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Is there a cure for corporate crime in the drug industry?

Effective enforcement of regulations needs more resources and the will to impose robust sanctions

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Nearly 30 years since Braithwaite's *Corporate Crime in the Pharmaceutical Industry* showed that unethical and corrupt behaviour was endemic in the sector, there is growing evidence that little has changed. Recent research suggests that violation of the law continues to be widespread. Most new medicines offer small advantage over existing products, so promotion plays a huge role in achieving market share. The temptation for companies to resort to misleading claims is great. According to Gøtzsche,[1] as of July 2012, nine of the 10 largest drug companies were bound by corporate integrity agreements under civil and criminal settlements or judgments in the United States. The corporate activity that has led to recent government investigations has involved unethical and unlawful practices that are well beyond mere administrative offences.

Whistleblowers' and other "insider" accounts in the US typically include allegations that companies systematically planned complex marketing campaigns to increase drug sales, which involved illegal and fraudulent activities. These included active promotion of off label, or otherwise inappropriate, use of drugs, despite company knowledge that such use could seriously harm patients.[2 3]

The recent introduction of Regulation 658/2007 in the European Union empowers the EU Commission to impose financial penalties for corporate violation of EU legislation on medicines. However, this may be too little, too late. Multi-million dollar fines imposed under US settlements seem to have failed to deter companies from violating regulations, given that several companies are repeat offenders. This has led to calls for sanctions to be strengthened. Imposing bigger fines is one option, but courts might be reluctant to impose penalties that would threaten the financial survival of companies. Other sanctions being debated include removing companies' patent rights and holding senior managers criminally liable.[4] Corporate integrity agreements could also serve as more effective vehicles for corporate probation by imposing escalating restrictions on company freedom appropriate to the offences committed. For instance, if companies hide clinical trial data, regulators could take control of future clinical trials and charge offending companies for the cost of doing so.

Although stronger sanctions are needed to deter drug companies from wrongdoing, this may be insufficient to protect the public because legal resolution of complex criminal and civil investigations takes years, during which time unethical and illegal behaviour may continue unabated. For example, during all phases of the US Justice Department's seven year investigation of Warner-Lambert's promotion of the drug's unapproved use, off label prescriptions for gabapentin (Neurontin) increased dramatically, which has raised suspicions that the firm's off label promotion persisted throughout.[5] Warner-Lambert, of which Pfizer is a parent company, pleaded guilty to charges of promoting gabapentin for the non-approved use. It was subsequently established that gabapentin was not efficacious for the non-approved indication.

In such cases, prompt action by regulatory agencies to prohibit further violation of the law is also needed to protect public health. However, it is striking that the Food and Drug Administration has played a marginal role in detecting cases of fraud or enforcing compliance with the law. Of the 11 civil or criminal cases involving off label promotion by major drug companies settled by the US Justice Department between 2003 and 2007, none was referred by the FDA.[6] In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) initiated 101 prosecutions for breaches of medicines legislation between 2005 and 2012, but none involved a large research based drug company. In addition, there was only one (unsuccessful) referral for potential prosecution of such a company—GlaxoSmithKline regarding paroxetine (Seroxat).[7]

Why have drug regulatory agencies played such a small role in prosecuting large companies given evidence of extensive illegal activity uncovered by other investigating bodies? The reality is that, with current resources, medicines regulators can police only a fraction of the industry's ever expanding promotional activities. The MHRA currently vets print advertisements for around 50 medicinal products each year.[8] Because of the complex and varied ways in which companies promote their drugs,[2] gathering evidence of systematic illegal marketing requires far greater commitment in terms of time, money, and human capital.

Increased resources and expanded legal authority may need to be backed up by a more probing regulatory culture. Both the MHRA and the FDA claim that they can generally achieve compliance through informal communication and negotiation with large firms, but regulators seem to treat evidence of non-compliance as isolated incidents rather than signals that firms may be engaged in extensive offending. Indeed, US government investigations indicate that even when faced with evidence of serious wrongdoing or persistent violation the FDA may be reluctant to initiate formal investigations or escalate its response against individual companies.[6 9] Such timid regulatory behaviour may be symptomatic of the extent to which regulators have been encouraged by governments to be responsive to the commercial interests of industry and to view large drug firms as clients whose fees increasingly fund these agencies.[10]

The FDA has been granted additional funding for fraud detection and prosecution and other signals from Congress suggest that the agency should increase its enforcement activity.[11] A similar shift in the UK is less likely given successive governments' determination to "reduce burdens on business." Whether government authorities in the EU are willing to take enforcement action against large drug companies will become clearer on resolution of the European Medicines Agency's investigation of Roche for safety reporting violations[12] and a French manslaughter investigation of Servier Laboratories' former president in relation to benfluorex (Mediator).[13]

Individual instances of corporate malfeasance are indicative of wider systemic problems. Whether companies continue to "get away with it" depends, in part, on whether regulators can develop credible systems of detection, enforcement, and punishment.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2013;346:f755
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Most trials that claimed to investigate the effect of exchanging saturated fat for linoleic acid involved multiple dietary changes or multiple interventions

American Heart Association advice on omega 6 PUFAs cast into doubt

Old study sheds new light on the fatty acids and cardiovascular health debate

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In a linked research paper, Ramsden and colleagues report "new" data from an old trial that shed light on the long running debate on whether increasing dietary linoleic acid intake reduces the risk of cardiovascular disease (CVD) or death.[1] Research conducted in the 1960s and 1970s suggested that some of the commonly occurring dietary saturated fatty acids raise total and low density lipoprotein cholesterol concentrations, whereas the omega 6 polyunsaturated fatty acid (PUFA) linoleic acid lowers total and low density lipoprotein cholesterol concentrations.[2]

Linoleic acid is present in high amounts in vegetable oils such as corn, sunflower, safflower, and soybean oils and in margarines made from these oils. It is the most prevalent PUFA and omega 6 PUFA in most Western diets. As a result of the effects of linoleic acid on cholesterol concentrations, lowering intake of saturated fat and increasing that of PUFAs has been a cornerstone of dietary advice, with the aim of decreasing the risk of cardiovascular disease (CVD).[3]

The American Heart Association recently repeated advice to maintain, and even to increase, intake of omega 6 PUFAs.[4] This advice has caused some controversy,[5-7] because evidence that linoleic acid lowers the risk of CVD is limited—most trials that claimed to investigate the effect of exchanging saturated fat for linoleic acid involved multiple dietary changes or multiple interventions (or both).[5] In particular, studies lowered trans fatty acid intake or increased omega 3 PUFA intake (or both) at the same time as increasing linoleic acid intake. The impact on CVD risk or mortality of replacing saturated fat with linoleic acid without changes in other fatty acids has rarely been investigated, and no large randomised controlled trial has recently explored this important question.

Secrets of old data unlocked

However, the newly analysed data from the Sydney Diet Heart Study, a randomised controlled trial conducted from 1966 to 1973 and comprising 458 men aged 30-59 years with a recent coronary event (myocardial infarction, acute coronary insufficiency, or angina), fills this gap. Participants were randomised to a diet rich in linoleic acid or continuation of their habitual diet.[8] Both groups were treated the same in other respects and received the same advice. Baseline dietary intake data showed an average linoleic acid intake of about 6% of energy and an average saturated fatty acid intake of about 16% of energy. The linoleic acid group was instructed to increase PUFA intake to 15% of energy and to reduce saturated fatty acid intake to less than 10% of energy; participants were provided with liquid safflower oil and a safflower oil based margarine to be used instead of animal fats for cooking, baking, and spreading. Safflower oil is 75% linoleic acid and does not provide other PUFAs. Follow-up was a median of 39 months. Total cholesterol was lowered by an average of 13% in the linoleic acid group. Despite this, higher all cause mortality in the linoleic acid group was reported in 1978,[8] but death from CVD and coronary heart disease (CHD) were not reported.

In the linked study, Ramsden and colleagues have analysed the original data using modern approaches to create a novel and interesting piece of work. The original data were recorded on a nine track magnetic tape and had to be recovered and converted to a useable format, a not inconsiderable task. The results confirm that the linoleic acid group had a higher risk of all cause mortality (hazard ratio 1.62, 95% confidence interval 1.00 to 2.64), and now show a higher risk of mortality from CVD (1.70, 1.03 to 2.80) and CHD (1.74, 1.04 to 2.92).

The authors then used the new data generated from the Sydney Diet Heart Study to update an earlier meta-analysis.[5] Two other linoleic acid intervention trials that reported CHD and CVD mortality were included.[9 10] This updated analysis reported an increased risk of death from CHD (1.33, 0.99 to 1.79) and CVD (1.27, 0.98 to 1.65), although the results were not significant. These findings argue against the "saturated fat bad, omega 6 PUFA good" dogma and suggest that the American Heart Association advisory that includes the statement "higher [than 10% of energy] intakes [of omega-6 PUFAs] appear to be safe and may be even more beneficial"[4] may be misguided. The more cautious UK dietary recommendations on fat and fatty acids, which include the statement, "There is reason to be cautious about high intakes of omega 6 PUFAs,"[3] seem fully justified in the light of the current study's findings.

The new analysis of these old data provides important information about the impact of high intakes of omega 6 PUFAs, in particular linoleic acid, on cardiovascular mortality at a time when there is considerable debate on this question.[4-7 11] The findings underscore the need to properly align dietary advice and recommendations with the scientific evidence base. It is important when assessing this evidence base that subtle, and in some cases unsubtle, aspects of study design are properly considered. For example, outcome of studies in which intakes of saturated and trans fatty acids are lowered while intakes of omega 6 fatty acids and omega 3 PUFAs are increased may be most strongly influenced by changes in trans and omega 3 fatty acids. They should not be interpreted as showing an effect of omega 6 PUFAs.

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2013;346:f493

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Tamiflu: 14 flu seasons and still questions

At best, and bearing in mind missing data, the drug shortens flu symptoms by a day

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In the midst of a worse than average influenza season, clinicians are increasingly prescribing antiviral agents, especially oseltamivir (Tamiflu). Oseltamivir, an oral neuraminidase inhibitor, was first approved for use by the US Food and Drug Administration in 1999. It is indicated "for the treatment of acute, uncomplicated illness due to influenza infection in patients 2 weeks of age and older who have been symptomatic for no more than two days," and, "for the prophylaxis of influenza in patients 1 year and older," with similar indications worldwide. Despite these broad indications, some government agencies promote even wider use. For instance, the website of the US Department of Health and Human Services states that oseltamivir may prevent serious complications of flu, and the US Centers for Disease Control and Prevention's website states that early antiviral treatment may reduce the risk of complications of flu and death.[1 2] Business analysts expect rising sales of oseltamivir to reach $750m (£474m; €562m) this year alone.[3]

With the huge number of people affected and such remarkable sales, the evidence to support the use of oseltamivir should be strong. Yet despite the 14 successive flu seasons since the FDA first approved the drug, definitive trials of oseltamivir across diverse populations for a variety of important outcomes are lacking. More importantly, results of many of the trials that have been conducted remain unpublished or only partially published (www.bmj.com/about-bmj/article-clusters/tamiflu).

The Cochrane Collaboration's most recent systematic review of neuraminidase inhibitors, including oseltamivir, for healthy adults and children states, "due to limitation in the design, conduct, and reporting of the trial programme, the data available to us lacked sufficient detail to credibly assess a possible effect of oseltamivir on complications and viral transmission." It concluded, "we found a high risk of publication and reporting biases in the trial programme of oseltamivir."[4] The review was based on 25 studies, 15 of which were on oseltamivir. Twenty other identified studies could not be included because of insufficient information or unresolved discrepancies in the data. Crucially, in an effort to include all identified studies, the Cochrane investigators requested full clinical study reports from Roche, the funder of all but one of the studies. But data from these studies were not provided, which prevented the inclusion of some studies in the systematic review and also prohibited scrutiny of the research.

The lack of benefit in reducing hospital admissions is particularly striking given that oseltamivir is listed as an essential drug by the WHO

Nevertheless, the Cochrane investigators obtained information directly from the European Medicines Agency, and a full examination of the available data failed to identify a benefit of oseltamivir on risk of hospital admission. There was still insufficient evidence to assess its effect on risk of flu complications.

So does oseltamivir work at all? The Cochrane investigators found that the available data showed that, when used early, oseltamivir shortened the duration of flu symptoms by 21 hours, from an average of nearly seven days to six. Unfortunately, they could not assess whether symptoms relapsed. Moreover, these findings were based on the results of only five of the 15 available studies (those that reported this specific outcome), of which only two were published. For all the available studies, unpublished clinical study reports were used. In addition, the investigators identified an additional three trials that reported this outcome that could not be included because data were not available.

The lack of benefit in reducing hospital admissions is particularly striking given that oseltamivir is listed as an essential drug by the World Health Organization, many government agencies recommend it, many clinicians prescribe it, and many patients seek it explicitly in the hope of avoiding complications once they have flu-like symptoms.

What is the way forward for patients and clinicians? Firstly, despite government claims, we should acknowledge the uncertainty surrounding oseltamivir's effectiveness and the gaps in publicly available evidence. On the basis of the available data, at best the drug shortens symptoms by about a day when used within the first two days of symptoms, but it has no effect on hospital admissions. In addition, trial data from which to draw conclusions about complications and transmission of flu are lacking. However, any effect of the drug on shortening symptoms is based on only a proportion of the identified studies; to trust the result, we must assume that data from all studies would concur.

The story of oseltamivir is an indictment of our current research enterprise. A blockbuster drug has been allowed to dominate a market in the absence of ample and rigorous evidence of effectiveness. A drug that is used so widely at great cost should require a commensurate evidence base.[5] We need non-industry sponsored comparative effectiveness trials to answer the questions of who benefits from the drug and by how much.

Independent trials of oseltamivir should be easy to conduct given the large number of eligible patients and short time needed to ascertain clinically meaningful outcomes. Some of the uncertainty about oseltamivir and other neuraminidase inhibitors could be mitigated immediately if the manufacturers made all related clinical trial data available for independent analysis. The medical profession and the public must insist that—for the privilege of selling any product, particularly one that generates substantial annual revenue and has marked public health implications—all available data relevant to risks and benefits are disclosed so that independent assessments can be performed.

Without stronger evidence generation and assurance that all previously collected data and findings will be disseminated, we are left guessing about the true effectiveness of this drug. How many more flu seasons will pass before we know the answers?

Competing interests: HMK and JSR receive support from Medtronic via a research grant through Yale University; HMK is supported by grant U01 HL105270-03 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute in Bethesda, MD, and chairs a scientific advisory board for United Health; JSR is supported by the National Institute on Aging (K08 AG032886) in Bethesda, MD, and by the American Federation for Aging Research in New York, NY, through the Paul B Beeson Career Development Award Program and is a member of a scientific advisory board for FAIR Health in New York, New York.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2013;346:f547

EvidenceLive 13

Where next for evidence based healthcare?

A *BMJ* conference aims to inspire a new generation of evidence creators and consumers

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Evidence based healthcare has taken root as one of the central pillars of modern medicine. Arguably, the delivery of healthcare based on evidence has never been more important as we grapple with unexplained variations in practice and spiralling healthcare costs. But despite its widespread acceptance as a mechanism for rational decision making, evidence based healthcare remains in many ways an ideal rather than a fully fledged reality. On top of its well rehearsed limitations,[1] new challenges are undermining its potential to improve healthcare outcomes.

First though, let us acknowledge the progress that has been made since evidence based medicine was first articulated in the early 1990s.[2] Systematic review was then in its infancy, and methods for searching, selecting, and meta-analysing data have advanced almost beyond recognition. Our expectations of the quality of reporting for clinical trials and other study designs have risen sharply thanks to the widespread adoption of checklists, such as those created by the Equator network (www.equator-network.org). Trial registration and protocol deposition now provide a means of tracking trials from their outset, with the potential to chase up trials whose results have not been published. And the growth in open access to research means that more and more studies are available in full online.

Yet these undoubted advances have been accompanied by less welcome realisations. The exponential growth in the number of reported studies stretches our ability to retrieve relevant reliable evidence and to keep synopses and clinical guidelines up to date.[3] And it seems that the more we scrutinise the available results of this growing body of research, the more sceptical about its credibility we become. Much published research is of poor or uncertain quality, and an unknown proportion of research is never published. A recent review of research funded by the National Institutes of Health found that only a small number of trial reports are analysed in up to date systematic reviews, and a seemingly obvious requirement—that all relevant evidence should be available for analysis when trying to answer a clinical question—remains unmet.[4]

This leaves us with increasingly sophisticated methodological tools but not the raw materials (reliable data) to answer with certainty some common clinical questions, such as is cholesterol lowering effective for primary prevention of cardiovascular disease, is breast cancer screening cost effective, what target blood pressure should we aim for when treating hypertension, how do we deliver care for chronic diseases in the developing world, and are antivirals effective for preventing and treating influenza?

The evidence base and the methods for evaluating diagnostic strategies continue to lag behind the far better resourced research on treatments

Better diagnosis is one key to unlocking unrealised health gains. Earlier diagnosis could be achieved by making some tests more available and easier to access, but how can we do this without increasing the burden of false positive results? Diagnostic tests need to be cheaper and more accurate. Yet the evidence base and the methods for evaluating diagnostic strategies continue to lag behind the far better resourced research on treatments. Without progress on this front, and on the communication of risk, the usefulness of decision aids for evidence based partnership between patients and their clinician advisers will be severely limited.

Nor do we yet have adequate infrastructures to protect the evidence base from avoidable bias. Healthcare is the fastest growing business in the world and is beset with commercial interests. Yet it is becoming increasingly obvious that current legislation and regulations on the safety and efficacy of drugs and medical devices are not fit for purpose.[5] The structures and culture of academic research also have ways of introducing bias.[6]

Then there is perhaps the most difficult question facing every health system in the world: how will we pay for healthcare? Only by rigorous application of the best evidence can we be sure that health systems will deliver true value. But what constitutes the best evidence and how do we apply it effectively to clinical practice and health policy?

Now in its third year, a partnership between the *BMJ* and the Oxford Centre for Evidence Based Medicine aims to provide a forum for exploring, if not answering, some of these questions. EvidenceLive, a conference in Oxford from 25 to 26 March, will bring together 500 participants including some of the world's most distinguished, informed, and argumentative evidence experts for two days of animated debate. A programme for students and junior doctors means that a new generation of creators and consumers of evidence will also have their say. For those who can't be there in person, there will be Twitter (use #ev2013 and #evidencelive), videos, and coverage in the *BMJ*.

We hope you will engage with EvidenceLive in whatever way you can. The future of healthcare depends to a large extent on how quickly and how well these challenges are dealt with.

Competing interests: CH and FG are co-chairs of EvidenceLive. Neither receives any financial benefit from the conference.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Cite this as: *BMJ* 2013;346:f766