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Feature Drug Regulation

Rosiglitazone, marketing, and medical science

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Ray Moynihan, conjoint lecturer

¹ *University of Newcastle, Newcastle, Australia*

ray.moynihan@newcastle.edu.au

Attempts to play down the potential cardiac risks of a popular diabetes drug raise questions about the need for fundamental changes in drug regulation, writes **Ray Moynihan**

Casually following the fortunes of the blockbuster diabetes drug **rosiglitazone (Avandia)**, you can't help but imagine a Hollywood thriller. There is the scene where a leading scientist secretly records a meeting with drug company executives, a high powered congressional investigation, and a bitter legal battle waiting in the wings. Yet when you look more closely, the **facts are even stranger than fiction**. An expensive new drug shown to raise the risk of **heart failure** and suspected of increasing the chance of **heart attacks** has been taken by **millions** of people around the world and is being kept on the market by an industry funded regulatory system, despite calls from senior safety experts to withdraw it. For its part, the drug's manufacturer strongly denies the link with heart attacks and points to evidence to back its claims. But the details of this unfolding real life drama suggest a now familiar merging of medical science and drug marketing.

Damning congressional report

Earlier this year a congressional committee in the United States released the results of an investigation into the diabetes drug rosiglitazone and its manufacturer **GlaxoSmithKline (GSK)**.¹ Investigators reviewed over 250 000 pages of corporate and government documents and conducted numerous interviews with both officials and **anonymous whistleblowers**. Central to the investigation was GSK's internal responses to the growing body of evidence linking its drug to potential heart problems. Revelations about what happened behind closed doors in the days leading up to the publication of an important meta-analysis in 2007 are a particularly illuminating example of the modern day intersection of science and marketing.

On 2 May 2007, Steven Nissen and Kathy Wolski, of the Cleveland Clinic, Ohio, submitted a draft manuscript of a meta-analysis of 42 trials to the *New England Journal of Medicine*. The meta-analysis had found that the

type 2 diabetes drug rosiglitazone was associated with a significant 43% increased risk of myocardial infarction, though absolute differences in event numbers between the group taking rosiglitazone and the comparator group were small.² On 3 May a peer reviewer—who happened to also be a consultant to GSK—leaked a copy of the manuscript to the company, which was then widely distributed inside the corporation. By 4 May, a GSK statistician attempting to find deficiencies in the leaked meta-analysis noted “there is no statistical reason for disregarding the findings as presented.”

On 8 May GSK’s head of research noted that Nissen and Wolski’s worrying results echoed similar evidence already collected by the company and the US Food and Drug Administration: “FDA, Nissen, and GSK all come to comparable conclusions regarding increased risk for ischemic events, ranging from 30 percent to 43 percent!”¹ Yet on the following day, the company was developing “key messages” to counteract Nissen and Wolski’s findings. By the time the meta-analysis was published less than two weeks later, complete with the authors’ acknowledgment of its limitations,² GSK announced it was based on incomplete evidence and that the company strongly disagreed with its conclusions. In their report, released this February, the congressional investigators concluded that corporate executives had “focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk.”

According to the report, one of the strategies GSK used to counter the meta-analysis findings was to try to shift the focus of attention onto a different study, called Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD), which was at that time still ongoing. Internal documents show company executives making a decision to try to urgently release interim results of the ongoing company run trial and to seek agreement to do so from the independent steering committee overseeing it. In one email a GSK official suggests that if the steering committee wouldn’t agree to publishing interim results, the company officials would pursue the line that “a decision has been made—live with it.”

As it happened the steering committee did agree to publish, and a manuscript with the interim analysis from the RECORD study was sent to the *New England Journal of Medicine*. That manuscript included a statement suggesting the RECORD results contradicted the findings of Nissen and Wolski’s meta-analysis about raised risk of heart attacks.¹ However, the journal’s editors responded to the draft manuscript by saying RECORD’s interim results were “completely compatible” with the Nissen meta-analysis, and the statement that they contradicted them must be removed or modified. The version of the article ultimately published claimed the data from the company’s study were “insufficient” to support a link between rosiglitazone and heart attacks.³

Of the eight named authors of the RECORD study, seven were paid consultants to GSK, among other companies, and the eighth was a GSK employee. An accompanying editorial pointed out that the design of the RECORD study raised questions about whether it had adequate statistical power to detect certain cardiovascular outcomes.⁴ That editorial also suggested GSK’s study had found an “exceptionally low” rate of events, including myocardial infarction, most likely explained by “incomplete ascertainment” of all the events that occurred.

After analysing many internal documents on the RECORD trial, the congressional investigators concluded the drug company was placing great emphasis on a study it knew to have important limitations: “It appears that GSK knew for years that the study was ‘underpowered,’ ie, the study did not provide sufficient data to test for cardiovascular safety.” When the full results of the RECORD study were published in 2009, it found

rosiglitazone significantly increased the risk of heart failure but was “inconclusive” about the effects of the drug on heart attacks.⁵

Responding to revelations in the congressional reports, two editors at *JAMA* wrote last month that “concerns about preserving market share apparently trumped concerns about the potential for causing patient harm.”⁶ The journal’s editor in chief and deputy editor argued GSK had exerted “inappropriate influence” over the conduct of the RECORD study by attempting to undermine the authority of the steering committee and fast tracking publication of unscheduled interim results, in order to counter the Nissen meta-analysis findings of increased risk of heart attack.

GSK defends its record and its drug

Rather than trying to counter the Nissen findings, GSK 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.”⁷ The company has also stressed that endorsement for the urgent interim analysis was sought and received from the steering committee before the analysis was conducted. In a 30 page response to the congressional investigation, GSK said the report did not represent an “accurate, balanced or complete view” of the currently available data on rosiglitazone.^{8 9} The company denies allegations in the report that it intimidated independent scientists or failed to appropriately inform the public about the drug’s risks, pointing to label warnings on heart failure dating back to 2001, and on the “inconclusive” risk of myocardial ischaemia dating to 2007. More broadly, the company says it welcomes and supports open and independent scientific debate, and as part of its commitment to transparency publishes protocols of all ongoing trials and summaries of the results of all completed studies, as well as payments to healthcare professionals and institutions.

On the specific suggestion that the RECORD study was underpowered to investigate any potential increased risk of heart attack, the company claims the study was adequately powered for its primary endpoints of cardiovascular death and hospital admission, which it says includes heart attacks. In a separate clarifying statement in response to questions from the *BMJ*, the company said: “Although there was some speculation in 2007 that RECORD might be underpowered, in the end, it was not,” and added that the study was designed in consultation with European regulators. The company further states that it now has six large randomised trials of rosiglitazone, including RECORD, none of which shows an increased risk of myocardial infarction. Five of those six were funded by GSK and two were run directly by it, though all of the trials also involved outside or independent committees of researchers. The company says that the congressional report misleadingly failed to mention or discuss recent data supporting the cardiovascular safety of rosiglitazone, including a newer more comprehensive meta-analysis which found no increased risk of heart attacks. To help support its position, GSK cited a consensus statement from a professional medical group that also points out that more recent evidence finds the drug has no effect on cardiovascular disease.

It seems, however, that in the ongoing battle over exactly what the scientific data show about this drug, much of the favourable analysis and comment has come from health professionals or medical organisations financially connected to GSK. The professional medical group cited by GSK, for example, was the American Association of Clinical Endocrinologists, which in the 12 months before its consensus statement in September 2009, received around \$330 000 in funding from the company, according to GSK’s publicly

available disclosures.¹⁰ Eleven of the 12 authors of the statement were heavily entangled with the drug industry, and half had financial ties to GSK. One of the latest meta-analyses of trials was conducted by an Italian research group that included two authors with ties to GSK and its competitors, including the first and last authors.¹¹ These ties were not published with the article, although the authors say they disclosed them as part of the submission process. Perhaps most importantly, a recent review of the medical literature about the potential heart risks of rosiglitazone found that authors with a favourable view of the drug's safety were more than three times more likely to have financial ties with drug companies than authors who had unfavourable views.¹² In the original meta-analysis article published in the *New England Journal of Medicine* in 2007, Dr Nissen had declared financial ties to several drug companies, excluding GSK but including a competitor in the diabetes market.

Move to the courts?

Drug company links with health professionals have also been the subject of attention in two recent high profile court cases, both focusing on the health risks of blockbuster medicines. In Australia, during hearings about rofecoxib (Vioxx) in the federal court last year, internal company documents dating from 1998-9 surfaced showing how the manufacturer Merck hoped to use paid medical experts to help promote its drug, while at the same time planning to "neutralise" and "discredit" critics.¹³ In the United States, as part of the historic criminal finding against Pfizer and a subsidiary in 2009, it was found that paid advisers within the medical profession, consultants and "purportedly independent continuing medical education programs" were used in the early 2000s to help illegally promote an arthritis drug.¹⁴ Although the circumstances surrounding rosiglitazone are different from those in these other cases, lawsuits are already being filed, and there are reports the company could face a potential liability of between \$1bn and \$6bn.¹⁵

Those figures are so high because the pool of potential litigants is large, especially in light of estimates from an internal government report on the numbers of people who may have been harmed by the drug. One of the confidential government documents released in February by the congressional investigators was an internal report written by two safety officers within the FDA. Their report argued that although the competitor drug pioglitazone also increased the risk of heart failure, it was safer overall. The investigators concluded that keeping rosiglitazone on the market was leading to an estimated excess of 500 heart attacks and 300 cases of heart failure every month, that a planned comparative trial between the two drugs should not go ahead, and that rosiglitazone should come off the market.¹⁶

One of the authors was David Graham, the senior safety official who had famously told a congressional hearing in 2004 that it was regulatory failure that was responsible for the harms associated with the arthritis drug rofecoxib. In 2007 its manufacturer settled lawsuits for almost \$5bn without admitting causation or fault.

GSK has strongly rejected the findings of Dr Graham's report, saying its "methodology is seriously flawed and based on incomplete data." Speaking in a personal capacity, Dr Graham responded directly to the company's criticism. "For the comparison we were exploring, our study was comprehensive and complete," he told the *BMJ*, arguing that GSK's focus on other studies was an attempt to create a distraction from the most pressing public health and medical problem: which of the drugs in this class was safer. In response to questions about the inconclusive nature of the evidence linking rosiglitazone to an increased risk of heart

attack, Dr Graham said:

“Why do we need to wait for conclusive proof of public health harm? **What we need is proof of safety.** There is **no unique health advantage of rosiglitazone over pioglitazone,** yet there is evidence it carries more risks. It should come off market.”

Three years ago a meeting of FDA advisers recommended keeping rosiglitazone on the market, despite acknowledging the possibility of an increased risk of heart attacks and warnings from Dr Graham at that time of widespread harm. After a close 8:7 vote by a drug safety oversight board, the regulator accepted the recommendation to keep the drug on the market, though with strengthened warnings on its label. A further meeting of advisers has been organised for July to assess more recent scientific data about its potential harms. But some voices are asking whether the structure of the agency is an obstacle to making important safety decisions and whether it is right that the same people responsible for approving drugs also make decisions about whether to withdraw them.

Proposed changes within the heart of drug regulation

In the days after the release of the congressional report the two most senior senate finance committee members wrote to the FDA asking why the agency was allowing a trial comparing rosiglitazone and pioglitazone, when two of the agency’s safety experts including Dr Graham, had described the trial as “unethical and exploitative” because of the potential risks of rosiglitazone.¹⁶ Two days later one of those committee members, Republican Senator Chuck Grassley called for fundamental reform of the powerful regulator. He said it made no sense to have safety experts “under the thumb” of the same officials who approved the drug and who have an interest in defending that decision.¹⁷ “Both the FDA and Congress need to take every step possible to establish independence for post-market surveillance,” he said.

Just four weeks ago a congressman from New York introduced a new bill that would radically transform the funding and structure of the regulator, ending its **controversial reliance on industry’s user fees** and creating a new centre for post-marketing surveillance. The FDA was **“too closely tied to the pharmaceutical industry,”** said Maurice Hinchey introducing his new bill.¹⁸ “It’s a situation that **has allowed the interests of powerful pharmaceutical companies to come before those of the American people and that’s simply a situation that needs to come to an end.**” Dr Graham agrees. “Until we have a separate centre for post-marketing which is independent from the control of those who approve drugs, we are defenceless against these types of disasters,” he said.

Unbelievable as it may sound, although there is evidence rosiglitazone can help lower the surrogate marker of blood glucose concentrations, which in turn can prevent “microvascular” disease affecting eyes, kidneys, and nerves, there is no well established good quality evidence that the drug can significantly reduce the risk of other serious and life threatening complications associated with type 2 diabetes.¹⁶ At best it doesn’t increase risks of major events like heart attack, though like its competitor, it is known to raise a person’s chance of heart failure. Analysing the complex science of the risks and benefits of any drug is clearly a difficult task. But perhaps that task might be made easier if those studying it, prescribing it, pronouncing on it, and regulating it could do so more often **in the sunshine of independence rather than the shadow of those seeking to maximise its sales.**

Evolution of rosiglitazone story

1999

May: Drug approved by FDA with label precautions for use in patients with heart failure

2000

July: Approved in Europe, with warnings on heart failure

2001

February: FDA approved new warnings on potential for heart failure

2005

September: Internal GSK meta-analysis finds 29% non-significant increased risk of ischemic cardiovascular events

2006

April: FDA approves new warnings on risks of cardiovascular events

May: Internal GSK meta-analysis finds 31% increase in ischaemic events

2007

May: *New England Journal of Medicine* publishes meta-analysis reporting 43% increase risk of myocardial infarction²

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

2010

February: US Senate finance committee releases report that includes internal FDA safety report calling for drug to be withdrawn

February: GSK responds with 30 page document

July: FDA advisory committee meeting scheduled

Notes

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Footnotes

- [Feature.doi:10.1136/bmj.c1849](https://doi.org/10.1136/bmj.c1849)
- [Observations.doi:10.1136/bmj.c1819](https://doi.org/10.1136/bmj.c1819)
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