

## GUEST EDITORIAL

### WHY THE AVANDIA SCANDAL PROVES BIG PHARMA NEEDS STRONGER ETHICAL STANDARDS

The US Food and Drug Administration's (US FDA) recent decision to keep the diabetes drug Avandia on the market – despite evidence suggesting the drug increases risk of heart attacks when compared with similar drugs – has caused plenty of outcry. Politicians publicized their outrage. Democratic Senator Max Baucus, Chair of the US Senate Finance Committee, was widely quoted as stating that, 'Americans have a right to know there are serious health risks associated with Avandia and Glaxo-SmithKline had a responsibility to tell them. Patients trust drug companies with their health and their lives and GlaxoSmithKline abused that trust.'<sup>1</sup>

According to the *New York Times*, internal documents show that GlaxoSmithKline (GSK) researchers had conducted a study in 1999 that suggested that Avandia might be less safe than a competing diabetes drug.<sup>2</sup> Yet data from this study were not provided to FDA regulators during their initial 1999 review of the drug, nor were they provided when outside experts first raised questions about Avandia's safety in 2007.<sup>3</sup> One internal email even warned against publishing the data and because it might threaten Avandia's substantial market share, calculating the potential loss to GSK to be as much as \$600 million.<sup>4</sup>

GSK executives have never apologized for their decision to suppress safety data in order to protect their economic interests. Instead, they used their well-oiled public relations machine not only to spin the findings of their own 1999 study, to challenge the methodologies and data from the myriad of external studies showing increased cardiac risks among Avandia users, but also to question the motives of US FDA regulators and independent experts calling for the withdrawal of Avandia from the market. This PR campaign has been remarkably successful, as a recent editorial in the *Wall Street Journal* suggests.<sup>5</sup>

GSK executives also show no signs of remorse, and certainly express no guilt about the deaths of the patients who might have survived had they been prescribed a diabetes drug that posed less of a risk of heart attack than Avandia. Perhaps they are inured against such criticisms. This is not the first time GSK has been so accused. In 2004, the company was alleged to have hidden evidence that its blockbuster antidepressant, Paxil, increased suicidal behavior in children and adolescents.<sup>6</sup> In settling the lawsuit, GSK promised to make data from all its trials publicly available. Unfortunately, that agreement only covered studies conducted since December 2000, not the earlier 1999 study of Avandia.<sup>7</sup>

The Avandia scandal, like the Vioxx and Paxil scandals that preceded it, raises a number of questions. Do for-profit pharmaceutical companies and researchers have a moral duty to warn physicians and patients about potentially unsafe drugs, or is that solely the responsibility of government regulators? When are drug companies and regulators obliged to inform physicians and patients about possible dangers? What reforms are necessary to ensure that pharmaceutical companies and government regulators meet these obligations?

Our field, bioethics, was created to address such questions, among a myriad of others. It emerged in the USA in response to public outrage over the Tuskegee syphilis experiments and similar research scandals. The founding generation of American bioethicists responded by crafting the Belmont principles – beneficence, justice, and respect for persons – principles that justify the prerogatives of researchers and pharmaceutical companies to develop beneficial new treatments, provided that the burdens and benefits of experimentation and the innovations they produce are justly allocated and that the experiments respect the rights and protect the safety of persons who volunteer for clinical trials.

We believe that implicit in this tacit compact, and enshrined in the principle of beneficence, is an obligation on the part of pharmaceutical companies to warn not only study participants but also patients, the end users of pharmaceutical innovations and the ultimate source of drug company profits, of any data that reveals potential risks associated with their products. Pharmaceutical companies have a responsibility to ensure that their drugs will be safe for consumers, and this entails informing consumers of any risks associated with their

<sup>1</sup> United States Senate Committee on Finance. 2010. *Press Release: Grassley, Baucus Release Committee Report on Avandia*. 20 February. Washington, DC: US Senate Committee on Finance. Available at: <http://finance.senate.gov/newsroom/> [Accessed 27 July 2010].

<sup>2</sup> G. Harris. 2010. Diabetes Drug Maker Hid Test Data, Files Indicate. *The New York Times* 13 July, A1.

<sup>3</sup> *Ibid*; also see S.E. Nissen & K. Wolski. Effect of Rosiglitone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Eng J Med* 2007; 356: 2457–2471.

<sup>4</sup> Harris, *op. cit.* note 2.

<sup>5</sup> Avandia on Trial. *The Wall Street Journal* 16 July 2010, A16.

<sup>6</sup> *People of the State of New York v. GlaxoSmithKline and SmithKline Beecham*. Available at: [news.findlaw.com/cnn/docs/glaxo/nyagglaxo60204cmp.pdf](http://news.findlaw.com/cnn/docs/glaxo/nyagglaxo60204cmp.pdf) [Accessed 10 August 2010].

<sup>7</sup> E. Marshall. In Settlement. Glaxo Agrees to Publicize Drug Trial Data. *Science* 2004; 305: 1387.

products – this moral duty, moreover, does not lapse after a drug is approved by the US FDA and regulatory oversight lessens.

Sadly, GSK seems to have shirked this responsibility. They appear to have put profits before patients, and in the process they broke the covenant with society that permits them to make a profit from risks taken by study volunteers. Moreover, they give no indication that they will not do so again in the future.

What will be the likely outcome of the Avandia scandal? Nothing. Once the media spotlight fades, the politicians will get off of their soapboxes and the vast majority of people will focus their rage on some more recent environmental catastrophe, economic disaster or political scandal. GSK may be asked to pay a small fine by government regulators and will likely face civil claims filed by Avandia users, but pharmaceutical companies typically regard such financial penalties as simply a cost of doing business (that can be ‘written off’ on their corporate taxes). Despite the harm caused to tens of thousands of Avandia users, it will soon will be business as usual for the drug industry.

It is our responsibility as bioethicists to ensure that this doesn’t happen. When drug manufacturers like GSK act in such a manner, we need to argue publicly and forcefully for the imposition of penalties and the creation of policies that impose some form of external or insitutional conscience on these companies. In 2009, Pfizer was fined a record \$2.3 billion for off-label promotion of drugs like Bextra, the first time such a substantial penalty has been imposed on a pharmaceutical. American bioethicists need to encourage the US FDA to impose increasingly larger financial penalties upon companies like GSK who repeatedly hide data that call into question the safety of pharmaceutical drugs – penalties large enough to discourage such unethical behavior in the future, rather than being seen as a financial ‘slap on the wrist’.

American bioethicists should also ensure that the US FDA be given the resources and authority to enforce laws that require all new clinical trials of US FDA-regulated

drugs and devices to be registered in a public database like ClinicalTrials.gov, such as the 2007 Food and Drug Administration Amendments Act. The US FDA should also require and enforce timely publication or public release of data from all trials so registered. A recent study published in *PLoS Medicine* found that publication rates for trials registered with ClinicalTrials.gov were exceedingly low, particularly for industry-sponsored trials.<sup>8</sup>

Finally, because the pharmaceutical industry is international, it recognizes few borders and easily moves its operations from one jurisdiction to another. The misbehavior of drug companies like GSK should not be seen as just an American problem, as an issue for US regulators and bioethicists to deal with. It concerns bioethicists around the globe. We need develop and strengthen transnational institutions both within and outside the pharmaceutical industry to strengthen drug companies’ institutional conscience and to offset the natural temptation to prioritize corporate profits over patient safety. We should, for example, campaign for the creation of an impartial pharmaceutical ethics consulting service of bioethicists and researchers empowered to advise companies on such issues as whether to publicize unreleased data that might call into question a drug’s safety. Should the pharmaceutical industry not take such an initiative on its own, we call upon our national governments and transnational organizations like the European Council, UNESCO, WHO and CIOMS, and the WMA to set standards requiring drug companies not only to publicize all clinical trial data, but to consult with bioethicists about these and other issues.

Sean Philpott, PhD, MS Bioethics is Director of the Research Ethics Program at Union Graduate College.

Robert Baker, PhD, is Director of Center for Bioethics and Clinical Leadership of Union Graduate College.

<sup>8</sup> J.S. Ross, G.K. Mulvey, E.M. Hines, S.E. Nissen & H.M. Krumholz. Trial Publication After Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. *PLoS Med* 2009; 6: e1000144.