as diet.

"The immediate benefit for us is that our chronic disease management of patients improves," said Dr Mehta.

"What happens to a patient who doesn't get what he needs? He ends up at the door of accident and emergency, perhaps attended by a junior member of the profession who tells him to go back to his GP. This is a bizarre waste of time and resources."

He dismisses the notion that doctors shouldn't get involved in contracting decisions, saying GPs have a dual role as both clinicians and custodians of public money.

"Unless we look at where the money is being spent, we can't possibly improve health care. A lot of wastage is never found unless you get involved."

However, there is uncertainty among GPs about the white paper, he concedes. For instance, who will be willing to take on the role of the accountable officer in the new consortiums?

Unless there is adequate training, backed up by firm financial governance and legal protection, he can't see why GPs would find such a responsible role attractive. Anyone who takes up the job also needs to be given a return road back to full time clinical work afterwards.

Laurence Buckman, chairman of the BMA's GP Committee, says GP commissioning could work well to benefit patients and save money.

"We see this as much more of an opportunity than a threat," he said, although he agrees key areas need to be clarified. Among these are potential problems if the process is thwarted by central government, underfunded to the point that no one can commission, or the whole process goes so fast that proper governance arrangements aren't put in place.

Other big worries are the effect on clinical care if practices are too busy commissioning, the risk of the private sector moving in, and what happens if the money runs out.

"We're very concerned about GPs being made the scapegoats for financial constraints or being made to look like they're the ones closing hospitals," he said.

The deadline for responses to the white paper is 11 October. All eyes will be on the government's reaction to the consultation and whether they move to clarify their radical plans.

Jane Cassidy is a freelance journalist, Hertfordshire
janecassi2@googlemail.com

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