Making A Killing

How Drug Company Greed Harms People and Animals

An Animal Aid Report
written & researched
by Toni Vernelli

ANIMAL AID

... this report is not based on campaign slogans or rhetoric. The raw material is from solid scientific, political, business and consumer advocacy sources – material that is already in the public domain, but which has never before been gathered together...

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How Drug Company Greed Harms People and Animals

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Executive Summary

More than half a million animals are used in drug development and testing every year in the UK, with millions more used for this purpose worldwide. Despite drug company claims that animal tests are a 'necessary evil' to ensure the safety of new medicines, more than one million Britons were hospitalised due to severe adverse drug reactions in 2006 and hundreds of drugs are either withdrawn or relabelled every year due to safety concerns. In addition to observational evidence, scientific studies examining the reliability of animal tests in predicting human outcomes have repeatedly shown that they are no more accurate than tossing a coin.

So why do drug companies, with a collective income of more than £300 billion in 2007, persist with such outdated and unreliable testing methods? In this report, we show that animal tests, along with many other pharmaceutical industry practices, are not done in the interest of patient health and safety but are instead designed to protect drug company profits. Using vivid – and often shocking – examples, this report illustrates the host of unsavoury practices – including misleading animal tests – that drug companies employ to drive up drug sales, often at the expense of people's health and undermining publicly-funded healthcare systems such as the NHS. These objectionable practices include:

- **Disease-mongering:** Creating new diseases or redefining existing conditions in order to expand the market for a drug. Often disguised as Corporate Social Responsibility, drug companies enlist doctors, patient groups and the media in 'disease awareness' campaigns for corporately created diseases such as Restless Legs Syndrome, Female Sexual Dysfunction and Social Anxiety Disorder in an attempt to increase drug sales.
- **Manipulating doctors:** From overt incentives such as consultancy fees and all-expenses-paid conference trips, to seemingly benign practices such as sponsoring medical education programmes and distributing free drug samples, drug companies are relentless in their efforts to influence doctors' prescribing habits. Many respected medical journals have been co-opted in these efforts, with drug company reps now 'ghostwriting' up to half the articles published about new drugs.
- **Exploiting patients:** Not content with targeting doctors directly, drug companies also target patients – through advertisements thinly veiled as 'awareness' campaigns – in the hope that they will pressurise their doctor to prescribe a drug. In the US and New Zealand – where advertising prescription drugs directly to consumers is permitted – drug companies spend more on advertising than either Coca-Cola or Pepsi, often enjoying a return on investment of £6 for every £1 spent. Despite virtual unanimity amongst health professionals, government bodies and consumer groups on the harm caused by direct-to-consumer advertising in these countries, the European Parliament is pressing ahead with proposals to allow drug companies to 'communicate directly with patients' here.
- **Research fraud:** While the widespread industry practice of suppressing negative clinical trial results has recently received much publicity, the devious ways in which drug companies manipulate trial designs to achieve favourable results have not received such wide exposure. Common tactics include: using insufficient or excessive doses of comparator drugs so that the sponsor's product looks more effective or safer; ending trials as soon as benefits appear or selectively publishing data from only part of a trial (when the full data set shows either harmful side effects or a decrease in effectiveness over time); and inappropriate analysis of data to portray their product in a better light.
- **Preying on the poor:** Because animal tests cannot reliably predict the effects a drug will

have in humans, clinical trial participants face great risks and recruitment of healthy volunteers can be difficult. To overcome this obstacle, healthy volunteers are usually paid – commonly £100 a day or more – attracting a high number of poor people who may agree to risks they might not otherwise take. Volunteer consent forms often use scientific or legal terminology so many volunteers may not be fully aware of the risks involved. Increasingly, drug companies are running their clinical trials in developing countries where there is less regulation and enforcement and where many people are desperate for access to drugs.

- **Prioritising lifestyle drugs over lifesaving ones:** Despite justifying animal tests as necessary in the search for lifesaving cures, the majority of drug company research is focused on areas of guaranteed profitability, such as lifestyle drugs (e.g. for erectile dysfunction or obesity) and copies of competitors' successful products (known as 'me-too' drugs). International figures show that between 68 and 94 per cent of new drugs approved in the last two decades have offered no substantial improvement over existing drugs – they were simply 'me-too' drugs. Meanwhile, diseases which mainly affect the world's poor – such as malaria, tuberculosis, sleeping sickness and pneumonia – have been virtually ignored by drug companies.

- **Anti-competitive practices:** Even though drug companies enjoy a substantial period of exclusivity for all new drugs they market, they constantly have tried to extend this period through a range of patent manipulations and legal action against generic competitors. Evergreening – extending the patent on a product by modifying it slightly – is a common tactic as companies can get an extra 20 years of patent protection by simply changing a drug from tablets to capsules. It is only now, as patents begin to run out on many blockbuster drugs and the industry looks for new sources of profit, that an interest in the generic drugs market is being shown.

- **Bullying tactics:** Those who do speak out about drug company corruption or express safety concerns often face lawsuits or smear campaigns designed to silence them. Even respected medical journals have come under attack by drug companies for publishing studies which highlight safety concerns about their products.

Introduction

Why is an animal rights group publishing a report on the failings of the pharmaceutical industry? What competence do we have to pronounce on this subject? And can any criticisms we level be trusted, given that drug companies conduct a good deal of animal research and we profoundly object to such activities? Aren't our findings bound to be less than scrupulously objective?

The answer to the questions about competence and objectivity is simple. This report is not based on campaign slogans and rhetoric. The raw material is from solid scientific, political, business and consumer advocacy sources – material that is already in the public domain, but which has never before been gathered together to paint such a comprehensive picture of what we regard as a dissolute industry.

We cite more than 400 references. They relate to material published by – among others – the US Food and Drug Administration, the House of Commons Health Committee, Consumers International, the Senate Finance Committee, leading specialist publications such as *Nature* and the *British Medical Journal* and 'quality' lay newspapers from around the world.

Have we gathered up this material and presented it fairly? The reader can be the judge. But suffice to say that we are aware of the scepticism and even hostility that some harbour for the anti-vivisectionist cause. Not a few people have been encouraged to believe that we put the life of a rat above that of a child and that we are, therefore, irrational and dangerous.

We do not conceal the fact that the bedrock of our opposition to animal research is that it is predicated on large-scale, systematic exploitation and cruelty. Animals of virtually every species are purpose-bred or captured in the wild so that they can be confined, damaged and killed.

Of course, objections on the grounds of animal suffering are unlikely ever to win the day for so long as the public believes what those with a stake in animal testing repeatedly tell them: *experiments on animals yield data that can reveal whether a new drug is safe and beneficial for human patients to take.*

This report summarises the evidence against that proposition. It illustrates why it is dangerous to extrapolate from animal to human – a current and dramatic example being the painkiller Vioxx, which is reported to have caused between 88,000 and 160,000 heart attacks and strokes in the US alone before being withdrawn in 2004. In laboratory tests, the drug was actually cardio-protective in some animal species.

Why, though, would drug companies use animals to test new compounds if the evidence is against animals producing reliable data? The answer is that animals are a remarkably flexible resource. Depending on the species chosen, and even the sex, age and strain of that species, you get varying answers to the questions posed. That assists a company to compile a body of evidence for the regulatory authorities that 'proves' the safety and efficacy of its candidate new compound compared with allegedly more dangerous and ineffective competitor products.

If drug companies are prepared to persist with a defunct and hazardous testing paradigm in order to get their drugs onto the market, in what other sharp practices are they prepared to engage?

The answer to that question forms the core of this report. We show, through the best available evidence, that, just as drug companies fail a basic test of honesty and ethical behaviour in their use of animals, so they keep on failing as they take new drugs through human clinical trials, and in their dealings with regulatory authorities, with doctors, scientific publications and patient groups.

According to Médecins Sans Frontières, which campaigns for essential medicines for the world's poorest people, more than three-quarters of the new products approved by the US Food and Drug Administration between 1989 and 2000 had no therapeutic benefit over existing products. And there is every reason to believe that the figures for the UK are likely to be similar. Yet the damage caused by officially sanctioned drugs – all of them having passed the animal tests – remains at a frightening level. Adverse drug reactions are responsible for more than 6.5% of all UK hospital admissions. In 2006, this translated into more than one million admissions.

Where research does show evidence of harmful effects, there is a reasonable chance that it will be concealed. A recent *New England Journal of Medicine* article found that studies involving a type of antidepressant known as Selective Serotonin Reuptake Inhibitors (SSRIs) were 12 times more likely to be published if the findings were positive. Hence, there emerged a falsely upbeat profile of a class of drug that was subsequently linked to a marked increase in suicidal behaviour in adolescents and adults. SSRIs also double the risk of stillbirths, babies of low birth weight and foetal malformations in women who take them during pregnancy.

Concentrating on the good news not only pays off for the drug makers, it also means a big payday for publishers of scientific journals. Dr Richard Smith, former editor of the *British Medical Journal*, says that drug companies will order hundreds of thousands of reprints of published articles for distribution by their reps in hospitals and GP surgeries. Journals have become reliant on this revenue, even though it is an income stream that saps their independence – making them, says Smith, 'little more than a marketing tool of the drug companies'.

Doctors are also on the receiving end of Big Pharma's largesse. Leading British physicians can earn scores of thousands of pounds for promoting a company's products through presentations, research papers, conferences and debates. And GP practices can generate profits of more than £50,000 a year by recruiting patients for clinical trials. While, in rich countries, such blandishments tend to be filed under 'education' or 'research', in countries not given to this kind of feeble subterfuge – such as Pakistan, India and Indonesia – the inducements can come undisguised. Here, drug companies keen to press doctors into prescribing their products will regularly hand out lavish gifts such as cars, air conditioners, laptops, refrigerators, TVs and child tuition fees.

Another vital drug company asset is the patient group, many of which will receive significant financial and other help from Big Pharma. In response, the groups' educational booklets might feature some product placement – and the media will be approached with a call for the NHS to stop penny-pinching and prescribe more generously a 'life changing' new drug. MP Paul Flynn told the House of Commons Health Committee that patient groups are used by drug companies as 'conduits to promote their products in a subtle form of marketing'.

How distant are such manoeuvres from the issue of animal testing?

All the activities dealt with in this report should ultimately be judged by the same criterion: are they characterised by honest and ethical behaviour? If not, who pays the price? It is clear that animals pay with their lives when they are used for 'safety' and 'efficacy' tests. But because the data the tests generate cannot be applied reliably to human medicine, patients also suffer. And people continue to suffer because of the sharp and corrupt practices we outline in relation to the trialling and marketing of drugs.

Transnational pharmaceutical companies are powerful bodies. By turns, they seduce and overawe regulators and legislators. This report makes the point that the public deserves better; the victims of animal research deserve better. Big Pharma must be reined in so that it serves the public as well as itself.

Andrew Tyler
Director of Animal Aid

Drug Discovery and Development

Pre-clinical Studies

Drug research usually begins with computer studies designed to analyse new molecules for their potential to treat or prevent human diseases. Those that show promise are then studied in a series of test-tube experiments, called assays, to determine whether they have a chemical effect on the relevant human enzymes, cells or tissues. Molecules or compounds which show desired effects in these *in vitro* studies (literally 'in glass') are then tested in living animals (*in vivo* studies).[1]

According to Home Office statistics, **more than 650,000 animals** were used in drug development and testing in the UK during 2007. These included:

- 571,557 small mammals (mice, rats, hamsters, gerbils and guinea pigs)
- 58,399 fish
- 7,490 rabbits
- 7,394 chickens
- 5,441 dogs
- 2,628 monkeys

Before a new drug can proceed to human clinical trials, regulatory authorities require that it be tested in two mammalian species – one rodent and one non-rodent – to demonstrate, in theory at least, its safety and effectiveness. Although beagles have traditionally been the most common non-rodent species used, non-human primates, particularly marmosets, are increasingly being used as the second species in drug testing.[2]

A range of toxicity tests are performed on animals in an attempt to demonstrate a drug's safety. Most tests involve force-feeding animals a drug by gavage (a long tube pushed down into the stomach), or injecting them with a drug, often in high doses to assess its poisonous effect (acute toxicity).[3] Some of the symptoms observed in acute toxicity tests include vomiting, internal bleeding, diarrhoea, salivation, coma, convulsions, tremors, loss of fur and hair, nasal discharge, breathing difficulties and death.[4]

After the acute toxicity tests, chronic or long-term studies involving repeated doses of a drug, lasting anywhere from 6 months to more than two years, are conducted to investigate its potential to cause mutations (mutagenicity), cancer (carcinogenicity), foetal malformations (teratogenicity) and reproductive problems.[5] Tests are also carried out to examine how the drug is absorbed, distributed around the body, metabolised and excreted (ADME).[6] These involve blood and other body fluid samples being taken repeatedly. Most animals used in chronic toxicity tests are killed at the end of the study so that the drug's effect on their tissues can be examined.

To test the effectiveness of a drug, animals may be physically or chemically damaged to produce some of the symptoms of human disease and then treated with the drug to observe its effects. For example, because dogs do not naturally develop atherosclerosis the condition is artificially induced by tying wire around their coronary arteries or blocking them with plastic beads.[7] Increasingly, animals are being bred with a specific genetic defect which causes them to display one or more characteristics of a disease.[8] This usually involves 'knocking out' a gene or inserting one from a human. However, genes do not exist in isolation but are part of an integrated system, and so removing or altering them can lead to unforeseen side effects. For example, creating 'knockout' mice missing a gene responsible for blood coagulation resulted in half of the altered embryos bleeding to death in the womb.[9]

The Home Office – Sanctioning Suffering

In the UK, animal experiments – including drug testing – are regulated by the Animals (Scientific Procedures) Act 1986, which requires scientists to obtain a project licence from the Home Office for procedures using live animals. According to the 1986 Act, project licences are only to be granted where there are no non-animal alternatives; where the benefits expected from the research are judged to outweigh the likely adverse effects on the animals involved (cost/benefit analysis); and where the number of animals used and their suffering are minimised.[10] However, when asked to provide figures on the number of licence applications it has refused, the Home Office could only confirm one formal refusal in recent years[11] – compared with more than three million licensed procedures taking place in 2007 alone.[12]

In July 2007, a high court judge ruled that the Home Office had downplayed the suffering of animals used in experiments by unlawfully licensing brain experiments on marmosets – which involved removing the tops of their heads to induce stroke – as causing 'moderate' rather than 'substantial' suffering.[13] As the level of 'adverse effects' caused to animals plays a critical role in the cost/benefit analysis of licence applications, the Home Office is effectively facilitating animal experiments by allowing applicants to use incorrect severity ratings, thereby skewing the cost/benefit ratio. Only two per cent of licences are currently classified as causing substantial suffering.[14]

Further evidence of the Home Office's failure to perform accurate cost/benefit analyses is provided by the number of drugs brought to the market every year that offer no therapeutic benefit over existing drugs – known as 'me-too' drugs. According to Médecins Sans Frontières, which campaigns for access to essential medicines, more than three-quarters of the new drugs approved by the US Food and Drug Administration (FDA) between 1989 and 2000 had no therapeutic benefit over existing products.[15] Although no figures are available for the UK, the House of Commons Health Committee believes the numbers are likely to be similar.[16] It should, therefore, be unacceptable to inflict any 'adverse effects' on animals in the development of these drugs as their benefits to society are negligible at best and may even be harmful. (For more on 'me-too' drugs see page 36.)

Clinical Trials

If a drug appears to have an acceptable safety profile in animal tests and shows promise in treating a condition in *in vitro* tests or in artificially 'diseased' animals, the manufacturer can apply to the appropriate government regulatory agency (i.e. Medicines and Healthcare products Regulatory Agency (MHRA) in the UK; Food and Drug Administration (FDA) in the US) for approval to begin human clinical trials. These trials are broken down into four phases:

Phase One trials – also known as 'first in human' trials – are performed on a small number (10-30) of healthy, usually male, volunteers.[17] These trials are performed primarily to determine the safety of potential new drugs in humans and to measure the toxic side effects that occur as the dosage is increased, as well as the way in which the drug is absorbed, distributed, metabolised and excreted from the body.[18]

Phase Two trials are normally conducted on patients with the illness that the drug has been developed to treat. These are also relatively small (up to a few hundred people) and short-term, and are used to determine the common short-term side effects and risks of the drug in therapeutic use.[19]

In Phase Three trials the drug is given to a larger number of patients (1,000-3,000) in different clinical settings, and over a longer period of time. These studies further test the drug's effectiveness, monitor side effects and determine the product labelling and how physicians are instructed to use the drug.[20]

After successful completion of Phase Three trials a drug company can apply to regulatory agencies for a marketing licence. The agency may request that Phase Four trials be conducted post-marketing to collect information on adverse reactions and long-term risks.[21]

An analysis of success rates for drugs that passed animal safety tests between 1991 and 2000 found that **only one in nine passed human trials** and was approved by European and US regulating agencies.[22] In a 2006 press release, the US Secretary of Health and Human Services – Mike Leavitt – confirmed this astonishing failure rate: 'Currently, nine out of ten experimental drugs fail in clinical studies because **we cannot accurately predict how they will behave in people based on laboratory and animal studies.**'[23]

Of the small percentage of drugs that do pass human trials and gain approval, more than half have label changes or are withdrawn because of major adverse reactions not detected in pre-marketing tests.[24] **Adverse drug reactions are responsible for more than 6.5% of hospital admissions in the UK – totalling more than 1 million people in 2006 alone – and cost the NHS more than £2 billion a year.**[25]

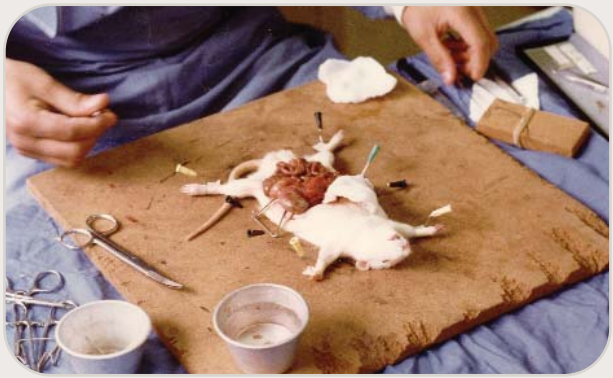
Animal Tests – Outdated and Unreliable

How Animals Came To Be Used in Drug Testing

The use of chemical compounds (as opposed to herbal remedies) to treat illness began in the late 19th century[26] but went virtually unregulated until the mid 20th century.[27] The deaths of more than 100 people in the US after taking a new drug – Elixir sulphanilamide – sparked the enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the first law requiring safety studies on new drugs before marketing.[28] Several other countries followed suit and the practice of using animals in drug testing became widespread.

The current system of medicines regulation in the UK, which requires proof of safety and efficacy in two species of mammal before a drug can be licensed, arose after the thalidomide tragedy.[29] The government had to be seen to be taking action and so it set up the Committee on Safety of Drugs in 1963. This subsequently became the Committee on Safety of Medicines (CSM) under the terms of the Medicines Act of 1968, which still provides the legal framework for the control of medicines in the UK today. In the US, the Kefauver-Harris Act was implemented in 1961 – amidst the thalidomide furore – requiring proof of efficacy as well as safety for all new drugs.[30]

While imposing stricter drug safety requirements in the wake of thalidomide was a necessary and responsible move, the specification for animal tests was more a product of convenience than the result of sound scientific analysis. In fact, thalidomide had been tested in a variety of mammal species before it was marketed and it appeared safe. And for drug regulators to continue relying on animal tests today, despite decades of research and human tragedies demonstrating their worthlessness, is a dereliction of duty so extreme it brings into question their true objective: are they protecting patients or protecting pharmaceutical interests?



Thalidomide and animal testing

Thalidomide was marketed in the UK under the brand name Distaval from April 1958. It was commonly given to women in the first trimester of pregnancy to combat morning sickness or sleeplessness. The drug was originally thought to be safe but in 1961 the connection was made between thalidomide and a huge rise in the number of malformed babies. Thalidomide was withdrawn from sale in December 1961.[31]

Supporters of animal testing often claim that this tragedy could have been prevented if thalidomide had been tested in pregnant animals prior to marketing (it was tested in animals but not – they claim – pregnant ones). However, after numerous malformed babies were born researchers began testing thalidomide in pregnant animals to determine whether it was the cause. After failing to produce similar birth defects in numerous species – including rats, mice, dogs, hamsters, cats and guinea pigs[32] **– scientists finally found one breed of rabbit, the New Zealand white, who also gave birth to malformed offspring, but only at doses between 25 and 300 times higher than those given to humans.**[33, 34, 35]

More animal testing would therefore not have prevented the release of thalidomide as it is unlikely scientists would have tested it in what was, at the time, an obscure breed of rabbit. Even if the New Zealand white rabbit had been used, thalidomide could still have been 'safely' marketed since the vast majority of species showed no ill effect from the drug.

Why Drug Companies Embrace Animal Tests

Although drug companies claim that they perform animal tests to fulfil the regulatory requirements of drug licensing, the pharmaceutical industry's influence on government regulators is substantial and it could push for a change in the law if it so wished. But animal tests are useful to drug companies. Careful selection of species can demonstrate whatever is required of a drug, whether it is safety or efficacy. And companies are not required to submit all their animal data to the regulators, but only that from any two mammals (one rodent and one 'higher' mammal). They can, therefore, test their drug in several different species of rodent or primate – or in different strains, sex or age of the same species – until they get favourable results. Dr Irwin Bross, former director of New York's Sloan-Kettering Cancer Institute, confirms this practice: ***'From the bureaucrat's standpoint, the beautiful aspect of animal research is that whatever you want to claim can be "proved" in this way. Among experienced public health scientists it is well-known that you can "prove" anything with animal studies. This is because there are so many different animal models and each system gives different results. By selecting whatever results happen to support a particular position (and ignoring the results to the contrary); one can come out with the desired "conclusion"'.***[36]

Animal experiments also provide pharmaceutical companies with a legal safety net. When their products harm or kill people, they defend themselves in court by claiming due diligence – that they fulfilled their legal obligation by proving the drug's safety in animal tests – and are therefore not liable for the damage it has done. Following the high profile withdrawal of the painkiller Vioxx – due to serious and often fatal side effects – and the 27,000 lawsuits its manufacturer Merck faced in the US, drug companies began lobbying for legal protection from lawsuits using the same defence – if they have fulfilled all safety requirements then the responsibility for any harmful reactions lies with the regulators who licensed the drug. The US Supreme Court is now considering a proposal, which would shield pharmaceutical companies from lawsuits if their product cleared the FDA's approval process – which is based to a significant extent on data from animal tests.[37]

Why Animal Tests Don't Protect People

The number of drugs that pass as safe in animal experiments and then either fail in human clinical trials or go on to cause death and disability is testament to the failure of animal tests in protecting people. Animal tests cannot reliably predict how a drug will affect people for several crucial reasons:

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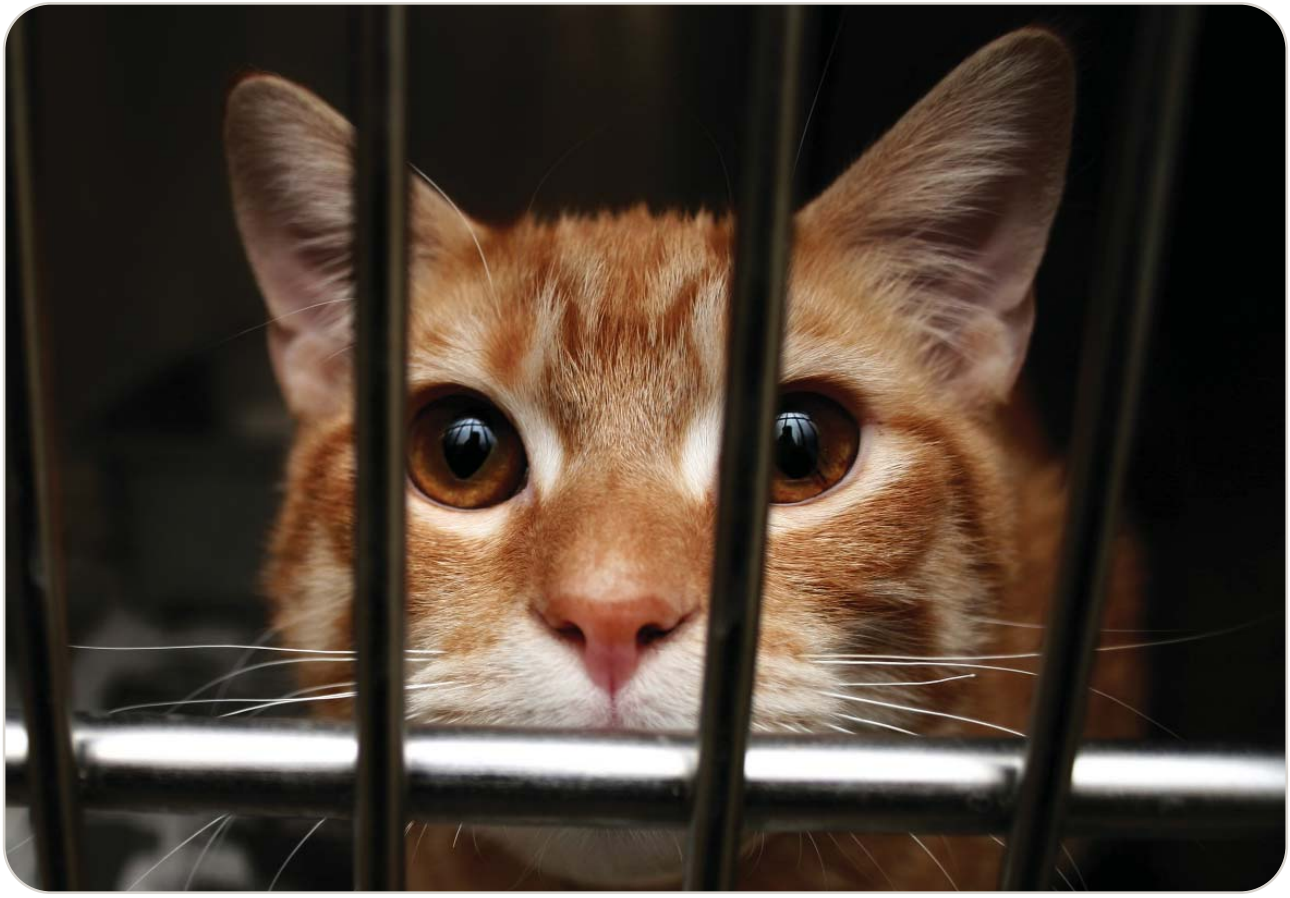
1) Species differences in anatomy, organ structure and function, metabolism, chemical absorption, genetics, mechanism of DNA repair, behaviour, lifespan and the inherent sensitivity of cell populations to toxicants. For example:

– Small animals have proportionately larger organs, a shorter blood circulation time and their metabolism is generally faster than that of larger animals.[38]

– Different species have different metabolising enzymes, which breakdown chemicals. The breakdown products generated (metabolites) can be highly toxic. A drug may therefore appear safe in tests on animals but be toxic



to humans because of a metabolite, which is only produced when broken down by human-specific enzymes.[39]

– The anatomy of the intestine, as well as the variety and abundance of bacteria it harbours, varies between species and affects the absorption of drugs from the gastrointestinal tract.[40]

– The cells or organs targeted by a drug may simply be more vulnerable to toxins in some species than in others.[41, 42] For example, human liver damage is the most frequent reason cited for withdrawal of a drug, with more than half of acute liver failures being caused by drugs. Yet liver toxicity in animal tests and human clinical trials correlate only 50 per cent of the time.[43]

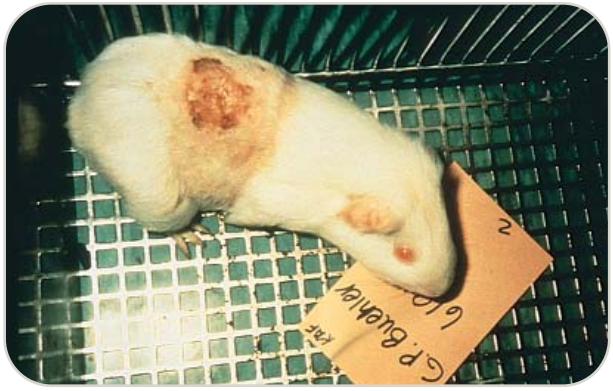
© PETA

– The placenta is more permeable in some species, such as rats and rabbits, than in humans, so teratogenicity (birth defect) tests in animals may give misleading results.[44] Even tests using non-human primates correlate with human teratogens only 50 per cent of the time.[45]

2) A homogenous group of animals living in well-controlled experimental settings cannot predict the response of varied human patients living in natural conditions.[46] For example:

– Test animals are usually all the same age, strain and sex (it is still common practice to use exclusively male rats[47]) and are not exposed to the variety of pathogens and chemicals, which free-living humans encounter on a daily basis.

– Unlike many human patients, animal models rarely suffer from multiple illnesses simultaneously and are not exposed to multiple drugs or treatments at the same time.[48]



3) Artificially created diseases in animals in laboratories do not reflect naturally occurring human illness. Therefore, responses to drug treatment cannot be extrapolated from one to the other. For example:

– For decades, pharmaceutical companies tested candidate anti-cancer drugs in animals carrying transplanted human tumours but very few drugs that appeared effective in the animal models worked in humans. More importantly, according to the US National Cancer Institute, the animal models missed effective human drugs.[49]

– More than 4,000 studies have been reported demonstrating the efficacy of more than 700 drugs in animal models of stroke.[50] About 150 of these drugs have been tested in human clinical trials and all failed to show benefit.[51]

4) The stress caused to animals by routine laboratory practices such as handling, blood collection, physical restraint, injections and gavage, results in altered physiological states, which compromise test results. For example:

– A review of 80 published animal studies found that routine laboratory procedures caused significant physiological changes associated with stress such as raised cortisol, prolactin and growth hormone levels; increased heart rate and blood pressure; and abnormal behaviours such as excessive grooming. The changes were pronounced and lasted for 30 minutes or longer.[52]

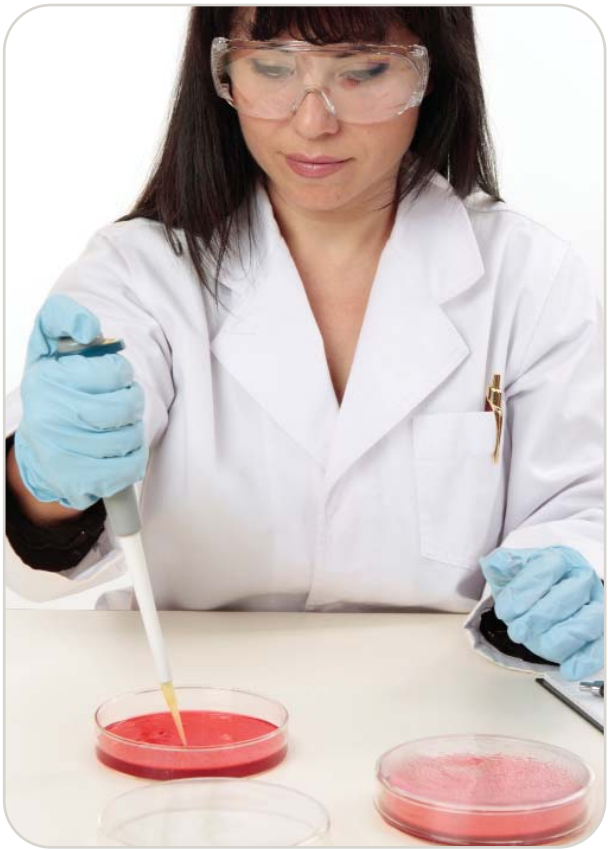
– Researchers at York's Central Science Laboratory found that having different experimenters perform the same test using the same equipment and rats from the same breeding colony within the same room of the same laboratory produced significantly different results depending on whether the handler was familiar to the rats or not.[53]

5) Many negative side effects of drugs are not outwardly visible or measurable and therefore cannot be detected in animal tests.[54] For example:

– Headache, nausea, dizziness, fatigue, depression, confusion and double vision are some of the most common, and often most debilitating, side effects of drugs yet there is no way to detect them in animals.

Scientific Evidence Against Animal Tests

Despite licensing more than three million procedures using animals in 2007, the Home Office has never 'commissioned or evaluated any formal research on the efficacy of animal experiments', according to former Home Office Minister Caroline Flint, nor does it have any plans to do so.[55] In fact, according to an article in a 2008 edition of *New Scientist,* ***'Despite decades of research involving animals, there have been few systematic attempts to see how reliable the outcome really is.***



Most attempts have been in the field of toxicity testing, and the results are far from encouraging. Few provide enough data to allow the value of animal studies to be worked out; those that do suggest they are no more informative than tossing a coin.'[56]

For animal tests to be of any use in drug development they must reliably predict human outcomes, yet we can only identify how 'predictive' they are retrospectively when the results of animal and human drug tests are compared. And those studies that were established to examine such comparisons show wildly varying results. For example:

- A 2008 study analysing the results from 27 systematic reviews (where all published papers on a given subject are reviewed and analysed to draw an overarching conclusion) comparing the results from animal tests and human clinical trials found that animal experiments had been useful in predicting human outcomes in only two cases, one of which was contentious. The author concluded that 'published systematic reviews have demonstrated that animal experiments are insufficiently predictive of human outcomes to provide substantial benefits during the development of human clinical interventions, or during human toxicity assessments.'[57]
- A 2007 study published in the *British Medical Journal* compared the results of animal studies and human clinical trials for six medical treatments. After reviewing more than 200 studies, the authors found that animal tests accurately predicted the human outcome only half of the time.[58]
- A 2006 study published in the *Journal of the American Medical Association* found that only a third of highly cited animal studies translated into successful human research. The authors warned that patients and physicians should be cautious about extrapolating the findings of animal research to the treatment of human disease.[59]
- A 2005 review looking at decades' worth of teratogenicity tests in animals revealed that everyday substances such as salt, water, sugar, cooking oil and many vitamins caused birth defects in animals, while correlation with true human teratogens occurred just 55 per cent of the time.[60]
- A 2000 study of 140 drugs that caused unexpected human toxicity during clinical trials showed that rodent tests predicted only 43 per cent of human toxicity. Including tests in 'higher' mammals did not offer much improvement, with the total predictivity of liver toxicity at 55 per cent and of cutaneous (skin) reactions at 35 per cent.[61]

US Agencies to Phase Out Animal Tests

In February 2008, key US government agencies issued the clearest and most authoritative statement to date that animal testing does not work. Under a five-year programme, government laboratories will start moving to non-animal methods such as the use of cells and computer models to test chemicals, drugs and toxins for safety. Such methods are faster, and are likely to be more accurate and far less expensive, officials of the National Institutes of Health (NIH) and the Environmental Protection Agency told a major science conference in Boston. The goal is to eliminate live animal use in toxicity tests within ten years.[62]

Dr Francis Collins, director of the National Human Genome Research Institute (NHGRI), told reporters covering the 2008 American Association for the Advancement of Science conference that animal testing does not predict very well what a chemical will do to a human being. 'It's slow. It's expensive,' Collins said. 'We are not rats and we are not even other primates... After all, ultimately what you are looking for is, does this compound do damage to cells? Can we, instead of looking at a whole animal, look at cells from different organs?'[63]

The NIH have been carrying out tests using high-speed robots that can screen 200,000 compounds in two days. It would take a researcher using traditional whole-animal tests 12 years working eight hours per day and seven days a week to do the same amount of work. Dr Christopher Austin, an NIH Director, added: 'Traditional animal testing is expensive, time-consuming, uses a lot of animals and from a scientific perspective the results do not necessarily translate to humans.'[64]

Adverse Drug Reactions

Convincing and powerful evidence against the reliability of animal tests is the harm that drugs continue to cause millions of people around the world. Some recent examples of harmful drugs that 'passed' regulatory animal tests include:

- **Vioxx:** the first of a new class of anti-inflammatory drugs known as COX-2 inhibitors, was reported to be responsible for between 88,000 and 160,000 heart attacks and strokes in the US alone before it was withdrawn in 2004.[65] Not only had animal studies failed to predict these safety risks, studies in four different species had shown that Vioxx was actually protective against heart attacks and vascular disease.[66] In November 2007, Merck, the drug's manufacturer, agreed to pay $4.85bn (£2.42bn) to settle 27,000 lawsuits filed in the US over the drug. The company still faces a host of lawsuits in other countries.[67] Two similar drugs, **Bextra** and **Celebrex**, are reported to carry similar risks. The former has been withdrawn and is also the subject of thousands of lawsuits, while the latter now carries a strong warning label.[68, 69]

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** a class of antidepressants that includes **Seroxat**, **Lustral**, **Efexor** and **Prozac**, was banned for use in children and adolescents after the drugs were shown to increase suicidal behaviour significantly.[70] Warnings have been issued that they double suicidal tendencies in adults as well.[71, 72] Studies have also shown that stillbirths, babies of low birth weight and foetal malformations are all twice as common in women who take SSRIs during pregnancy.[73, 74] New research has demonstrated that SSRIs are not even effective in treating most cases of depression,[75] despite costing the NHS more than £200m a year.[76]

- **Hormone Replacement Therapy:** prescribed to millions of women to combat the negative effects of the menopause and protect them against heart disease, has been shown to increase substantially the risks of heart attacks, strokes and blood clots in several large-scale studies.[77, 78, 79] These findings contradict decades of animal research – including studies on mice, rabbits, pigs and monkeys – which consistently showed that oestrogen reduced signs of vascular damage and prevented heart disease.[80] An increased incidence of breast cancer has also been found in women taking HRT.[81] It is estimated to have caused 20,000 cases of breast cancer in Britain in a decade,[82] with the increased cancer risk lasting for at least three years after a woman stops taking the drug.[83] Wyeth, one of the main manufacturers of HRT drugs, has had to pay out millions in compensation for failing to provide adequate warnings about the increased health risks associated with the drugs, despite knowing about them for decades.[84]

- **Avandia:** GlaxoSmithKline's (GSK) blockbuster diabetes drug prescribed to more than six million people worldwide, has repeatedly been shown to increase the risk of heart failure by more than 40 per cent.[85, 86] A study published in late 2007 concluded that its harms outweighed its benefits.[87] However, the FDA decided not to withdraw it but simply to strengthen the severity of the warning. The FDA has also warned doctors of excessive bone fractures associated with the drug after GSK's own research showed that women taking Avandia suffered significantly more fractures of the hand, foot or arm than those on other diabetes medications.[88] Health Canada, the Canadian health regulator, as well as the FDA have issued warnings that Avandia may cause vision impairment due to macular oedema – swelling of the retina.[89]

- **Zyprexa:** an antipsychotic prescribed to more than 20 million people worldwide,[90] causes severe weight gain and substantially increases the risk of diabetes and hyperglycaemia (high blood sugar).[91] Eli Lilly, the drug's manufacturer, has agreed to pay out $1.7bn (£535m) to settle 46,500 lawsuits brought by people whose

health was damaged by Zyprexa. Internal company documents revealed in court show that Eli Lilly was aware of the increased health risks as early as 1998[92] but waited until 2007 to put a strong warning on the label.[93]

- **Ritalin** and other stimulants such as **Adderall** and **Concerta**, prescribed for Attention Deficit Hyperactivity Disorder (ADHD), can cause 'serious cardiac events' and have been linked to the deaths of at least 60 people.[94] They now carry a 'black box' warning alerting patients to an increased risk of heart attack, stroke and 'sudden death', as well as psychotic symptoms including hallucinations, delusional thinking or mania in children and adolescents without prior history of psychotic illness.[95, 96] Studies have also shown that they stunt children's growth and do not actually provide any long-term improvement in behaviour – despite costing the NHS £28m a year.[97]
- **Roaccutane** (Accutane in the US): a treatment for severe acne, is highly teratogenic and has caused spontaneous abortions, premature births and severe birth defects.[98] It has also been linked to depression and suicidal behaviours, including 45 suicides or attempts in the UK,[99] as well as an increased risk of liver damage.[100]
- **Rezulin:** a treatment for type-2 diabetes, caused severe liver failure and was linked to the deaths of 391 people during its three years on the market.[101]
- **Lipobay** (Baycol in the US): a cholesterol lowering drug, caused severe rhabdomyolysis (muscle wasting)[102] leading to more than 100 deaths before its withdrawal.

- **Prepulsid:** used to treat gastric and digestive disorders in adults and children, caused heart rhythm disturbances, which resulted in 302 deaths including at least 24 children.[103]
- **Opren:** a non-steroidal anti-inflammatory drug (NSAID) prescribed for arthritis, caused severe liver toxicity and phototoxicity leading to more than 3,500 serious adverse reactions and 61 deaths in Britain in just two years.[104]

These high profile incidents are compounded by the often excessive and inappropriate prescribing of well-known medicines that contribute to the hospitalisation of more than one million people in the UK every year. Commonly prescribed medicines such as warfarin, diuretics, aspirin and other NSAIDs are implicated in a significant number.[105] These astonishing figures, which are similar to other Western countries such as the US[106] and Australia[107], do not include adverse reactions that occur while patients are already in hospital or those that do not result in hospitalisation, so the true number of people hurt by drugs intended to help them could be very much higher. The British Medical Association believes that only 10 per cent of serious drug reactions experienced by patients in primary care are reported.[108]

A more comprehensive – but far from exhaustive – list of drugs that have recently been abandoned during human clinical trials, withdrawn from the market or given a serious warning label due to severe adverse effects is included as Appendix 1 (see page 52).

How Big is Big Pharma?

GPs in the UK now write out nearly one billion prescriptions a year,[109] compared with just under 400 million in the early 1990s.[110] The annual cost of drugs to the NHS has risen accordingly – from £3.1bn in 1993[111] to £11bn today.[112] In the United States – the world's biggest consumer of pharmaceuticals – $286.5bn (£143bn) was spent on prescription drugs in 2007.[113] That same year, global prescription drug sales totalled $712bn (£356bn).[114] This staggering figure does not include sales of over the counter (OTC) medicines, a growing market which saw more than 900 million purchases in Britain in 2006.[115]

Thanks to these colossal sales figures, the pharmaceutical industry is one of the most profitable on the planet. According to *Fortune* magazine, it is the second most lucrative industry in America after the oil trade, enjoying a profit margin of 19.6 per cent – compared with an average of only 6.6 per cent for the rest of the industries listed.[116] In the UK, it is the third most profitable industry after banking and tourism.[117]

Of the ten largest drug companies in the world, often collectively referred to as Big Pharma, five are American and five are European.[118] The American company Pfizer, maker of Viagra, tops the list with revenues of $48.6bn (£24.3bn) in 2007. Its drug Lipitor, one of many cholesterol-lowering products known as statins, is the world's number one selling drug with sales of $12.7bn (£6.3bn) in 2007.[119] In second place is Britain's GlaxoSmithKline, maker of the antidepressant Seroxat, with sales of $45bn (£22.5bn) in 2007.[120] The other members of the top ten are Novartis, Sanofi-Aventis, Johnson & Johnson, AstraZeneca, Merck, Roche, Abbot and Amgen.[121]

With such enormous amounts of money behind them, it is no surprise that the pharmaceutical industry wields a great deal of power. According to the House of Commons Health Committee: ***'The industry is hugely influential, affecting every aspect of the medical world, including prescribers, patients, academics, the media, and even the institutions designed to regulate it. Its influence in Parliament is extensive.'***[122]

In the US, the pharmaceutical industry has the largest lobby in Washington – spending more than $1.3bn (£515m) on lobbying in the past decade.[123]

It also gave more than $119m (£58m) in federal campaign contributions in the same period.[124] Its return on investment has been substantial. According to US Senator Mark Montigny, who chaired the National Legislative Association on Prescription Drug Prices in 2005, ***'We are being backed up and squashed by the pharmaceutical industry money. They have killed lots and lots and lots of legislation in Massachusetts and across the country.'***[125]

The remaining chapters of this report reveal just how far Big Pharma will go in its pursuit of profits. Far from being magnanimous entities striving to rid the world of disease – which regrettably have to 'sacrifice' millions of animals in the process – this report shows how drug companies employ a host of corrupt practices, including unreliable animal tests, in order to drive up sales and protect their profits. These questionable practices jeopardise people's health and undermine publicly-funded healthcare systems such as the NHS.

Masters of Marketing

Drug companies defend the high cost of brand name drugs, and the use of lengthy patents to prevent generic competitors, by claiming that they need to recoup the large amounts spent in the research and development (R&D) of new drugs. Indeed, they argue, without these high prices and period of exclusivity, many life-threatening illnesses would go untreated because drug companies could not afford to undertake as much research. However, this is not the full picture.

According to an industry-funded report on the future of pharmaceuticals, sales and marketing is by far the biggest industry expense, accounting for 33 per cent of corporate spending in 2005 compared with 17 per cent for R&D.[126] This ratio is mirrored in the annual reports of the top drug companies. In 2007, Pfizer spent twice as much on sales and marketing ($15.2bn) than on R&D ($7.5bn),[127] as did GlaxoSmithKline (£6.9bn on sales and marketing versus £3.3bn on R&D).[128] The House of Commons Health Committee's 2005 report confirmed that drug marketing and promotion was increasing at the expense of R&D, with research staff numbers falling by two per cent during the preceding decade while marketing staff numbers increased dramatically.[129]

Selling Sickness

A drug company, like any business, wants lots of people to buy its products. The challenge it faces is that its products have a very specific purpose: to treat an illness or set of symptoms. In order to enlarge their customer base, drug companies must expand the definition of an illness to include 'symptoms' experienced by a larger number of people – they need to convince healthy people that they are sick.[130]

Creating new diseases, or redefining existing conditions in order to expand the market for a drug, is known as 'disease mongering', and, according to Roy Moynihan – author of *Too Much Medicine* – it is now an 'established and integral part of the promotion of any new blockbuster drug'.[131] In a 2002 issue dedicated to the subject, an article in the *British Medical Journal* concludes that '***Global pharmaceutical companies have a clear interest in medicalising life's problems and there is now an ill for every pill'.***[132] In its 2005 report, the House of Commons Health Committee accused the pharmaceutical industry of contributing to the medicalisation of society by 'categorising more and more individuals as "abnormal" or in need of drug treatment'.[133] The Royal College of General Practitioners accused drug companies of disease mongering to boost sales and warned that they are taking the NHS to the brink of collapse by encouraging unnecessary prescribing of costly drugs.[134] Even the industry acknowledges the use of disease mongering in its marketing strategies. An article in *Medical Marketing and Media* boasts that ***'recognised symptoms and/or diagnoses can be assembled into an ownable "syndrome" that can be tagged to a product'.***[135]

Disease mongering can take many forms: classifying the ordinary processes of life, such as the menopause or baldness, as medical problems; portraying mild symptoms as a sign of underlying serious illness; treating personal or social problems as medical ones; and framing a risk factor, such as high cholesterol as a disease in itself.[136, 137] The marketing strategy is virtually identical regardless of

the illness being sold. Drug companies recruit doctors and patient groups, usually with financial incentives, for 'disease awareness' campaigns and use the media to spread their message, often unquestioningly, so that the illness becomes a household name – then they market their new 'cure'. Some particularly egregious examples include:

Restless Legs Syndrome

In 2003, GlaxoSmithKline began issuing press releases about restless legs syndrome (RLS), 'a little known and often misdiagnosed disorder'[138] that was 'keeping America awake at night',[139] citing internally funded studies showing that 10 per cent of the population suffer from the condition. At the same time, its Parkinson's drug Requip was being trialled as a treatment for RLS[140] – a disputed condition that GSK says is characterised by cramps, pins and needles and an irresistible urge to move one's legs.[141] GSK's PR efforts generated widespread media coverage that, according to an analysis published in the *Public Library of Science Medicine*, '***exaggerated the prevalence of the disease and the need for treatment, and failed to consider the problems of overdiagnosis. In essence, the media seem to have been co-opted into the disease mongering process.***'[142] A 2004 piece in *The Observer* provides a striking example, stating as fact that 6-8 million Britons are thought to suffer from the disease but GPs are failing to diagnose it. The article even names Requip as a 'more effective' treatment waiting to be licensed.[143]

When Requip was eventually approved for RLS in 2005, GSK stepped up its campaign to 'push restless legs syndrome into the consciousness of doctors and consumers alike'.[144] Within weeks of the drug's approval, more than 200 doctors attended a GSK-sponsored 'educational meeting' about RLS.[145] By the end of 2005, GSK had spent $27m (£13.5m) advertising first the disease and then the cure.[146, 147] It also gave significant funding, $450,000 (£225,000), to the Restless Legs Syndrome Foundation,[148] a 'nonprofit' group widely quoted in media coverage about the drug (but without mention of its financial ties to GSK).[149] The marketing strategy paid off as, less than a year after it was approved for RLS, Requip's sales had increased from $97m (£48.5m) to $146m (£73m) in the US alone.[150] Sceptics doubt that these sales figures are representative of those who truly suffer from the condition, and the advocacy group Adwatch confirms that people with no evidence of the syndrome have 'begged their doctor for the drug' after seeing promotional materials.[151]

Female Sexual Dysfunction

According to journalist Roy Moynihan, writing in the *British Medical Journal*: '***The corporate sponsored creation of a disease is not a new phenomenon, but the making of female sexual dysfunction is the freshest, clearest example we have.***'[152] He cites a series of pharmaceutical industry sponsored conferences on the subject that took place around the same time that Viagra was licensed for 'erectile dysfunction' in men. Notably, there was a 1998 conference consisting of 19 sexuality researchers and clinicians (18 of whom had financial ties to a total of 22 drug companies) that revised the definition of female sexual dysfunction (FSD) to facilitate a 'new era of physical medicine'.[153] This was followed in 1999 by an article in the *Journal of the American Medical Association* claiming that 43 per cent of women suffer from sexual dysfunction – with two of the three authors having close links to Pfizer.[154] In 2000 and 2001, Pfizer was a key sponsor of the newly formed Female Sexual Dysfunction Forum's annual conference.[155] During this time, Pfizer was running clinical trials of Viagra in women for the treatment of 'female sexual arousal disorder'.[156] Experiments were also performed on female rabbits to 'prove' the physiological – as opposed to psychological – basis of women's sexual problems and involved highly invasive procedures such as administering an electric shock to the surgically exposed pelvic nerve.[157]

In 2004, Pfizer announced that it would not seek FDA approval for Viagra to treat FSD because clinical trials had shown it to be no more effective than a placebo,[158] and the focus of drug companies quickly switched from products to treat

'arousal problems' to those for 'desire problems' – primarily using testosterone.[159] Within a few months Procter & Gamble declared that it was seeking FDA approval for Intrinsa, a testosterone patch to treat 'Hypoactive Sexual Desire Disorder' (HSDD).[160] In anticipation of the drug's approval, P&G 'unleashed a global multilayered marketing campaign', which included distributing a medical education package to doctors entitled *Renewing sexual desire: understanding HSDD in postmenopausal women*, as well as a *Reporter's guide to testosterone and its role in women's health.*[161] The company also sponsored the annual conference of the International Society for the Study of Women's Sexual Health – whose key office holders have close financial ties to P&G – and asked the Society to speak on behalf of Intrinsa at the FDA review.[162] Despite P&G's best efforts, the FDA did not approve the drug, stating that the benefit (an average of one additional sex act per month) was outweighed by the potential health risks[163] – including increased risk of cardiovascular disease and breast cancer.[164]

Although no drug has yet been licensed for FSD, many of the drugs approved for erectile problems in men – Viagra, Levitra, Cialis, AndroGel and Testim – are prescribed 'off-label' to women who discuss sexual problems with their doctors. Testosterone researcher Jan Shifren estimates that one-fifth of all prescriptions for testosterone products licensed only for men are actually written for women.[165] FSD, and its treatment, continue to be the subject of medical education conferences where doctors are encouraged to view women's sexual problems as physical and treatable with medication.[166] And despite widespread criticism of the 43 per cent sexual dysfunction statistic, and subsequent studies indicating much lower rates of female sexual problems and supporting social-psychological causes rather then physical ones, the pharmaceutical industry and co-opted media continue to use this inflated figure in their quest to make FSD a medical reality.[167]

Social Phobia/Social Anxiety Disorder

Pharmaceutical Marketing magazine highlighted social phobia as a positive example of drug companies shaping medical and public opinion about a disease, specifically citing how the industry created recognition in Europe of social phobia as

a distinct clinical entity and the potential of antidepressants to treat it.[168]

Roche was the first drug company to market a drug for social phobia,[169] its antidepressant Manerix (Aurorix in Australia), and launched a PR campaign designed to expand the disorder from an extremely rare condition where individuals are so affected that they avoid public activity altogether, to include common conditions that affect many people, such as fear of public speaking and shyness.[170] It issued a press release in Australia claiming that one million people suffered from this underdiagnosed 'soul destroying condition' and quoted a psychologist who strongly endorsed using antidepressants to treat it.[171] Roche also funded a large conference on social phobia and worked with a patient group called the Obsessive Compulsive and Anxiety Disorders Foundation of Victoria whose chief executive confirmed that, 'Roche is putting a lot of money into promoting social phobia'.[172] Several years later the managing director of Roche in Australia, Fred Nadjarian, admitted that the company had exaggerated the prevalence of the condition, acknowledging that ***'Behind every statistic there is a vested interest'***.[173]

When the sales of GlaxoSmithKline's antidepressant Seroxat (Paxil in the US) did not match those of rival SSRIs such as Prozac and Zoloft, GSK decided to position it as an anti-anxiety drug instead of an antidepressant and applied for approval to market it for social phobia.[174] It began marketing its new disease 'Social Anxiety Disorder (SAD)' with the slogan 'Imagine being allergic to people' emblazoned on bus shelter adverts across America. The adverts did not name the drug or the company but bore the insignia of the Social Anxiety Disorder Coalition. However, GSK's PR firm Cohn & Wolfe handled all media inquiries on behalf of the group.[175] The PR firm also issued video news releases and press statements claiming that SAD is the third most common psychiatric disorder in the US, and provided patients and doctors for media interviews. The campaign paid off. Within two years of winning FDA approval for the treatment of social phobia, Seroxat had succeeded Zoloft in becoming America's second best selling SSRI, with sales nearly on a par with Prozac.[176]

Persuading people to take medicines they do not need not only exposes them to unnecessary risks from side effects but also jeopardises publicly funded healthcare systems by inflating prescription costs, and may prevent people from receiving truly life-saving treatments due to a lack of funds. It also diverts money and energy away from finding new treatments for serious illnesses that are not as marketable, such as virulent infections in need of new antibiotics. Because these are only taken short-term and cannot be 'sold' to a wide audience, developing such drugs is a low priority for most companies.

Marketing the 'Cure'

Once the need for a drug has been created, companies aggressively promote the 'cure'. According to the House of Commons Health Committee: '***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.***'[177]

The pharmaceutical industry is a global industry and its relentless promotional efforts are not limited to Britain but occur in every country where its products are sold. The methods used may vary slightly depending on a country's laws, but the target audience and the intensity of its marketing efforts are usually the same. While the US may be the most heavily targeted country, establishing a market for the drug there will, like so many other products, have a knock-on effect in other countries, including the UK.

Targeting Doctors

As most drugs can only be purchased on prescription, doctors are the main target of pharmaceutical promotion worldwide. A survey of American physicians published in the *New England Journal of Medicine* in 2007 revealed that 94 per cent of doctors have some type of relationship with the pharmaceutical industry, mostly in the form of receiving food in the workplace or drug samples.[178] More than a third received funding for professional meetings or continuing education and more than a quarter received payments for consulting, giving lectures or enrolling patients in clinical trials. The survey also showed that drug companies specifically target doctors whose prescribing behaviours are likely to influence others, such as cardiologists – who were more than twice as likely as GPs to receive direct payments from companies – as well as physicians who are involved in developing clinical practice guidelines or those who train new doctors. These practices are not unique to the US, nor are they the only tactics drug companies employ to influence doctors.

Direct Payments

In most developed countries the pharmaceutical industry is governed by a self-regulating code of practice, which prohibits bribing doctors with cash incentives or lavish gifts. However, a 2006 study by Consumers International examining drug promotion practices in Europe found 'large numbers of serious, recent and repeated breaches of marketing codes', with more than half of companies implicated in controversies regarding kickbacks and gifts to medical professionals.[179] Some recent examples include:

- In 2004, Italian authorities charged 273 GSK employees over the corruption of 4,400 doctors. According to Italy's Guardia di Finanza, the law enforcement body which investigates financial violations, GSK and its predecessor firm spent €228m (£152m) on 'sweeteners' for doctors, chemists and others over four years. The alleged bribes ranged from cameras, computers and holidays, to outright cash payments. The 4,440 doctors were also charged.[180]
- In 2004, Pfizer pleaded guilty to criminal charges brought over its payments to doctors for prescribing its epilepsy drug Neurontin.[181]
- In 2006, the Swiss biotech company Serono was reprimanded for offering 'inappropriate payments' to British doctors for prescribing its multiple sclerosis drug Rebif.[182]

The Consumers International report also found that payments to healthcare professionals were often disguised in some way, such as:

Consultancy Fees: Drug companies hire leading doctors as consultants and pay them to promote the company's products via presentations, research papers, conferences and debates.[183] British doctors told the House of Commons Health Committee that senior medical consultants receive payments of more than £20,000 from drug companies for a few hours' work and experts could earn £4,000 extolling the virtues of new drugs to other doctors.[184] During a US investigation into the marketing practices of Schering-Plough, it was revealed that liver specialists were paid consultancy fees to keep them loyal to the company's products. According to one liver specialist, the letter accompanying a cheque for $10,000 (£5,000) explained that it was for consulting services outlined on the accompanying Schedule A. However, the only words printed on the attached sheet were 'Schedule A'.[185]

Clinical Trials: Drug companies often pay doctors large amounts for enrolling patients in Phase Four trials, which can be part of a marketing strategy. In 2005, Bristol-Myers Squibb paid doctors €100 for each patient they enrolled in post-marketing research for the drug Ability.[186] GP practices can earn profits of more than £50,000 a year by recruiting patients for clinical trials, the House of Commons Health Committee was told.[187]

Continuing Medical Education: This can include all-expenses-paid trips to attend conferences, workshops, courses or meetings, often held at holiday resorts or including expensive social events.

For example, in 2004 AstraZeneca provided airfare and accommodation for doctors to attend a conference in Cannes on bipolar disorder.[188] And in 2006, Roche treated doctors attending a symposium on cancer treatments to a £90 a head dinner in a restaurant overlooking Sydney harbour.[189] A 2007 poll of British GPs revealed that a quarter had been sponsored to attend a conference, seminar or training event in the previous 12 months.[190] Studies have shown that physicians who accept money to travel to symposiums are 4.5-10 times more likely to prescribe the sponsoring company's drug after such sponsorship than before.[191]

In developing countries, where systems and resources for monitoring the marketing practices of drug companies are not in place, doctors regularly receive from drug companies lavish gifts such as cars, air conditioners, laptops, refrigerators, TVs and tuition fees for their children.[192] According to Consumers International (CI), doctors in Pakistan, India, Sri Lanka and Indonesia are often paid commissions to prescribe drugs, such as the down payment on a brand new car as a reward for writing 200 prescriptions. This means that patients often get medicines they don't need. CI estimates that up to 50 per cent of medicines in these countries are inappropriately prescribed, dispensed or sold.[193]

Influencing Education

Concern has also been raised over the content of continuing medical education sponsored by drug companies. Documents leaked to the *British Medical Journal* in February 2008 revealed that drug company sponsors had input into the selection of speakers and topics at educational seminars that were advertised as being 'independent of industry influence'.[194] The American Medical Association's ethics journal has suggested stopping drug company funding of continuing medical education because it 'marginalises diet, exercise and other drug-free approaches to preventing and treating disease' and aims to 'expand diagnostic categories so that more people are eligible for treatment and doctors are convinced that drugs are the appropriate treatment'.[195] The House of Commons Health Committee believes that this 'promotional hospitality masquerading as education' contributes to the inappropriate prescription of medicines.[196] According to the Association of the British Pharmaceutical Industry (ABPI), drug companies currently fund half of all postgraduate education for GPs in the UK.[197]

In December 2007, a lawsuit was filed against Pfizer for illegally boosting sales of its blockbuster drug Lipitor through misleading educational programmes for doctors.[198] A former Pfizer official, Dr Jesse Polansky, claimed that the educational programmes deliberately misrepresented the drug's label to encourage doctors to prescribe Lipitor for people at moderate risk of heart disease who didn't need the drug, as well as deliberately promoting the idea that kidney disease patients may need to be treated with statins – an unapproved use of the drug. According to Polansky, the educational programmes were integrated into the marketing plan for the drug and 'led thousands of physicians to prescribe Lipitor for millions of patients who did not need medication.'[199]

Sales Representatives

In 2006, drug companies in the US spent more than $6.7bn (£3.35bn) on 'detailing' – the one-to-one promotion of drugs to doctors by sales representatives.[200] Between 1995 and 2005 the number of drug reps in the US rose from 38,000 to 100,000 and now stands at one for every 2.5 doctors targeted.[201] A 2007 survey of British GPs found that they received an average of four visits per month from drug reps.[202] According to a former

sales rep for Eli Lilly, when drug reps visit doctors' offices they look for details such as family photos, religious symbols or hobbies that they can use to forge relationships. They then tailor their gifting to the individual, with some doctors receiving pens, notepads and coffee mugs emblazoned with a drug name, while higher prescribers receive expensive gifts such as golf bags and silk ties.[203] Another former drug rep confirms these practices, stating: '***The importance of developing loyalty through gifting cannot be overstated.***'[204]

The most popular gift that drug reps give to doctors is drug samples. According to a former rep, even physicians who refuse to see drug reps usually want samples – and they are denigrated as 'samplegrabbers'.[205] Reps only provide samples of new, usually expensive, drugs, and they are only intended to be used for part of a course of treatment, requiring doctors to write a prescription for the rest of the treatment – it is hoped of the new drug.[206] And it works. Studies consistently show that samples influence prescribing choices, increasing the prescription of more expensive brand name drugs.[207]

Concern has also been raised about the content of detail visits. A study analysing the content of detail visits for Pfizer's epilepsy drug Neurontin between 1995 and 1999 found that they often involved messages about unapproved uses (38 per cent of visits) and in 23 per cent of visits *only* unapproved uses were mentioned.[208] Despite the brevity of the visits, half of all doctors in the study stated that their prescribing or recommending of Neurontin would increase in the future. In 2004, Pfizer pleaded guilty to charges that it had promoted Neurontin for uses not approved by drug regulators and agreed to pay a fine of $430m (£215m).[209] Similarly, in 2007, Purdue Pharma and three of its executives were ordered to pay a $634.5m (£317m) fine after pleading guilty to telling doctors that OxyContin was less addictive and less subject to abuse than other pain medications.[210] It was, in fact, highly addictive and resulted in thousands of people being admitted to hospital.[211] According to US federal officials, Purdue Pharma allowed its sales reps to draw their own fake scientific charts that they then distributed to doctors to support the misleading claims.[212]

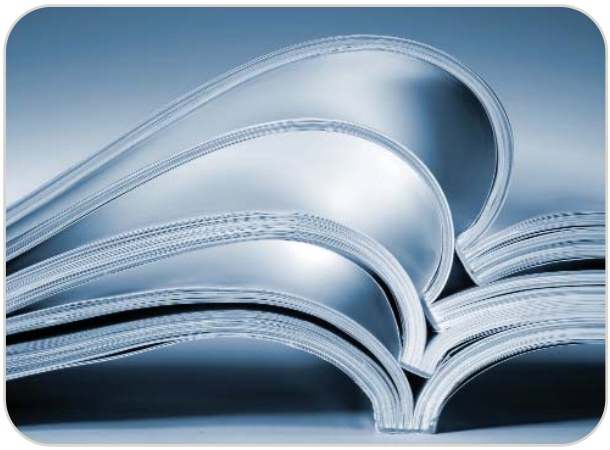
Promotional Mailings

In addition to visits from sales reps, doctors also regularly receive promotional mailings about new drugs. According to the 2007 poll of British GPs, they receive on average five promotional mailings a week from drug companies.[213] As with detail visits, these mailings often provide misleading information. For example:

- In 2004, the Institute for Evidence Based Medicine analysed the promotional mailings received by 43 doctors in Germany and showed that 94 per cent were not supported by scientific evidence.[214] Individual claims about the drugs included benefits that were not mentioned in the accompanying research articles, omitted adverse effects and gave false descriptions of the patient groups studied.
- In 2006, AstraZeneca received a warning from the FDA over promotional materials for its antipsychotic drug Seroquel. According to the warning letter, the sales material minimised the risk of hyperglycaemia and diabetes and completely failed to mention several other important risks.[215]
- In 2007, the FDA issued a warning letter to Eli Lilly about promotional material sent to doctors for its antidepressant Cymbalta, stating that it was 'misleading in that it overstates the efficacy of Cymbalta and omits some of the most serious and important risk information associated with its use'.[216]
- Early promotional materials for the antidepressants Prozac (Eli Lilly), Seroxat (GSK) and Zoloft (Pfizer) claimed that they reduced the likelihood that people would harm themselves.[217] However, subsequent studies have shown that the drugs do not reduce the incidence of self-harming and may, in fact, increase the risk.[218]

Medical Journals

While drug companies do advertise their products in medical journals, the amount they spend on this pales in comparison to detailing and, in countries where it is allowed, direct to consumer advertising (DTCA). In the US in 2006, drug companies spent only $463m (£231m) on advertisements in medical journals, compared with $6.74bn (£3.4bn) on detailing and $4.8bn (£2.4bn) on DTCA.[219] An even more important element of drug companies' marketing strategy is to get favourable articles about their drugs – preferably authored by respected clinicians – printed in medical journals as this has a greater influence on



doctors than blatant advertising.[220] Deputy editor of the *Journal of the American Medical Association*, Drummond Rennie, suggests how these favourable articles come to be written:

'I'm the advertising guy for the drug. I tell a journal I will give them $100,000 to have a special issue on that drug. Plus I'll give the journal so much per reprint and I'll order a lot of reprints. I'll select the editor and all the authors. I phone everyone who has written good things about the drug. I say, "I'll fly you and your wife first class to New Orleans for a symposium. I'll put your paper in the special issue of the journal and you'll have an extra publication for your CV." Then I'll put a reprint of that symposium on some doctor's desk and say, "Look at this marvellous drug".'[221]

Ghostwriting

According to Professor David Healy, director of the North Wales School of Psychological Medicine, drug company advisers write up to half the articles about new drugs that are published in respected journals and that are read by doctors to help them learn about new drugs. Esteemed clinicians are then paid to put their names to the articles – even though they may not have seen the raw data. According to Prof. Healy, these articles have far more effect on which drugs doctors prescribe than Caribbean conferences and gifts.[222] Dr Richard Horton, editor of *The Lancet*, told the House of Commons Health Committee that ghostwriting – where articles are written by professional medical writers but appear under the name of independent physicians or academics – is 'standard operating procedure', particularly in the promotion of off-label uses of drugs.[223] He cited SSRIs as an example of drug companies seeding journals with ghostwritten articles suggesting the drugs may be useful in treating conditions for which they were not licensed. This encouraged doctors to try the drugs in patients with those conditions, contributing to the millions of prescriptions issued in the early 2000s for SSRIs in the under-18s, despite no licensed indication for it.[224]

Internal company documents disclosed during litigation reveal how publication of ghostwritten articles plays a key role in the marketing strategies of drug companies. For example, in the mid to late 1990s Parke-Davis (now Pfizer) employed a 'publication strategy' to increase off-label prescribing of its epilepsy drug Neurontin.[225] In addition to promoting off-label uses to doctors in detailing visits, Parke-Davis hired medical communication companies to write review papers, original articles and letters to the editor about Neurontin, and paid physicians or chemists a $1000 (£500) honorarium to be named as the author. The proposal from one communications company noted that 'all articles submitted will include a consistent message... with particular interest in proper dosing and titration as well as emerging [off-label] uses'. Drug company sponsorship was often not disclosed, with six out of seven articles not acknowledging receipt of an honorarium. Similarly, court documents obtained during litigation against Merck indicated that it manipulated dozens of publications to promote its deadly arthritis drug Vioxx. The documents outlined how Merck's marketing employees developed plans for manuscripts of scientific review papers, contracted with medical communication companies to ghostwrite the papers, and recruited academically affiliated investigators to be authors by offering them honoraria. Only 50 per cent of review articles published disclosed Merck's sponsorship.[226]

In the US alone there are more than 200 medical education and communication companies (MECCs) that ghostwrite journal articles for the pharmaceutical industry.[227] One of these companies, Complete Healthcare Communications, boasts that it has submitted more than 500 manuscripts to journals for clients such as Pfizer, Sanofi-Aventis, Wyeth, Schering-Plough and AstraZeneca, with an acceptance rate of more than 80 per cent.[228]

Dr Richard Smith, former editor of the *British Medical Journal*, says that drug companies will order hundreds of thousands of reprints of any

published articles for their reps to distribute in hospitals and GPs' surgeries, and journals have become reliant on this money – making more from reprints than they do from advertising. This, says Smith, makes medical journals 'little more than a marketing tool of the drug companies'.[229]

Targeting Patients

In most countries – exceptions being the US and New Zealand – drug companies are prohibited from advertising prescription drugs direct to consumers and, instead, promote their products in more subtle ways. According to Consumers International, drug promotion in the EU is characterised by 'nice and friendly' marketing – where drug companies provide disease information without actually promoting a specific product. This, it says, creates a false sense of trust amongst consumers as they often view these marketing efforts as genuine corporate social responsibility.[230]

Disease Awareness Campaigns

The House of Commons Health Committee recognised that disease awareness campaigns contribute to the 'medicalisation' of society as they 'encourage individuals to seek advice or treatment from their doctor for previously undiagnosed conditions'. It also acknowledged that these campaigns can act as advertisements for prescription-only drugs, particularly where there is a well-known brand of treatment.[231] A recent report by Consumers International found that more than half of the 20 drug companies it examined had been implicated in marketing scandals involving direct to consumer adverts (DTCA) disguised as disease awareness campaigns.[232] Some flagrant examples of this practice include:

- In 2006, Eli Lilly sponsored a TV advertising campaign in the UK for a website called Love Life Matters which urges women whose husbands have an erection problem to see their doctor. The website, which is still running, bears the Lilly logo and a downloadable booklet highlights the Lilly sponsorship.[233]
- In 2006, GSK posted a video on You Tube featuring a man kicking violently in his sleep and setting off an elaborate series of dominoes. The sponsored message at the end of the video reads 'My dad is one of a Million people in the UK who suffer from RESTLESS LEG SYNDROME' and points viewers to a GSK sponsored website for more information. The advert has so far been viewed by more than 187,000 people.[234]

- In 2007, Pfizer sponsored beer mats that appeared in pubs across the UK, urging patrons to 'seek new ways to quit' smoking. No product was mentioned but the campaign coincided with Pfizer's 'stop smoking' drug Champix being approved in Britain.[235]

Patient Groups

Many drug companies have forged close associations with patient groups, often providing them with substantial financial support and resources, such as the use of the company's PR firm.[236] The MP Paul Flynn told the House of Commons Health Committee that pharmaceutical companies use patient organisations as 'conduits to promote their products in a subtle form of marketing'.[237] Some obvious examples of this underhanded tactic include:

- Allergy UK distributed thousands of copies of a children's book, called *Mr Sneeze and his Allergies,* to clinics in Britain. It included two pages citing anti-allergy drugs made by GSK – which had funded its publication. Regulators ruled that this violated the ban on DTCA.[238]
- Pfizer, the maker of Viagra, sponsored an Impotence Association campaign in which the company's logo featured prominently on adverts. Regulators ruled that this was inappropriate.[239]
- Eli Lilly was told to withdraw a diabetes information booklet aimed at doctors, which the company had written and funded, but that carried only the Diabetes UK logo.[240]

Drug companies also use patient groups to pressure regulators into approving high profile and expensive new drugs. For example, the Alzheimer's Society, which campaigns for the dementia drugs Aricept, Reminyl and Exelon to be available on the NHS, received a total of £58,000 in 2005 from the companies who manufacture the three drugs.[241] Similarly, Cancerbackup, one of the most vocal charities in the campaign for wider availability of the breast cancer drug Herceptin, received £29,000 from the drug's manufacturer Roche.[242] A survey conducted by the MP Paul Flynn found that only six out of 24 major patient organisations did not accept drug company money.[243] The National Institute for Health and Clinical Excellence (NICE) is an organisation that provides guidance on appropriate medical treatments. Its chairman, Sir Michael Rawlins, accused drug companies of covert and distasteful tactics in funding patient groups that campaign for wider use of medicines they manufacture.[244] Sometimes, drug companies target desperate patients directly, using them as part of their marketing strategy.[245] One breast cancer sufferer told *The Guardian* how a PR agency working for Roche offered to pay her to speak at seminars aimed at increasing the availability of Herceptin on the NHS.[246]

Direct to Consumer Advertising

Although advertising prescription-only drugs directly to consumers (in the hope that they then pressurise their doctors to prescribe them) is currently only allowed in the US and New Zealand, the European Commission – under the guise of improving information to patients – is drafting legislation to allow the pharmaceutical industry to promote its products directly to the public. In a confusing and seemingly contradictory statement, the EC consultation document proposes:

'Under the clear safeguard that all advertisement to the public is banned, it should be possible for the pharmaceutical industry to disseminate information on prescription-only medicines through TV and radio programmes, through printed material actively distributed, through information in printed media or through audiovisual and written material provided to patients by healthcare professionals.'[247]

An international alliance of consumer and health groups has attacked the proposal, warning that it will jeopardise European citizens' health and the financial security of the member states' health systems.[248] It argues that any information provided by drug companies is inherently promotional as their primary interest is to champion their products.

Drug company spending on DTCA has grown exponentially in the US, from $1bn (£500m) in 1997 – when the FDA relaxed regulation of DTCA – to $4.8bn (£2.4bn) in 2006.[249, 250] According to Dr Michael Wilkes, Vice Dean for Medical Education at the University of California, 'Drug companies' direct to consumer advertisements are now the lifeblood of television stations. More than ever, pharmaceutical companies provide a larger portion of television advertising budgets.'[251] In 2002, Pfizer had one of the ten biggest advertising budgets in the US, spending more than Coca-Cola and McDonald's.[252] In 2004, AstraZeneca spent $216m (£108m) advertising its cholesterol-lowering drug Crestor, surpassing the $212m (£106m) spent on advertising Pepsi that year.[253] These huge sums pay good dividends. A Harvard-MIT study released in 2003 found that for every dollar spent on DTCA, the companies made $4.20 in sales.[254] For some drugs the return is as high as $6 for every $1 spent.[255]

Almost all government, health professional and consumer inquiries have concluded that DTCA causes net public harm.[256] This occurs in several ways:

1) Increased adverse reactions

Drug companies concentrate their spending on relatively few drugs – mostly new, expensive drugs for long-term use by large population groups.[257] This focus greatly increases the uptake and overuse of new drugs, before flaws and safety problems have been discovered. For example, Vioxx – which caused tens of thousands of deaths at a minimum – accounted for the highest percentage of all DTCA in the US in 2000 (with a bigger advertising campaign than Pepsi that year) and its retail sales quadrupled from 1999 to 2000.[258] The American Medical Association has proposed a moratorium on DTCA for all newly approved drugs, allowing doctors to learn about their efficacy and side effects before they are widely prescribed.[259]

Direct to consumer adverts often mislead people about the safety or efficacy of drugs, contributing to increased – and often inappropriate – drug use and associated adverse reactions. Content analyses of DTCA have found that the information provided is usually flawed or incomplete.[260] A 2007 study published in the *Annals of Family Medicine* found that few TV drug adverts described condition causes, risk factors or prevalence, and none mentioned lifestyle changes as an alternative to drug treatment.[261] Similarly, a study in *Health Communication* found that information on side effects constituted 15 per cent or less of total advertising time, usually at the end, with 12 per cent of TV adverts studied either breaking the law or meeting bare minimum requirements.[262] From 1997 to 2005, the FDA issued regulatory letters for misleading advertisements for 89 different drugs, and some companies, including GSK, Schering-Plough and Merck, received multiple regulatory letters over time for new adverts promoting the same drug.[263]

2) Increased 'medicalisation' of society

Charles Medawar, a consumer protection advocate who sits on the World Health Organisation's Expert Advisory Panel on Drug Policies and Management, argues that the most dangerous effect of DTCA is to encourage healthy people to believe they need medical attention.[264] According to a 2006 report by the US Government Accountability Office (GAO), 30 per cent of consumers who have seen DTCA, discussed either the advertised condition or drug with their doctor – evidence of the pressure doctors come under to prescribe named drugs as a result of DTCA.[265] A survey published in *Journal of the American Medical Association* found that nearly 80 per cent of doctors thought that DTCA encouraged patients to seek treatments they did not need.[266]

Consumer drug adverts often create or exacerbate unhappiness or anxiety about normal life experiences or mild symptoms and convince people that they may be at risk of a wide array of health conditions.[267] A particularly unsavoury example is the advert for Paxil (Seroxat in Britain) that GSK ran in the *New York Times* in October 2001, just a few weeks after the attack on the World Trade Centre.[268] It featured a woman with a pained expression walking on a crowded street, under the headline 'Millions suffer from chronic anxiety. Millions could be helped by Paxil'. The symptoms highlighted included worry, anxiety and irritability – all normal responses to a tragic event that many New Yorkers were understandably experiencing.

3) Increased burden on publicly-funded healthcare systems

Sharp increases in annual spending on medicines have been observed in the US and New Zealand following the introduction of DTCA.[269] In countries with publicly funded healthcare systems, the extra costs associated with DTCA – from both an increase in the use of expensive drugs and the associated adverse reactions – divert resources from other, more beneficial, treatments.

Research Fraud

According to the House of Commons Health Committee, drug companies conduct or commission 90 per cent of clinical drug trials and 70 per cent of trials reported in major medical journals. This, it says, inevitably means that '***industry not only has a major effect on what gets researched, but also how it is researched and how results are interpreted and reported'.***[270] Many medical experts believe that this stranglehold has led to biased results, under-reporting of negative findings and selective publication driven by commercial interests.[271] While drug companies and their executives enjoy increasing sales and hefty profits, doctors and other healthcare professionals have to make medical decisions based on publicly available evidence. If the evidence is flawed their decisions may not be the optimal ones and patients may suffer.

Suppressing Negative Data

In March 2008, after a four-year investigation, the UK government reprimanded GSK for withholding negative data from regulators about its antidepressant Seroxat. However, GSK did not face criminal charges because, according to the government, 'the legislation in this area is insufficiently clear'.[272] The UK investigation into GSK was sparked by a lawsuit filed against the company in June 2004 by the New York State Attorney General, Eliot Spitzer, who accused GSK of engaging in 'repeated and persistent fraud by concealing and failing to disclose to physicians information about Paxil' (Seroxat). Specifically, he claimed that GSK conducted at least five studies on the use of the antidepressant in children and adolescents yet only published and disseminated one (which it deemed positive). The results of the other studies were never released. These showed an increased risk of suicidal behaviour in under-18s and failed to find Seroxat effective in treating depression.[273] A leaked internal company document showed that GSK was aware of these negative findings as early as 1998, but did not hand the data to drug regulators until 2003 – a delay of five years.[274] In August 2004, GSK agreed to a settlement of $2.5m (£1.25m) and a requirement to publish all of its data – positive or negative – on a public database.[275]

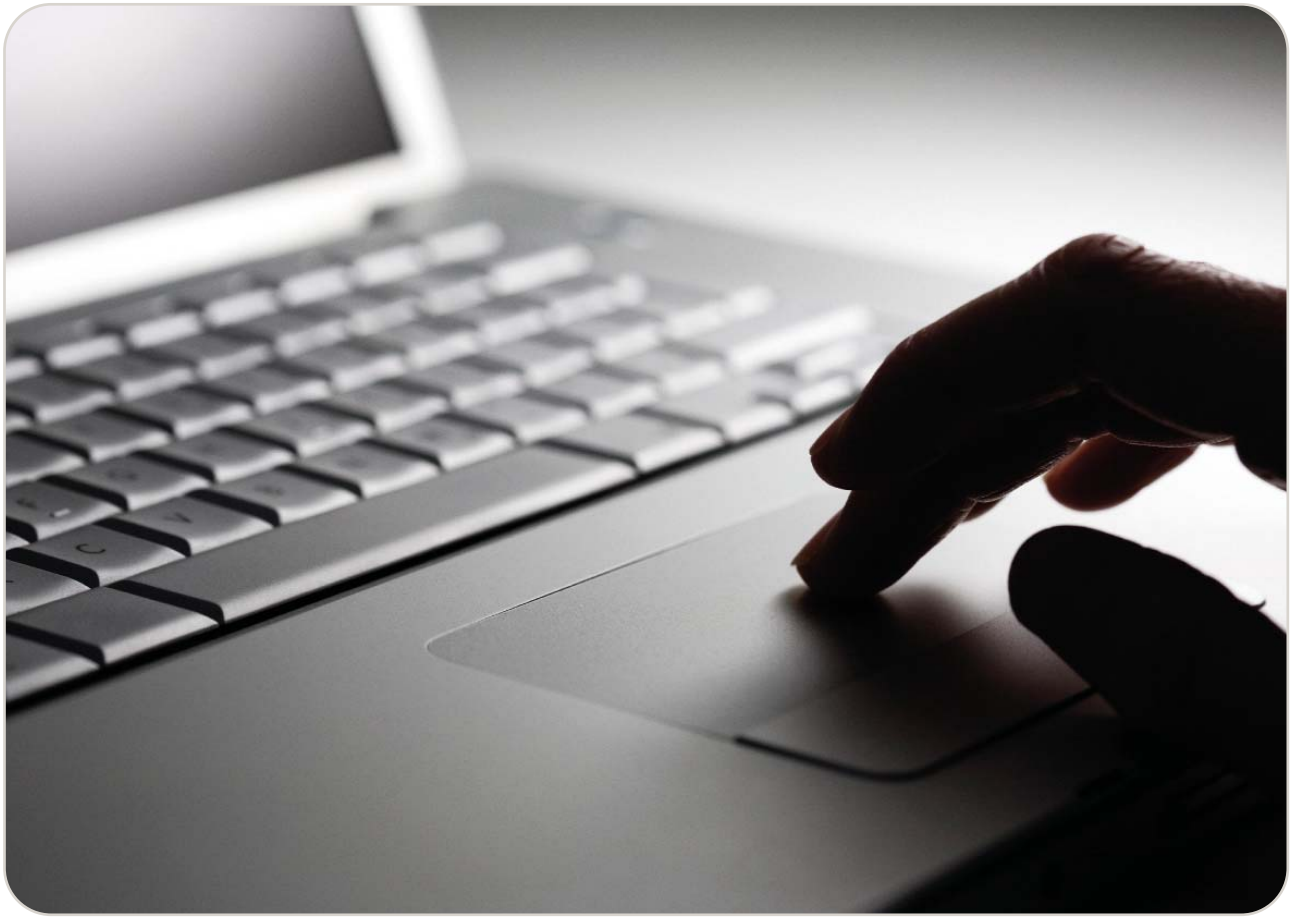
According to Dr Harvey Marcovitch, chairman of the Committee on Publication Ethics, ***'incomplete reporting of results is a big problem and is far more common with pharmaceutically funded studies'.***[276] Some high profile examples include:

- The most notorious and tragic example is certainly Merck's selective reporting of mortalities associated with its painkiller Vioxx. Company documents obtained in litigation over the drug reveal that an internal Merck analysis of two studies in 2001 showed a threefold increase in mortality associated with Vioxx. But the data Merck supplied to the FDA minimised that risk by presenting the numbers differently.[277] Merck did not submit the full analysis to the FDA until 2003, despite the FDA raising questions about the original data in December 2001. Similarly, a Merck-funded study submitted to the *New England Journal of Medicine* in 2000 omitted information on three Vioxx patients who had suffered unexpected heart attacks, data that would have made the drug look significantly riskier.[278]

- In addition to GSK's suppression of negative studies relating to its antidepressant Seroxat, two reports released at the beginning of 2008 showed that negative trial results for several SSRI antidepressants had been suppressed. The first, published in the *New England Journal of Medicine*, found antidepressant studies with positive findings were 12 times more likely to be published accurately than were studies with negative or questionable results. According to the published literature, it appeared that 94 per cent of the trials conducted were positive. By contrast, the FDA analysis showed that only 51 per cent were positive.[279] The second report, published in the *Public Library of Science Medicine*, used freedom of information legislation to obtain unpublished data relating to four of the most widely prescribed SSRI antidepressants.[280] The analysis of all data on these drugs – published and unpublished – revealed virtually no difference in the improvement scores for drug and placebo in patients with moderate depression and only a small, clinically insignificant difference in those with very severe depression.
- In March 2008, Merck and Schering-Plough published a study showing their blockbuster cholesterol lowering drug Ezetrol (Vytorin) was ineffective – but only after a US Congressional inquiry was set up to investigate why the study remained unpublished two years after it was completed. Prescriptions for Ezetrol cost the NHS £40m in 2006.[281]
- In 2006, Bayer withheld a report from the FDA showing a significantly increased risk of kidney failure associated with its drug Traysol – used to limit post-operative bleeding.[282] The company had previously hidden unfavourable data on its cholesterol-lowering drug Baycol, which was taken off the market in 2001 due to serious adverse reactions.

Manipulation of Trial Design and Data

Studies have repeatedly shown that research funded by a drug company is significantly more likely to yield a positive result for the company's product than research funded by other



sources.[283, 284] To achieve these favourable results, drug companies often manipulate trial designs to show their product in a misleadingly positive light. Some of the most common methods used include:

- **The use of inappropriate comparator drugs**, such as those known to have a higher risk of side effects than others in the therapeutic class.[285] According to an FDA drug safety officer, Merck employed this tactic in a key study of its painkiller Arcoxia – a potential successor to Vioxx – where the new drug was deliberately compared with another painkiller with high heart risks. Had Arcoxia been compared with a painkiller that posed fewer heart risks, it would have looked as unsafe as Vioxx.[286]
- **Selecting non-equivalent doses of comparator drugs.**[287] By using an insufficient dose of a competing product, the sponsor's drug will appear more efficacious. One review of nonsteroidal anti-inflammatory drug trials found that 48 per cent used a higher dose of the sponsoring company's drug than the comparator.[288] Alternatively, the comparator drug can be used at a much higher dose than the test drug, making the sponsor's drug look safer than it really is.[289]
- **The use of surrogate endpoints**. Drug companies may prematurely end a trial as soon as benefits appear. A 2008 study published in the *Annals of Oncology* found cancer drug trials were increasingly being stopped early when they showed benefits.[290] Eleven of the 14 trials stopped early in the past three years were used to support a drug licence application. The researchers concluded that there was a commercial component in stopping trials early as it could guarantee quicker access to the market for companies.[291] They also expressed concern that this may cause harm resulting from unreliable findings prematurely translated into clinical practice, particularly as five of the 14 studies had enrolled less than 40 per cent of the target number of patients.[292] Companies may also study the data from completed trials and publish only the results for a timeframe that favours their product.[293] For example, a published study showing that Pfizer's painkiller Celebrex caused fewer gastrointestinal ulcers than similar drugs after six months, failed to disclose that the 12 month data showed no such benefits.[294]

- **Misleading data analysis.** Although drug trials may be carried out at academic institutions or contract research laboratories, the sponsoring company usually keeps hold of the raw data and may only provide portions of the data to the researchers who write up the study.[295] In some cases, the company may analyse the data internally and provide researchers only with the final analysis.[296] This, according to analysts, allows companies to 'provide the spin on the data that favours them'.[297] A senior lecturer at Sheffield University, Dr Aubrey Blumsohn, lost his job when he questioned some of the findings about Procter & Gamble's (P&G) osteoporosis drug Actonel published in his name, even though he was never allowed to see the full analysis of the data. The University, which had a substantial research contract with P&G, accused Blumsohn of misconduct for talking to journalists and professional bodies about his concerns. P&G defended its actions in the press, stating that it is 'standard industry practice' to limit authors' access to data.[298] In another case, internal GSK memos and reports – obtained in litigation – showed that an inappropriate analysis of clinical trial data by GSK had obscured the suicide risks associated with Seroxat for 15 years. A Harvard University psychiatrist who studied the papers for the lawyers said it was 'virtually impossible' that GSK simply misunderstood the data.[299]

Conflicts of Interest

The vast scale of the global pharmaceutical industry and its research efforts means that many medical professionals and academics, as well as legislators and regulators, in wealthier nations – and in a growing number of 'developing' countries – have ties to drug companies. A 1996 survey in the US found that half of university professors who conduct life science research have 'substantial financial arrangements with industry'.[300] Now, more than a decade later, 75 per cent of clinical trials funded by drug companies take place in private, for-profit centres where scientific integrity may be less important than winning more contracts.[301] A former editor of the *New England Journal of Medicine*, Jerome Kassirer, told the campaigns group Transparency International that, during his tenure, it became increasingly difficult to find authors with no financial ties to a company whose products were featured in the article.[302] For this reason most journals accept research articles and drug reviews from authors with drug company ties as long as they disclose them, but authors often 'forget' to do so.

In July 2006, just days after announcing a crackdown on researchers who do not disclose drug company ties, the editor of the *Journal of the American Medical Association* had to admit publicly that she was misled again – the third time in two months – when six authors of a paper linking severe migraines to heart attacks in women failed to disclose that they had all done consulting work or received funding from the makers of treatments for migraines or heart disease.[303] Earlier that year, the journal printed a study claiming women who stop taking antidepressants during pregnancy were at a high risk of relapse, but the 13 physicians who co-authored the study failed to disclose more than 60 financial relationships to drug companies that manufacture antidepressants.[304] Several previous and subsequent studies have shown that infants exposed to SSRI antidepressants during development have significantly higher incidence of respiratory problems and lower birth weight.[305]

According to Catherine DeAngelis, editor in chief of the *Journal of the American Medical Association*, another conflict of interest that can contribute to the manipulation of research studies is peer reviewers who have ties to industry. '***Such reviewers may provide biased reviews that favor [sic] products of companies with which they have strong financial relationships, may fail to disclose their conflicts of interest to journal editors, or may even provide for-profit companies with confidential information obtained during the peer review process,***' she wrote in the April 2008 issue.[306] For example, last year a peer reviewer for *The New England Journal of Medicine* broke confidentiality and leaked a damaging report about the blockbuster diabetes drug Avandia to GSK, the drug's manufacturer, weeks ahead of its publication. The reviewer had previously served on the steering committee of a GSK sponsored clinical trial of Avandia and had given many talks for the company.[307]

Unethical Clinical Trials

Just as animals suffer and die so that drug companies can claim 'due diligence' when their products harm or kill people, many human clinical trial volunteers are also injured or even killed in risky drug tests. In fact, drug companies may employ the same contract research organisations (CROs) to perform their animal tests and clinical trials. Two of the largest international CROs conducting human drug trials, Quintiles and Covance, also run some of the largest animal testing centres.[308] Although the use of human subjects is more tightly regulated than animal tests, the commercial interests of privately owned, for-profit CROs, and their drug company clients, mean that regulations can be ignored and human volunteers put at risk.

The Medicines and Healthcare products Regulatory Agency approves around 1,000 clinical trials a year in the UK, involving about 2,500 people.[309] In the US, where most drug research and development takes place, 2.5 million people participate in medical studies every year.[310] The pharmaceutical industry has an 'insatiable demand for people to be in clinical trials' according to Marcia Angell, a senior lecturer at Harvard Medical School and former editor of the *New England Journal of Medicine*.[311] As the patents begin to run out on many blockbuster drugs, Big Pharma is desperately searching for the next money-spinner and this is fuelling a surge in drug testing. But unlike animal subjects, who can be bred to meet demand, human subjects are much more difficult to find and, according to Angell, 'there are sometimes terrible ethical violations'.[312]

Preying on Poverty

Most Phase One drug trials pay participants, as the risks are great and the healthy volunteers get no personal benefit from testing experimental drugs. Volunteers in the UK are generally paid £100 a day or more, depending on the level of risk and how long the trial lasts. CROs advertise on job sites, particularly student job sites, and in local papers, playing up the pay and perks of drug testing while minimising the risks. Biotrax, a company that recruits for drug trials across the UK, boasts, 'Volunteering for UK medical trials and medical research studies can be an excellent way to help pay educational costs, supplement your income whilst working, or fund your travels...

All medications tested go through very extensive preclinical trials.'[313] The final sentence is particularly unreliable considering the substantial body of scientific evidence demonstrating the failure of animal tests to predict human drug reactions.

Critics argue that payment is a stronger incentive for the poor than the wealthy, tempting them to agree to risks they might not otherwise take.[314] In December 2005, the web-based business news service *Bloomberg Markets* revealed that North America's largest for-profit drug testing centre, SFBC International Inc, regularly uses poor immigrants from Latin America, some of whom are in the country illegally and therefore cannot do 'legitimate' work.[315] Many of those interviewed said they are so desperate for money that they covertly participate in more than one study at a time or go from one test to another without the required waiting period, increasing their risks and invalidating

the test results. Although the FDA requires drug companies to hire monitors to audit clinical trials to ensure patient safety and scientific validity, Daniel Federman, Senior Dean of Harvard Medical School, says they actually spend most of their time scrutinising the test results. Ken Goodman, director of the Bioethics programme at the University of Miami, says pharmaceutical companies are shirking their responsibility to develop medicines safely by using poor, desperate people to test drugs.[316]

Volunteers who take part in a study must be informed of the risks involved. However, consent forms often contain legal and scientific terminology that can obscure important information on the risks.[317] For example, while consent forms may state that the test is a Phase One trial, they often do not explain that this means the side effects and safety of the drug in humans is so far unknown. Instead, they state that the aim of the test is to determine how the compound is 'absorbed, distributed, decomposed and eliminated from the body' – an approach criticised for masking the substantial risks.[318] According to Laura Dunn, professor of psychiatry at the University of California, ***'Decades of research show that poor understanding of informed consent documents is widespread'.***[319] In 1999, a CRO in Switzerland was found to be recruiting people from Eastern Europe and asylum seekers for drug trials, using consent forms in languages the participants did not understand.[320] A 2005 CBS News investigation revealed that staff at a state mental hospital in Texas were helping to recruit patients into studies of experimental drugs. Hospital officials defended their actions, claiming the patients had signed consent forms, but critics have questioned how informed the mentally ill patients' consent could have been.[321]

According to Harvard's Daniel Federman, nobody has ever tracked how many people are injured or killed each year while participating in clinical trials.[322] However, a clinician who has supervised many trials told *Science*: '***If you were to look in [a big company's] files for testing small-molecule drugs, you'd find hundreds of deaths.***' Although it's a shock when a patient dies, he said, it is not unusual.[323] Some recent high-profile incidents include:

- In July 2007, Jolee Mohr, a 36-year-old American woman, died from internal bleeding and multiple organ failure after receiving the second injection of an experimental anti-inflammatory drug. The consent form used by Targeted Genetics – the drug company behind the trial – was thick with technical descriptions and thin on explaining what was actually going to happen, according to a medical ethics expert from the University of Pennsylvania. 'Even a smart person would have a very hard time figuring out what they're talking about,' he said.[324]

- In March 2006, six British men taking part in a Phase One trial were rushed to hospital shortly after being given the test drug, known as TGN1412. They all suffered multiple organ failure and spent weeks in hospital. One man's head swelled up so much that he was dubbed the Elephant Man. The worst affected, Ryan Wilson, spent 147 days in hospital and almost died. He lost several fingers, all of his toes and now lives in 'constant agony'.[325] He and three others have been warned that they are highly likely to develop incurable autoimmune diseases.[326] For more on this trial disaster, see the box opposite.

- In December 2006, Pfizer suddenly stopped a Phase Three trial of a drug intended to increase 'good' cholesterol levels after an independent safety monitoring board found substantially more deaths and heart attacks in the group taking the drug than in the control group.[327] More than 15,000 people were involved in the worldwide study, which showed a 58 per cent increase in the risk of death among patients taking the test drug than in those taking a different cholesterol drug.[328]

- In April 2002, Garry Polsgrove – a homeless US war veteran – died in a clinical trial for a schizophrenia drug. According to his sister, he had entered the trial in order to have a bed and earn some money. The drug caused his heart to swell up, a risk recognised by the FDA before authorising the trial but which was not mentioned on the consent form.[329]

TGN1412 – A Drug Trial Disaster

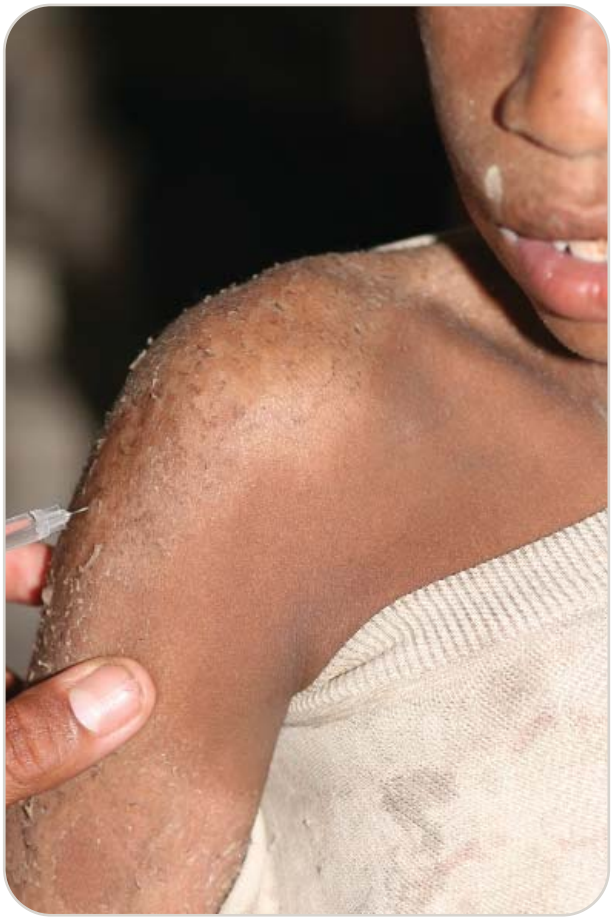
On March 13 2006, six healthy male volunteers rapidly developed multiple organ failure after being injected with an experimental antibody drug.[330] Despite both rhesus monkeys and cynomolgus monkeys tolerating large doses of the drug without any serious side effects,[331] the men were reportedly writhing in pain, tearing at their clothes, screaming and retching within minutes of receiving a dose 500 times smaller than that used in the monkeys.[332] The tragedy made headlines around the world and highlights how human volunteers are put at risk by dubious research protocols, unreliable animal data, financial inducements and insufficient risk awareness.

On the website of Parexel International, the CRO that performed the human TGN1412 trial, prospective subjects are tempted with a range of incentives: 'You'll receive a thorough medical check-up – FREE! You'll be paid for your time and inconvenience... Free food for the duration of your stay... You'll have plenty of free time to read or study, or just relax – with digital TV, pool table, video games, DVD player and now FREE internet access!'[333] Once on the company's books, volunteers regularly get offers to participate in other studies. '£650 for three days here, £1000 for a week there,' according to one former Parexel volunteer.[334]

The TGN1412 trial paid £2,000, a substantial amount to the young men, mainly students, who took part.[335] However, like many clinical trials, the 13-page consent form stipulated that the men would only receive the full amount when they completed the trial,[336] a provision which prevents subjects from leaving a trial early if they experience side effects or simply change their mind. The men were also not made fully aware of the potential risks and side effects before starting the trials. According to experts who reviewed the consent form, 'the document didn't sufficiently inform participants of the therapy's possible dangers or properly depict the treatment as a novel drug that can disrupt the body's immune system'. [337]

Several aspects of the TGN1412 research protocol have been criticised. Some have argued that a drug specifically designed to stimulate the immune system should not have been tested in healthy volunteers with intact immune systems.[338] Critics have also questioned why all six men were given the drug at the same time and have suggested that a single dose should have been administered to a single volunteer and the effects monitored before proceeding with the full trial.[339] Others have suggested that, when deciding to proceed with human trials, results from *in vitro* tests showing that TGN1412 had a dramatic effect on human T-cells were overlooked in favour of animal tests showing no TGN1412 related adverse reactions.[340]

The Medicines and Healthcare products Regulatory Agency (MHRA) investigated the incident and concluded that TGN1412 was manufactured correctly and that there were no signs of contamination of the batch administered to the volunteers. It also concluded that the correct dose was used and that the trial was run according to the agreed protocol.[341] Thomas Hanke, chief scientific officer of TeGenero – the drug company that manufactured TGN1412 – defended its decision to proceed with human trials based on information from monkeys because the targeted molecule, CD28, is 100 per cent identical in humans and cynamolgus monkeys.[342] On the assumption that all of the above is correct, the only explanation for the serious side effects experienced by the six men is that animal drug responses do not reliably predict human responses.



Drugs in Developing Countries

In May 2007, Nigerian authorities pressed criminal charges against Pfizer in relation to a clinical trial it conducted there during a meningitis epidemic ten years earlier. The lawsuit alleges that Pfizer researchers gave an unlicensed antibiotic called Trovan to 100 children and infants without the consent of their families and in spite of research showing the drug might have life-threatening side effects.[343] The researchers also allegedly gave a comparator drug to another 100 children but deliberately underdosed them to make Pfizer's drug look more effective. Eleven children in the trial died and an unknown number suffered deafness, blindness, paralysis and other disabilities.[344]

Over the past two decades, drug companies have increasingly been running clinical trials in developing countries.[345] According to the director of the University of Pennsylvania's Centre for Bioethics, Arthur Caplan: 'Sometimes they go because that's where the disease is. Sometimes they go because it's cheaper and easier to get things approved.'[346] But they also go because clinical trials in wealthier countries are increasingly failing to recruit enough people. For drug companies, each day a potential blockbuster remains locked up in R&D can equal $1m (£500,000) in lost sales.[347]

Critics have expressed concern over the potential for exploitation and violations of research ethics in countries with limited resources for enforcement. Of particular concern is the issue of informed consent. According to Sonia Shah, author of *The Body Hunters: Testing new drugs on the world's poorest patients*, a steady stream of people dropping out of trials is generally interpreted as confirmation of voluntary consent, with up to 45 per cent of subjects dropping out in some Western trials.[348] But in poor countries the attrition rate is often frighteningly low. Some CROs operating in developing countries tout the low drop-out rate as a reason to site more trials there. One New Delhi-based company boasts that it retains 99.5 per cent of enrolled subjects.[349]

It is estimated that by 2010, India will host nearly a fifth of all clinical trials.[350] Most of the world's largest drug companies have already established a presence in India, with Pfizer, GSK and AstraZeneca all having clinical trial centres there.[351] The Indian government has responded to the demands of the pharmaceutical industry and has made experimental drugs exempt from custom duties and offered drug companies generous tax concessions.[352, 353] However, few changes have been made to ensure trials are done transparently and safely.[354] Critics fear that, in a country where half the population is illiterate, people will be lured into trials by offers of free health care and medicine without being fully aware of the risks.[355] They also question whether new drugs tested in India will actually benefit patients there, pointing to the recent trial of Herceptin – an expensive breast cancer drug that few Indians are likely to be able to afford.[356]

A BBC investigation in 2006 found that some Indian patients were unaware they were being used to test new drugs. Parshottam Parmar, a psychiatric patient who took part in a trial of an antipsychotic drug for Johnson & Johnson, told the BBC reporter: 'I didn't know that experiments were being carried out on me. I was told that the old drugs were discontinued and were no longer available in the pharmacies... I don't know a lot about all these things. I am poor and I live in a small hut and I don't understand many things. The doctors are intelligent. They write the drugs for me so I have to take them accordingly.'[357] Johnson & Johnson claims that it

got consent from the patient or a relative in every case, but according to Mr Parmar, 'We just sign because I believe the doctor takes the signature to help us. That's why I sign it.'[358] The investigation also revealed that most consent forms were written in English, which many patients could not read, let alone understand, and some could only give a thumbprint to signal their 'consent'.

Ignoring Women and Minorities

It is widely recognised that gender, race and age affect susceptibility to disease and the way diseases progress in the body. Drugs can also act differently in men and women, in the old and the young and in people from different ethnic backgrounds. Despite regulatory guidelines encouraging drug companies to include a broader selection of people in clinical trials, women, the elderly and ethnic minorities are still under-represented, putting them at greater risk of adverse reactions once the drugs are marketed. For example, one US study found that only 2.1 per cent of people in trials of nonsteroidal anti-inflammatory drugs were over 65 even though these drugs are more commonly used by, and have a higher incidence of side effects in, the elderly.[359] Similarly, a 2001 study published in the *Journal of the American Medical Association* found that women and elderly people remain under-represented in published trial literature relative to the prevalence of disease found in these groups, undermining efforts to provide safe and effective drugs for these patient groups.[360] And a 2008 study found that fewer than one in 10 participants in US cancer trials are from ethnic minorities even though they make up a quarter of the population.[361]

Drug Priorities: Lifesaving or Lifestyle?

Although drug companies justify poisoning animals in toxicity tests by claiming that they are searching for lifesaving 'cures', the majority of their research is focused on highly profitable lifestyle and 'me-too' drugs, not breakthrough treatments. While there are now 19 beta blockers (to control blood pressure) on the market,[362] diseases such as malaria, tuberculosis and pneumonia have been largely ignored by drug companies.[363] According to Médecins Sans Frontières (MSF), which campaigns for access to essential medicines, drug companies steer their research and development toward areas of guaranteed profitability.[364]

'Me-too' Drugs

The House of Commons Health Committee recognised in 2005 that there has been a drop in the number of new molecular entities (NMEs) entering the market and an increase in 'me-too' drugs – medicines that perform the same or almost the same therapeutic function as one or more products already on the market.[365] While no figures are available for the UK, a 2005 investigation by the US Government Accountability Office found that 68 per cent of new medicines submitted to the FDA for approval between 1993 and 2004 were modified versions of existing drugs – 'me-too' drugs.[366]

A second 2005 survey also revealed that 68 per cent of new drugs approved in France between 1981 and 2004 offered nothing new to the market.[367] More worryingly, a Canadian study published in the *British Medical Journal* showed that only 5.9 per cent of drugs approved there between 1990 and 2003 provided a substantial improvement over existing drugs, the remaining 94.1 per cent were 'me-too' drugs.[368]

'Me-too' drugs come about in two ways. A drug company may try to grab a share of an established, lucrative market by copying a top-selling drug made by a competitor.[369] SSRI antidepressants are a prime example, with brands such as Prozac, Seroxat, Lustral and Ciprimal all made by different companies but doing virtually the same thing. Similarly, most of the top drug companies market their own brand of statin (cholesterol lowering drug) and Pfizer, Eli Lilly and Bayer all manufacture similar drugs for erectile dysfunction. Alternatively, a company can release a 'new' drug that is simply a modified version of a drug it already manufactures. It may do this to reach a new audience, such as when Eli Lilly repackaged Prozac in a lavender coloured pill and marketed it as Sarafem – a drug for 'premenstrual dysphoric disorder'.[370] Or it may make a strategic modfication when the patent on a top-selling drug is about to run out, a practice known as 'evergreening'.[371] For example, a few months before the patent expired on Pfizer's blockbuster allergy drug Zyrtec, the company brought out a patented spin-off called Zyrtec-D, an extended-release version of the same drug.[372] According to Marcia Angell, former editor of the *New England Journal of Medicine*, drug companies

don't 'waste' money on risky endeavours looking for new drugs when they can just tweak an existing drug and get 20 more years of patent rights.[373]

The House of Commons Health Committee acknowledged that the presence of so many 'me-too' drugs on the market creates difficulties for prescribers and the NHS.[374] A study examining the per capita expenditure on drugs in British Columbia, Canada, found that 80 per cent of the increase in drug expenditure between 1996 and 2003 was due to the use of new, patented drugs that did not offer substantial improvements on less expensive alternatives.[375] Based on the fact that many of the 20 best selling drugs in the world are newly patented versions of long established drugs, the authors conclude that 'me-too' drugs probably dominate drug spending in most developed countries. This has obvious implications for publicly funded healthcare systems with finite resources.

The proliferation of 'me-too' drugs raises serious concerns about the Home Office's licensing of animal experiments. When considering licence applications for procedures using animals, the Home Office is legally obliged to weigh the cost to the animals, i.e. the amount of suffering, against the potential human benefit the experiment could bring. As the vast majority of drugs brought to market in the last two decades have offered no new therapeutic benefit,[376] the Home Office has acted improperly in licensing much of the drug research using animals. It has also betrayed the British public, as most people who support animal research do so under the strict proviso that it brings significant health benefits to humans. In the case of 'me-too' drugs, it is incontestable that no such benefits are forthcoming.

Neglected Diseases

According to Médecins Sans Frontières, 'Research and development (R&D) into diseases for which there is little commercial market remains grotesquely insufficient, depending heavily on philanthropic funding'.[377] Ninety per cent of global pharmaceutical R&D is currently spent on the health problems of less than 10 per cent of the world's population – the rich nations.[378] This is commonly referred to as the 10/90 gap. As a result of this imbalance in research spending, only one per cent of drugs launched between 1974 and 2004 targeted tropical diseases and tuberculosis, which

account for 12 per cent of the total global disease burden.[379]

While 25 companies had anti-obesity drugs in clinical trials in 2007,[380] malaria, which affects up to 500 million people a year and claims the lives of one million, is still virtually untreatable. In 2000, GSK launched the first new anti-malarial developed by a drug company in 40 years. It was, however, a prophylactic, not a treatment for those already infected. The drug was not intended for the millions of poor people living in countries where malaria thrives, it was aimed at rich Western tourists who holiday in those regions.[381] Similarly, the most recent medicine for tuberculosis, which kills two million people a year, is 30 years old, while sleeping sickness – a disease which threatens 60 million people – is still treated with a toxic arsenic derivative in use since the 1940s.[382]

Keeping Prices High

The NHS currently spends about £11bn a year on pharmaceuticals, with branded drugs accounting for £8bn of this.[383] A 2007 report by the Office of Fair Trading said that the NHS is paying drug companies too much for some drugs, particularly those for cholesterol, blood pressure and stomach acid that are prescribed in large volumes. It recommended a new system where the price of a drug is based on its health benefits.[384] This would have a major impact on 'me-too' drugs as they offer little benefit over existing drugs yet cost substantially more than older, generic versions.[385] But the pharmaceutical industry is unlikely to accept such changes without a fight. The trade body representing the industry has already won the right to challenge the UK government in court over its attempt to encourage doctors to prescribe generic statins in place of more expensive branded versions, a change that could save the NHS at least £84m a year, according to the Department of Health.[386] However, this is just one of the many manoeuvres drug companies employ to keep their prices, and more importantly their profits, high.

Patent Manipulation

According to the House of Commons Health Committee, the leading drug companies systematically employ 'a range of product- and law-based strategies intended to subdue or delay competition from generic manufacturers', including: seeking reclassification as an over-the-counter medicine; intensified promotion before patent expiry to enhance brand loyalty; pressing for longer processing times for generic licence applications compared with brand name products; and evergreening – extending the patented life of a product by modifying it slightly.[387]

The range of drug attributes eligible for patent protection has increased dramatically in the past two decades and now extends to the packaging, dosing route (e.g. oral or nasal), dosing regime (e.g. once or twice daily) and drug delivery system (e.g. tablet or capsule).[388] Brand name manufacturers can, therefore, obtain separate patents on different aspects of a single product, entitling them to another 20 years of patent protection each time they change one of these characteristics. For example, within one year of Prozac's patent expiring, Eli Lilly introduced a new version that was taken weekly instead of daily.[389] In 2004, King Pharmaceuticals extended the patent on its blood pressure drug Ramipril by switching it from capsules to tablets three months before the patent expired.[390] The year the patent was due to expire on Schering-Plough's anti-allergy drug Clarityn, US consumers were bombarded with adverts for Clarinex, a 'new' product by Schering-Plough that was essentially just a more potent version of Clarityn.[391]

It is only now, as patents begin to run out on many blockbuster drugs and Big Pharma looks for new sources of profit, that an interest is being shown in the generic drugs market. According to Simon Friend, head of PricewaterhouseCoopers' pharmaceuticals division, drug companies are now diversifying to 'have a foot in both camps'.[392]

Anti-competitive Practices

In January 2008, European Commission officials raided the offices of Pfizer, GSK, Sanofi-Aventis and AstraZeneca as part of an investigation into industry efforts to delay the arrival of generic drugs.[393] While specific details about these allegations have not been released, several drug companies have been prosecuted in recent years for anti-competitive practices aimed at keeping low-cost generic drugs off the market. For example:

- In 2003, Bristol-Myers Squibb was ordered to pay a total of $265m (£133m) in settlements relating to its fraudulent use of patent laws to maintain its monopoly on the anti-cancer drug Taxol.[394]
- In 2004, the European Commission fined AstraZeneca £40m for misusing the patent system to delay generic rivals to its ulcer drug Losec.[395]
- In 2006, GSK was ordered to pay $65m (£33m) for using lawsuits against its competitors to stop them from selling generic versions of Paxil (Seroxat). Just one year earlier, GSK had to pay $75m (£37m) for using the same tactic to keep generic versions of its painkiller Relafen off the market.[396]
- In 2008, BBC's Newsnight programme obtained documents indicating that executives at Reckitt Benckiser, maker of the blockbuster drug Gaviscon, sought to string out the process of a cheaper, generic version of the drug being brought to market through legal challenges and scares over the safety of competing drugs.[397]

Generic drug companies are not always innocent victims in the drug price wars. In 2002, the UK Serious Fraud Office raided 30 offices and houses of generic drug companies and their executives as part of an investigation into price-fixing.[398] Five generic drug manufacturers were eventually charged with conspiring to defraud the NHS of more than £100m by fixing the prices for generic versions of some of the most commonly prescribed drugs: Warfarin, a blood-thinner; Zantac, a stomach ulcer medicine; and a range of penicillin-based antibiotics.[399] At least three of the companies agreed to a compensation settlement with the Department of Health, and the case against one firm is ongoing.[400] Brand name manufacturers and generic companies also often collude in what is known as the pay-for-delay settlement tactic.[401]

For example:

- In 2001, the FTC charged Schering-Plough, Upsher Smith and American Home Products with entering into anti-competitive agreements after Schering-Plough offered the two companies multi-million dollar payments in exchange for their commitment not to release generic versions of Schering's drug K-Dur 20.[402]
- In 2007, Bristol-Myers Squibb pleaded guilty to making false statements to a federal agency during a criminal case brought against the company for entering into a secret deal to head off generic competition to its blockbuster blood-thinning drug Plavix.[403]
- In 2008, the US Federal Trade Commission (FTC) filed charges against Cephalon Inc for paying four companies to refrain from selling generic versions of its drug Provigil – used to treat narcolepsy and sleep apnoea.[404]

Depriving the Poor

According to Oxfam, '***Poor people are dying needlessly because global pharmaceutical giants continue to monopolise drugs for diseases like cancer and Aids.***'[405] The United Nations echoes this view, stating in a 2007 report that simply 'improving access to existing medicines could save 10 million lives a year.'[406] Both organisations believe that generic competition is essential in order to bring down drug prices and ensure access to medicines for all.[407] Yet Big Pharma, which includes some of the world's most profitable companies, continues to try to prevent poor countries from buying or producing cheap generic drugs by lobbying for a uniform global patent regime through the World Trade Organisation (WTO).[408]

In May 2006, Novartis launched a legal challenge to India's patent laws – which prohibit patents on new forms or new uses of known substances – after an Indian company began manufacturing a generic version of Novartis' anti-cancer drug Glivec.[409] India's patent office had refused to grant Norvartis a patent for Glivec because it involved minor modifications to an old molecule.[410] The legal challenge threatened India's large generic drug industry, which is the main supplier of inexpensive generic medicines to developing countries.[411] For example, nearly 85 per cent of the antiretrovirals Médecins Sans Frontières provides for people infected with HIV come from Indian generic manufacturers.[412] Fifty-two eminent personalities and organisations signed a letter to Novartis urging them to drop the action in the interest of public health, but Novartis persevered.[413] In August 2007, the Madras High Court dismissed Novartis's petition and upheld India's patent laws, which permit a thriving generic industry.[414]

Novartis's suppression of a generic version of Glivec in South Korea is a particularly shameful example of drug company greed given that leukaemia patients in South Korea had taken part in clinical trials that helped get the drug approved in record time.[415] Once the trial was over, the patients had little hope of affording the drug, which costs more than £25,000 for a year's treatment. A group of patients lobbied the government to import the generic version from India, at a cost of less than one dollar a pill. However, while the South Korean Ministry of Health was considering the proposal, it received a written threat from the US Secretary of Commerce, presumed to be at the request of Novartis, warning the Ministry that if it went ahead with the importation it could escalate into a full-blown trade dispute.[416] The patients then tried to talk to Norvartis directly but were denied a meeting with the company's Korean director, so they held a demonstration outside the company's office. After a four hour peaceful protest they were violently arrested by police, with two demonstrators hospitalised.[417] In 2003, they lost their fight to import the generic drug.

Pfizer was also inflexible when it launched a lawsuit against the Philippines government, and government officials personally, to try to stop the import of cheaper versions of Pfizer's blood pressure drug Norvasc.[418] The suit was filed after the Philippines drugs bureau approved the import of a generic version of Norvasc from Pakistan that is nearly four times cheaper than Pfizer's selling price.[419] According to Mercy Fabros of AGAP, a coalition campaigning for cheaper medicines, hypertension is a leading killer in the Philippines, and for Filipinos, Norvasc's cost 'is really a matter of life and death'.[420]

Relatively well-off patients in rich countries also sometimes have difficulty accessing medicines because of their inflated costs. The National Institute for Health and Clinical Excellence (NICE) came under fire in 2007 for refusing to allow two drugs for wet macular degeneration – a common cause of blindness in the UK – to be used on the NHS.[421] While the media and patient groups berated NICE, no-one seemed to question why the drugs are so incredibly expensive or hold the companies that manufacture them to account. But an article in *The Guardian* a year earlier revealed that one of the 'new' drugs, Lucentis, was actually a repackaged version of an existing drug, Avastin, designed to treat colon cancer.[422] Ophthalmologists around the world had successfully been using the cancer drug to treat wet macular degeneration by injecting small quantities into the eyes of sufferers. Because one phial could be split and used for several patients the treatment was very inexpensive. However, because the drug was not approved by NICE for this use it was not universally available on the NHS. Genentech, the drug's manufacturer, refused to apply for a licence for this use of Avastin. Instead, it repackaged it in tiny quantities suitable for eyes and renamed it Lucentis, a 'new' drug that costs 100 times more than Avastin.[423]

Bullying Tactics

While some doctors, researchers and regulators are willing to turn a blind eye to drug company misconduct or safety concerns as long as the price is right, those who do speak out often face lawsuits and smear campaigns designed to silence them.

When GSK launched its blockbuster diabetes drug Avandia in 1999, Dr John Buse – a diabetes expert based at the University of North Carolina – raised concerns about its potential heart risks. GSK quickly threatened him with a $4bn (£2bn) lawsuit to try and silence him. The company also launched a smear campaign against Buse, dismissing him as a liar and saying he was 'for sale'.[424] Eight years later, a study published in the *New England Journal of Medicine* (NEJM) found patients on Avandia suffered 43 per cent more heart problems than other diabetics.[425] The lead author of the report, Dr Steven Nissen, also faced a smear campaign, but at the hands of the FDA not GSK. Embarrassed that a drug it had licensed now appeared to be extremely risky, FDA staff circulated baseless allegations that Dr Nissen was biased against companies that did not fund his clinic.[426] GSK, meanwhile, turned its attention to the NEJM, publicly criticising the respected journal and accusing it of 'smearing the drug' in an effort to demonstrate that the FDA was not doing its job.[427]

In 2004, Dr David Franklin received a $26m (£13m) payout from Pfizer, his former employer.[428] He joined the company as a medical liaison in 1996, when it was Warner Lambert, and was expected to promote the seizure medication Neurontin for off-label uses including bipolar disorder, ADHD, migraines and alcohol withdrawal. When he found evidence of serious side effects in some children with ADHD he was ordered not to tell doctors. When the company announced that anyone who was not comfortable with aggressively selling Neurontin should leave, he did – after only four months of employment. He was then threatened by at least one company executive, warning that if he spoke publicly about his concerns he would be made a scapegoat and be described as a rogue employee in a company that played by the rules.[429]

He decided to blow the whistle, revealing evidence he'd collected – including documents and tape-recordings – showing that the company bribed doctors with cash and expensive gifts to increase their use of Neurontin. A seven-year legal battle ensued, ending in 2004 with Pfizer paying a $240m (£120m) criminal fine and $152m (£76m) to state and federal healthcare programmes, as well as the payout to Dr Franklin.[430]

Conclusion

This report demonstrates, above all else, that the global pharmaceutical industry is devoted not to altruism but to maximising profits. For that reason, its marketing rhetoric should be as carefully scrutinised as the claims of good deeds done and miracles accomplished by, for instance, the oil industry.

While the media, from time to time, does a creditable job in exposing drug industry sharp practice, all past sins tend to be forgotten when the next share price-boosting 'breakthrough' comes along (usually heralded as being just 'five to ten years' away). This combination of amnesia and giddy hope is not so surprising. People are ultimately frail. They and the ones they love will at some time fall prey to disease or injury that leaves them feeling that they are dependent on the medical therapy industry. They need hope and they need to believe. They also need to be protected from the kind of faked evidence and exploitation described in this report. That is why, when the companies hold out the promise of salvation, they should be held properly to account – by legislators, regulators and opinion formers. The objective scrutiny should begin at the drug development stage, where it is claimed that experimenting on animals is key to producing drugs that are safe and effective. For the sake of the animals themselves and for the human patients in whose name the animals are tormented, testable evidence must be produced.

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Appendix 1

While some adverse drug reactions and product withdrawals attract significant media attention (see pages 13-14), many drugs are relabelled, withdrawn or abandoned in late stage clinical trials every year because of harmful side effects.

Below are just a few recent examples of products that were determined to be safe in animal tests and have since proved to be harmful to humans.

Drug Withdrawals

Exubera: In April 2008, Pfizer and Nektar Therapeutics issued a warning about an increased risk of lung cancer associated with their inhaled insulin drug Exubera. Pfizer had already stopped marketing the drug in October 2007 and, after issuing the lung cancer warning, said it would discuss withdrawal of the marketing licence with regulatory agencies.[1]

Over-the-counter cough medicines: In March 2008, the Medicines and Healthcare products Regulatory Agency (MHRA) ordered that six cough products aimed at children under two be removed from sale, with a further 100 cough remedies being put 'under-the-counter' and sold only to parents of older children. The drug regulator was responding to the deaths of at least five British children and more than 100 adverse reactions linked to the drugs.[2]

Trasylol: In November 2007, the FDA ordered Bayer to withdraw its drug Trasylol – used to control bleeding during heart surgery – almost two years after the publication of an observational study showing an increased risk of death in patients treated with the drug. According to the author of the study, Dr Dennis Mangano, 22,000 lives could have been saved if Trasylol had been taken off the market when he published his report in January 2006. During an FDA meeting in September 2006 to discuss the findings of Mangano's report, Bayer failed to disclose that it had conducted its own research, which confirmed the same dangers, enabling the drug to stay on the market for a further 14 months.[3]

Prexige: In August 2007, Australia's drug regulator revoked Novartis's licence to market its painkiller Prexige – used to treat arthritis – after several incidents of liver damage and death linked to the drug.[4] Three months later, drug regulators in the UK, Germany and Austria also suspended sales of the drug after high incidences of liver damage were observed.[5]

Permax: In March 2007, the FDA ordered Valeant Pharmaceuticals to withdraw its drug Permax[6] – used to treat Parkinson's disease – following two studies published in the *New England Journal of Medicine* showing that serious heart valve damage occurred in a quarter of Parkinson's sufferers prescribed the drug.[7]

Zelnorm: In March 2007, the FDA ordered Novartis to withdraw its drug Zelnorm – used to treat gastrointestinal problems such as constipation – due to the risk of serious adverse cardiovascular events (i.e. angina, heart attack and stroke) associated with the drug.[8]

Drug Warnings

ESAs: In March 2008, the FDA ordered new black box warnings on the labels of three drugs used to treat anaemia in chemotherapy patients – Aranesp, Epogen and Procrit – known as erythropoiesis-stimulating agents (ESAs). The new label will warn that the drugs may shorten survival times in patients with certain types of tumours as well as cause tumours to spread more quickly.[9] A previous black box warning, added in November 2007, detailed the risk to cancer sufferers and patients with chronic kidney failure, of heart attack, stroke and heart failure associated with the drugs.[10]

Prezista: In March 2008, the FDA warned doctors of the risk of potentially fatal liver damage associated with Johnson & Johnson's HIV drug Prezista. Johnson & Johnson changed the drug's label to include the warning.[11]

Champix: In February 2008, the FDA issued a warning to doctors and patients about the risk of 'serious neuropsychiatric symptoms' associated with Pfizer's drug Champix (Chantix in the US) – used to help people stop smoking. The symptoms include depression, suicidal ideation and attempted and completed suicide. Pfizer was requested to change the drug's label to reflect these elevated risks.[12]

Tamiflu: In February 2008, Roche strengthened the warning label on their prescription flu medication Tamiflu to include potentially fatal incidences of delirium and abnormal behaviour.[13]

Antiepileptic Drugs: In January 2008, the FDA warned doctors that antiepileptic drugs doubled a patient's risk of suicidal behaviour or ideation. The warning followed the agency's analysis of placebo-controlled clinical trials for 11 drugs commonly used to treat epilepsy as well as psychiatric disorders. The FDA believes the increased risk of 'suicidality' is shared by all antiepileptic drugs, not just the 11 that were included in their analysis.[14]

Xolair: In February 2007, the FDA ordered Genentech Inc to add a black box label on its asthma drug Xolair warning that it may cause a potentially deadly allergic reaction. According to the FDA, anaphylaxis – a dangerous inflammatory reaction characterised by shortness of breath, rash, wheezing and low blood pressure – occurs in about 1 in 1,000 patients taking the drug.[15]

Abandoned Late-Stage Clinical Trials

Recentin: In February 2008, AstraZeneca stopped the Phase Two trial of Recentin – an experimental drug to treat lung cancer – because of 'problems of toxicity'.[16]

Torceptrapib: In January 2007, Pfizer halted the late-stage clinical trial of its drug Torceptrapib – the first of several new drugs thought to help clear deposits from arteries – after it was found to produce high risks of death and heart problems.[17] In November 2007, the results of the 15,000-patient study were published, showing that the drug raised the rate of heart attacks and other potentially deadly events by 25 per cent. It was also found to have an unexpected 'off-target' toxicity on the adrenal gland, which led to an increase in blood pressure and damage to artery walls.[18]

Vectibix: In March 2007, Amgen discontinued a clinical trial of Vectibix – an experimental drug to treat colon cancer – after discovering that it reduced patients' chances of survival. Adding the drug to existing colon cancer drugs appeared to increase toxicity without improving efficacy.[19]

Cellcept: In March 2007, Roche stopped a clinical trial of its cardiac drug CellCept after four heart transplant patients suffered acute rejection. The company also reported an incidence of adverse events greater than 30 per cent in the study population.[20]

SPP301: In January 2007, the Swiss biotech company Speedel halted the Phase Three trial of SPP301 – an experimental drug intended to treat diabetic kidney disease – due to 'patient safety fears'. The drug was found to cause a significant imbalance in fluid retention in patients on the trial.[21]

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