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Big pharma under the spotlight

In February 2013, in what the *British Medical Journal* called a 'spectacular public relations coup', Andrew Witty, the chief executive officer of GlaxoSmithKline (GSK), announced that the company would sign up to AllTrials – a campaign that has been pressing drug companies to disclose *all* detailed clinical study reports and drug trial results, not just those with favourable results.[1]

The story behind this announcement goes back a long way. GSK itself was fined $3 billion in 2012 in the USA for selling the antidepressant drug paroxetine for unapproved use in children, for concealing safety evidence on the company's leading diabetes product from the Food and Drug Administration, and for offering doctors lavish incentives to prescribe its medicines.[2]

In 2009 the *BMJ* started its first 'open data campaign'. The drug under the spotlight was Tamiflu, produced by Roche and recommended for the treatment of influenza. In that year, Roche made a public promise to release full trial reports for Tamiflu, in response to an investigation by the *BMJ* and Cochrane collaborators Peter Doshi and Tom Jefferson.[3-6] In September 2009 Jefferson asked Roche for the unpublished data set that Roche used in an analysis published in 2003, for use the following month to update the Cochrane Collaboration's review on neuraminidase inhibitors in healthy adults. After asking Jefferson to sign a confidentiality agreement promising that he would not publish the data in full, Roche declined to supply the data set because they had also been approached by another group doing a similar meta-analysis and didn't want conflict. According to Roche, their study reports had also been shared with the regulatory authorities.

Jefferson never received the study reports, and the Cochrane review published 2 months later in the *BMJ*[6] said that because 8 of the 10 randomised controlled trials on which effectiveness claims were based were never published, the evidence could not be relied on. The 2 published studies were funded by Roche and authored by Roche employees and external experts paid by Roche. Roche promised to make full study reports on the 10 trials available.[3] To date, this has never happened. In the meantime several organisations, including the World Health Organization, the National Health Service in the UK, the Centers for Disease Control in the USA and the European Medicines Agency, have encouraged the use and stockpiling of Tamiflu – all without seeing the full study and trial reports.

Tamiflu was the final insult that instituted the open data campaign. But it was not the first example. Looking back through the literature, there are myriad reports of drugs that have come to market on the back of trials that have never been seen in full by regulators. Rofecoxib (Merck) was introduced in 1999 as an effective, safer alternative to non-steroidal anti-inflammatory drugs for treating pain associated with osteo-arthritis. It was subsequently withdrawn in September 2004 after being found to increase the risk of cardiovascular disease, and Merck faces claims from nearly 30 000 people who had cardiovascular events while taking the drug.[7] In November 2004 *The Lancet* published a meta-analysis of the available safety studies of rofecoxib.[8] In this, the authors concluded that, because of its cardiovascular risk, rofecoxib should have been withdrawn several years earlier.

The list goes on – rosiglitazone, approved in 2000 for diabetes treatment, was withdrawn by the European Medicines Agency in 2010 because of increased rates of myocardial infarction in some patients receiving the drug. The UK's Medicines and Healthcare Products Regulatory Agency concurred, saying that the risks associated with the drug outweigh the benefits – but it has yet to release the clinical trial data to explain its decision.

In his controversial book *Bad Pharma*, Ben Goldacre[9] says that 'drugs are tested by the people who manufacture them, in poorly designed trials, on hopelessly small numbers of weird, unrepresentative patients, and analysed using techniques which are flawed by design, in such a way that they exaggerate the benefits of treatments'. If this sounds extreme, take a look at *Minerva*, published recently in the *BMJ* – '*Diabetologia* reports this week [17 April 2013] that the majority of current trials in diabetes registered on ClinicalTrials.gov exclude older people, are of short duration, involve drug therapy rather than preventive or non-drug interventions and do not focus on important cardiovascular outcomes.'[10]

The *BMJ* made the decision that, as of January this year, it will no longer publish any trial of drugs or devices where the authors do not commit to making the relevant anonymised patient level data available, upon reasonable request. Regulators, doctors and patients, take note.

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