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# Misplaced trust? Gaping flaws in drug approval and licensing

When a medical practitioner writes a prescription, he or she takes it on faith that the substance he or she is prescribing is safe (within the bounds of disclosed potential adverse effects) and efficacious by virtue of its having been rigorously tested, approved and registered by a statutory regulatory agency such as the Medicines Control Council (MCC) in South Africa, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, or the Food and Drug Administration (FDA) in the USA. The FDA mandate as stated on its website echoes that of other regulatory agencies, namely to be 'responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products … [and] medical devices'.

But questions have long lingered regarding the integrity and reliability of the system by which new drugs are evaluated, regulated and promoted, bolstered by revelations of inconsistencies and dubious conclusions in the evidence (clinical trials) used to support the licensing of certain drugs already on the market. The power and influence of drug companies in the registration process is a continuing source of much disquiet among honest clinical researchers and medical journal editors. The clinical trials used to support drug registration are almost always funded and directed by the manufacturer, with a huge financial interest in the outcome. More often than not, such evidence is shrouded in secrecy on the excuse of protection of intellectual property.

The FDA requires just two placebo-controlled trials with positive results to approve a drug indication, regardless of how many other trials fail to corroborate this outcome. As a rule, negative trials are rarely published in medical journals. And it doesn't matter if the difference in effectiveness between the drug and a placebo is slight, as long as it is statistically significant.

## The soft underbelly of clinical trials

For some years now, oseltamivir (Tamiflu), a neuraminidase inhibitor, has been the mainstay of treatment for influenza, and was accordingly stockpiled by many nations at a cost of billions of US dollars in the wake of the H1N1 pandemic. Tamiflu was said to prevent secondary complications such as bronchitis, pneumonia and sinusitis by 67% in otherwise healthy persons infected with the influenza virus, thus helping to reduce hospitalisations by over 60%. This reputation stemmed from a highly influential meta-analysis of clinical trials published by Kaiser *et al*.[1] showing that oseltamivir had these benefits. But when a Cochrane Collaboration group sought to replicate Kaiser's review in 2009, it transpired that the review had been based on 10 clinical trials held by the manufacturer, 8 of which had not been published or peer reviewed.[2] Furthermore, the Kaiser review was funded by the company. Four of Kaiser's co-authors were employees of the manufacturer, and one a paid consultant. Curiously, the key authors of the two trials that were published were not named in documents submitted for registration purposes, and those named in these documents were not listed as authors in the published papers.

Concerted attempts by the Cochrane group to get access to these company-held trials ran up against a brick wall. When the *BMJ* and the UK's Channel 4 News launched a joint investigation into this matter and attempted to gain access to the original registration trials, they too were frustrated by 'a complex interplay between politics, public health planning, availability of trial data, publishing, and drug regulation'.[3]

In 1998 Kirsch and Sapirstein[4] upset the pharmaceutical applecart with the publication of their article entitled 'Listening to Prozac but hearing placebo'. The authors analysed 38 published clinical trials involving more than 3 000 depressed patients, and found that placebos were 75% as effective as the antidepressant drugs studied, whereas the drugs incurred serious adverse effects that included sexual dysfunction and suicide risk. Kirsch and co-workers followed up this work with an analysis of the original trials (obtained with great difficulty) submitted to the FDA for purposes of licensing, and found an even larger placebo effect. Their findings have been replicated by others such as Fournier *et al*.[5] who, as recently as early 2010, concluded that there is little evidence that antidepressants have a specific pharmacological effect relative to placebo.

Conflict of interest and self-aggrandizement are pervasive in the business of drug trials, with many investigators and institutions standing to make tons of money from the drug industry. Former *NEJM* editor Marcia Angell asserts bluntly that 'it is often possible to make clinical trials come out pretty much any way you want, which is why it's so important that investigators be truly disinterested in the outcome of their work'.[6]

The point of this editorial is not about the cited examples, but rather about flaws in the drug regulatory system that made these detractions possible. There is a crying need for greater transparency, integrity and independence from big pharma if the regulators are to earn the complete trust of the practitioner and the consumer.

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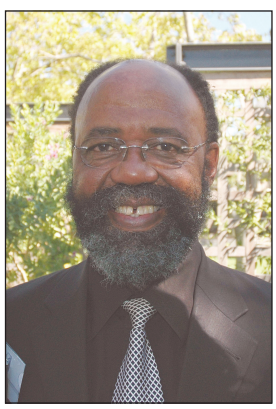

References available from the Editor at profdjn@gmail.com