

## LETTER TO THE EDITOR

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### The painful truth

Medical journals play a pivotal role in discussion of scientific issues and healthcare policy. This attempt by a large pharmaceutical company (GSK) to censor public debate about a critical public health issue is unacceptable and represents a grave threat to academic freedom. Pharmaceutical companies have abundant resources for delivering their messages to physicians and the public. Physician–scientists essentially have only medical journals through which we communicate our scientific ideas and concerns. If we allow a pharmaceutical company to control what we are allowed to publish, scientific discussion and debate would suffer irreparable harm. This demand from GSK constitutes an unacceptable attempt to interfere with the editorial decisions of a major medical journal.

The assertions by GSK in Dr Slaoui's Letter are categorically incorrect and distort the facts. The following represents a point-by-point response to the GSK letter:

1. The rosiglitazone development programme was small, although typical of diabetes drugs in that era, consisting of five trials involving 2902 patients, mostly short-term (26 weeks) glycaemic control studies.

The FDA reviewer makes it clear that the studies involving 2902 patients formed the primary basis for approval.<sup>1</sup> (Table 8.H.3.2) Studies done early in a development program, particularly those using subtherapeutic dosages of drugs or very short-term therapy are not considered part of the primary basis for approval. Furthermore, the FDA now recognizes that 1 year follow-up in a minority of patients is inadequate. In their recent guidance to Industry, the Agency states that: 'It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g. minimum 2 years) for these chronically used therapies'.

2. The effect on LDL-C was largely dismissed.

The Advisory Committee that approved rosiglitazone focused primary on hepatic safety. Virtually all media reports covering the

Advisory Committee emphasized the lack of troglitazone-like hepatotoxicity, which was the principal area of concern discussed by the Advisory Committee.<sup>2</sup>

3. However, one prominent diabetes expert was...persuaded to sign an agreement barring him from publicly expressing concerns about the safety of the drug.

The intimidation of Dr John Buse by GSK was fully described in a report issued by US Senate Committee on Finance.<sup>3</sup> The Senate Report quotes an e-mail message from Dr Buse to me dated 23 October 2005 following publication of our manuscript describing the risks of the diabetes drug muraglitazar. In that e-mail, Buse stated: 'Steve: Wow! Great job on the muraglitazar article. I did a similar analysis of the data at rosiglitazone's initial FDA approval based on the slides that were presented at the FDA hearings and found a similar association of increased severe CVD events. I presented it at the Endocrine Society and ADA meetings that summer. Immediately the company's leadership contact (sic) my chairman and a short and ugly set of interchanges occurred over a period of about a week ending in my having to sign some legal document in which I agreed not to discuss this issue further in public. I was certainly intimidated by them but frankly did not have the granularity of data that you had and decided that it was not worth it'.

In an e-mail to GSK, Dr Buse wrote: 'Please call off the dogs. I cannot remain civilized much longer under this kind of heat'.<sup>3</sup>

4. Although the ADOPT study was actually performed, it was not powered to assess cardiovascular outcomes and did not adjudicate cardiovascular events.

Dr Slaoui doesn't challenge my assertion that the Adopt Trial did not adjudicate cardiovascular events and was not powered for cardiovascular outcomes. He says the study was designed, among other goals, to examine 'cardiovascular and haematological events'. How exactly would this be accomplished without systematically recording and adjudicating of cardiovascular events?

5. In January 2007, concerned about the cardiovascular safety of the TZD class, we requested access to patient-level data from the manufacturers of both

rosiglitazone, GlaxoSmithKline (GSK) and pioglitazone, Takeda. The makers of pioglitazone agreed, but the manufacturer of rosiglitazone declined.

In an e-mail to me dated 26 February 2007, a GSK senior vice president wrote: 'The analyses must be undertaken as collaboration between the academic group and GSK scientific personnel (e.g. statisticians, clinicians)... GSK would conduct the agreed analysis'.

I responded with the following comments: 'It would be acceptable for GSK to conduct an analysis, but our standards (and current journal rules) require independent analysis by an academic coordinating centre. Accordingly, the contract would need to stipulate that the complete database would be transferred to the coordinating centre for independent confirmation of the results'.

The company was unwilling to agree to an independent analysis. The full e-mail messages were provided to the US Senate for their investigation. The Senate report provides additional details.<sup>4</sup>

6. Both GSK analyses revealed an increased risk of ischaemic myocardial events and were quietly posted on the company's clinical trials register and actually shared with the FDA. However, throughout this period, neither the company nor the FDA revealed these findings to the medical community nor to the public.

Neither the company, nor the FDA, made any public statement warning about the risk of adverse ischaemic events until after our meta-analysis was published in May 2007. Physicians and the public were shocked by these revelations when our article appeared 21 May 2007. The posting of results on an obscure website is not a substitute for a peer-reviewed publication or clear public statements warning about the risk of the drug. When GSK first discovered an increased risk of myocardial ischaemia in 2005, they had an implicit moral obligation to warn physicians and patients, which they failed to do.

7. When a meta-analysis of rosiglitazone was eventually submitted for publication, the company subverted the editorial review process by stealing a copy of the manuscript and used this advance knowledge inappropriately to unblind an ongoing randomized trial.

According to the US Senate Report, the company surreptitiously obtained a copy of the manuscript in violation of the rules of the New England Journal of Medicine.<sup>4</sup> Such an action is a blatant subversion of the editorial process and is abhorrent to the academic community and Journal editors. Instead of destroying the improperly obtained manuscript, this document was subsequently circulated among more than 40 company executives and statisticians prior to publication by the NEJM.<sup>4</sup> This manuscript was the property of the authors, not GSK, and the exploitation of this document by the company was morally and ethically indefensible. According to the US Senate Report, the company unblinded the RECORD trial prior to the appearance of our meta-analysis.<sup>4</sup> The company deceived the RECORD Steering Committee into believing that the physician leadership was responsible for this decision. In an internal company e-mail, a GSK official writes, 'if the SC believe that publishing interim data will fatally damage their ability to bring the study to a completion', GSK will inform them 'that a decision has been made, live with it'.<sup>4</sup>

8. The FDA finally added a 'black box warning' about the risk of ischaemic myocardial events to the label of rosiglitazone in October 2007.

Dr Slaoui does not dispute that a black box warning for myocardial ischaemia was first added to the drug label in October 2007.

9. This study postulated an 11% annual event rate, but observed only a 2.5% rate. GSK disagrees with the implication that it intentionally underpowered the RECORD study.

In the US Senate report, the problems with underpowering of RECORD are widely discussed within internal GSK communications.<sup>4</sup> The 11% annual event rate was postulated in the RECORD design manuscript. The actual event rate is reported in the RECORD manuscript.<sup>5</sup> The extent of mismatch of postulated and observed event rates is very large and nearly unprecedented in the medical literature.

10. The HR for myocardial infarction was 1.14, but upper 95% CI reached 1.63.

Dr Slaoui is not disputing the HR and upper confidence interval that I cited in the Editorial. In a safety study, the upper confidence interval for the HR is the most appropriate safety parameter. Since our original meta-analysis focused on the risk of MI, this is the most relevant safety measure in the

context of the discussion. Accordingly, RECORD cannot rule out an increase in risk of MI of up to 63%.

11. About 40% of patients were no longer taking rosiglitazone by the end of the trial, further diluting any safety signals.

Dr Slaoui does not challenge my assertion that 40% of patients assigned to rosiglitazone were no longer taking the drug at follow-up. The figure he supplies (88% of total person-years of follow-up) is misleading. In the manuscript, the authors state that '75% of person-years' follow-up were on dual oral therapy and 13% on triple oral therapy'.<sup>5</sup> They do not actually claim that these patients were taking rosiglitazone. In the publication of the interim analysis, the authors reported that 27% of rosiglitazone randomized patients were no longer taking study drug.<sup>6</sup> Accordingly, the assertion of 88% compliance in the final RECORD manuscript seems mathematically implausible.

12. A consensus treatment algorithm issued by the American Diabetes Association and European Association for the Study of Diabetes 'unanimously advised against using rosiglitazone'.

The title of the document: 'Medical Management of Hyperglycaemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy'.<sup>7</sup> The consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes' speaks for itself. My editorial accurately refers to this document as a consensus algorithm, which is precisely correct. The text 'unanimously advised against using rosiglitazone' was the precise language used in the document.

13. In December 2008, the FDA issued a new guidance for development of drugs to treat diabetes, requiring cardiovascular outcomes trials, sufficient to rule out an upper 95% CI for the HR of 1.8 prior to approval and 1.3 in a Phase IV trial.

Dr Slaoui does not dispute that the FDA issued a new guidance in December 2008, nor does he dispute the required hazard ratios. The statement contained in the editorial is precisely correct.

14. Although early warnings were issued for the risk of heart failure, these warnings went largely unheeded in the face of aggressive marketing and promotion suggesting cardiovascular benefits.

In 2006, rosiglitazone became the largest selling diabetes drug in the world, reaching

sales of more than \$3 billion annually. My statement that the risk of heart failure went unheeded is self-evident.

15. FDA rushed to approve rosiglitazone because of hepatotoxicity concerns about troglitazone, resulting in failure to consider the 'signals' suggesting cardiovascular toxicity.

The statement contained in the editorial is precisely correct. Many media reports at the time emphasized the lack of hepatotoxicity. In retrospect, the medical community should have more carefully considered the potential risk of administering a new diabetes drug that substantially increased LDL-cholesterol. I remain convinced that the focus on hepatic safety detracted from a more thorough examination of the cardiovascular safety issue.

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