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Has the pharmaceutical industry commandeered evidence-based medicine? 1) Problems

Dr David Christmas (Consultant Psychiatrist, Advanced Interventions Service, NHS Tayside)
Correspondence to: David Christmas: david.christmas@nhs.net

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ABSTRACT

The pharmaceutical industry has come under increasing scrutiny in recent years because of its practices. For example, financial penalties imposed by the US Government and other agencies on pharmaceutical companies between 1991 and July 2012 exceed $30 billion. More worryingly, in recent years there has been increasing attention on some of the failures of multiple parts of the wider system including pharmaceutical development, safety monitoring and regulation.

This paper will examine some of the techniques used by the pharmaceutical industry to market their drugs, and examine the reliability of some of the claims and counter-claims being made regarding the impact that such practises have upon evidence based medicine.

Key Words: pharmaceutical company; research malpractice; Big Pharma

Introduction

The pharmaceutical industry has come under increasing scrutiny in recent years because of its practices. For example, financial penalties imposed by the US Government and other agencies on pharmaceutical companies between 1991 and July 2012 exceed $30 billion (1). It is often argued that because cases take many years to court, these reports are describing out-dated and corrected practices. However, settlements between November 2010 and July 2012 account for approximately one-third of this ($10.2 billion) and the recent bribery scandals in China admitted by GlaxoSmithKline[1] suggest that problematic practices have not been completely eradicated.

Are the pipelines drying up?

Of concern is the announcement in the last few years that many companies are withdrawing funding into research and development into brain disorders, citing the high risk of experimental drugs failing to reach market (2). However, many commentators have called into question the current process of drug development; highlighting the fact that most drug classes have come about because of serendipitous discovery rather than planned development (3). The current approaches to drug-discovery for CNS disorders have arguably struggled to deliver on their promises over the last two decades.

Failures of regulation

More worryingly, in recent years there has been increasing attention on some of the failures of multiple parts of the system: pharmaceutical development; safety monitoring; and regulation. For example, Rofecoxib (Vioxx) was withdrawn from the market by the FDA after concerns about cardiac

[1] http://www.bbc.co.uk/news/business-23402154

safety, but the manufacturer (Merck) had played down such risks for a long time beforehand. In fact, it is likely that the use of Vioxx resulted in over 2,000 excess deaths in the USA alone (4).

More recently, after a reanalysis of efficacy data by the Institute for Quality and Efficiency in Health Care, IQWIG (the German equivalent of NICE), the antidepressant Reboxetine was reported to be not only ineffective but harmful (5). There are still withheld data regarding Tamiflu (Oseltamivir) which leave considerable doubt over its effectiveness and safety, despite most countries continuing to stockpile the drug in an attempt to militate against pandemic flu.[2] Recently, substantial concerns over publication bias have led to a reconsideration of the evidence for efficacy of the melatonergic antidepressant Agomelatine (6).

The need for transparency in trial reporting has, hopefully, reached a crescendo with the British Medical Journal announcing that they would not be publishing trials unless the raw data were made available to researchers.[3]

This paper will examine some of the techniques used by the pharmaceutical industry to market their drugs, and examine the reliability of some of the claims and counter-claims being made regarding the impact that such practises have upon evidence based medicine.

Collaboration or covert marketing?

In 2012, the Ethical Standards in Health & Life Sciences Group published 'Guidance on collaboration between healthcare professionals and the pharmaceutical industry', a document endorsed by most of the UK Royal Colleges (7) at the time. Some of the problems with this document have been highlighted (8) with *The Lancet* withdrawing their support for the guidance shortly after publication; closely followed by the BMA[4].

The guidance, however, provides a useful framework for critically exploring some of the claims made, and also affords opportunities to reflect on the compelling evidence that contradicts most of the claims.

1. "*Industry is responsible for the vast majority of medicines research and development (R&D) in the UK…*"

This may be true for the UK, but in the USA more than half of new compounds were discovered by Universities and/ or biotechnology companies, and later transferred to pharmaceutical companies (9). Further, most drugs are marketed internationally so the 'origin' of a particular drug is less relevant. The importance of UK-based R&D is an important symbol for the pharmaceutical industry, so it's a shame that Novartis and Roche have threatened to pull out of the UK[5] and Pfizer has closed its research plant in the UK[6].

2. "*It takes 10 to 15 years to develop a new medicine and typically costs £550 million to do all the work necessary before a medicine can be licensed for use*."

This often-repeated figure comes from research (sponsored by the pharmaceutical industry) conducted in 2003 (10), but these costs have been challenged, along with the assumptions used,

[2] http://dx.doi.org/10.1136/bmj.e7305
[3] http://dx.doi.org/10.1136/bmj.e7304
[4] http://bma.org.uk/news-views-analysis/news/2013/march/bma-withdraws-from-pharma-standards-group
[5] http://www.theguardian.com/business/2010/apr/11/novartis-roche-threaten-quit-uk
[6] http://www.bbc.co.uk/news/business-12335801

resulting in protracted debates about how to determine the costs of drug discovery (11-14). More conservative estimates have suggested much lower figures (15).

Whatever the real costs, a significant proportion of industry spend in recent years has been on incremental improvements to existing drugs, rather than new 'breakthrough' compounds. Only about 10% of new drugs offer significant benefits over existing drugs (16). For these 'me-too' drugs (a drug that is structurally very similar to already known drugs) and 'evergreening'[7], the development process is much shorter, and consequently, much cheaper. Evergreening also has the important consequence of delaying the entry of generic drugs into the market (17). Other examples of patent-extension include the licensing of unusual doses – for example, a 23mg dose of Donepezil which offered no additional benefits but could not be made up of generic 20mg and 5 mg tablets (18).

Finally, the high costs of drug discovery are often used to justify the high prices of new drugs. Industry claims that more money is spent on drug development than promotion are easily deconstructed, suggesting that promotion is the largest component of the costs of drugs (19).

3. "*…the results of controlled clinical trials are made available in the public domain through clinical trial registries and portals, peer reviewed publications, medical meetings and company websites*."

This claim is spurious. As discussed above in the case of Reboxetine, unfavourable clinical trial data are often withheld by pharmaceutical companies because they are not obliged to produce it when submitting applications to regulatory bodies. In addition, despite the existence of trial registries and mandatory reporting, approximately 50% of trials used in support of marketing approval are never published (20). Further, there is compelling evidence of publication bias for antidepressants and antipsychotic drugs (21, 22). There is convergent evidence that studies sponsored by industry are more likely to report positive results (23, 24). Despite apparent mandatory reporting of data from trials in registries within one year of completion, most trials fail to comply (25, 26) and fewer than half of such studies are ever published in peer-reviewed journals (27). In summary, anywhere between 25% and 50% of trial data involving patients never reaches the light of day.

4. "*Industry plays a valid and important role in the provision of medical education.*"

This suggestion is not supported by the evidence. Unfortunately, industry-sponsored medical education creates clear conflicts of interest (28) and has been shown to be biased (29). In 2005, the House of Commons Health Committee concluded that: "*The pharmaceutical industry's promotional efforts are relentless and pervasive. The evidence presented showed the lengths to which the industry goes to ensure that promotional messages reach their targets, and that these targets include not only prescribing groups, but patients and the general public*." (17).

Many doctors fall foul of the 'third-person effect', *i.e.* they believe that others are more susceptible to influence than themselves (30). It is commonly assumed by people that they are immune from the influence of promotional strategies, but it is not the case – we are all vulnerable to such tactics (31).

[7] "*Evergreening involves extending the patented life of a branded product, typically by reformulating the drug, for instance by using a different drug delivery system, changing a dosage form, or presentation (e.g. from tablet to capsule).*"(17)

5. "*Whilst medical representatives are employed to promote medicines, they can be a useful source of information for healthcare professionals and are another vital feedback mechanism to the companies they represent*."

There is no evidence to support the claim that information from industry is consistently reliable, accurate, or free from bias. Information from pharmaceutical companies is associated with higher prescribing frequency, higher costs, and lower prescribing quality (32). Large conferences organised by independent groups provide ample opportunity for industry to gain contact with doctors and influence the scientific programme through satellite meetings (33).

The main reason for having representatives is to influence the prescribing patterns of doctors. The influence of medical reps on prescribing has been demonstrated repeatedly (34). In addition, the 'gifts' commonly-received (such as pens, notepads, etc.) and free samples all impact upon behaviour (35-38).

With regards to feedback, there are already well-established mechanisms by which health professionals can supply post-marketing data on the drugs they use; for example, the Yellow Card Scheme[8], managed by the Medicines and Healthcare products Regulatory Agency (MHRA). Giving feedback to representatives from pharmaceutical companies is unlikely to result in safer or better drugs since the information is not shared between companies or reported centrally.

6. "*Industry is able to provide factual information to patients about the medicines they have been prescribed including patient information leaflets and websites.*"

Direct to Consumer Marketing (DTCA) is not permitted in the UK and many other countries. It has been shown to have no clear benefits and results in increased prescribing of advertised drugs (39). As discussed above, the information from drug companies is often of low quality. Such schemes are typically used to generate demand for a product (40) and/or galvanise support among patients groups. Such a process is often called 'astroturfing' because of its ability to generate an artificial 'grass-roots' community. The funding of patient groups by the pharmaceutical industry is concerning to many (41).

7. "*Strict rules govern adverse event reporting. Companies have pharmacovigilance teams dedicated to post-marketing surveillance…*"

This would be reassuring if it wasn't for a number of high-profile examples where either information about safety was withheld by the company, *e.g.* Vioxx (42), or Rosiglitazone (43); or marketing was initiated to downplay potential risks of the drug, in the case of Olanzapine (44). This claim is perhaps most concerning given that it is offering false reassurance of safety when the track record of the pharmaceutical industry suggests that active attempts at hiding or downplaying risks are often employed. Further examples of drugs where risks outweigh benefits include Reboxetine, which turned out to be ineffective and harmful, largely due to the fact that 74% of the patient outcome data held by Pfizer had never been published (5).

Regulatory bodies, historically, have not been quick at removing potentially dangerous drugs from the market. For example, Benfluorex (Mediator) is estimated to have resulted in over 1,000 excess deaths before it was removed from the market (45).

[8] https://yellowcard.mhra.gov.uk/

Conclusions

The pharmaceutical business is just that – a business. Whilst its products have the potential to improve health and benefit patients, the magnitude of benefit to public health is difficult to quantify. Whilst some studies have suggested that many of the recent gains in life expectancy can be attributed to new drugs (46), these assumptions have been challenged (47).

Critics will argue that the business element of the industry has led to some of the practices described above, with a focus on profit, sales, and marketing over genuine improvements in patient benefits. Further, the need to maximise profit over a relatively short period of time leads to the suppression of concerns over risks associated with novel compounds.

The number and size of fines imposed on the pharmaceutical industry in recent years would suggest that many of the more questionable practices are not products of a bygone age. The wider implications include the overpromotion of new drugs that offer little benefit over existing drugs, and the risk of patient harm that is downplayed for as long as possible, in order to maximise the return to shareholders.

Evidence-based medicine, rather than providing a mechanism to challenge questionable claims has become another tool through which covert advertising and promotion furthers the industry's aims, rather than benefiting patients. We will look at some of the other techniques, and discuss solutions in the second paper.

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