



A BITTER PILL TO SWALLOW

Drugs for people,
not just for profit

Jon Cruddas
and Zoe Gannon

compass
DIRECTION FOR
THE DEMOCRATIC LEFT

A BITTER PILL TO SWALLOW

Drugs for people not just for profit

Jon Cruddas
and Zoe Gannon

compass

Published by Compass – Direction for the Democratic Left Ltd
Southbank House, Black Prince Road, London SE1 7SJ
T: +44 (0) 207 463 0632 zoe@compassonline.org.uk
www.compassonline.org.uk

Designed by SoapBox, www.soapboxcommunications.co.uk

Contents

Acknowledgements	4
Executive summary	5
Introduction	8
The growth of the pharmaceutical industry	10
The problem	
1. Cost of drugs and declining innovation	13
The drugs industry	13
Executive pay	16
Blockbuster drugs	17
Me too, me again and me as well	18
Where is innovation actually coming from?	19
2. Bias in industry-sponsored clinical trials	21
The gold standard of science: randomised controlled trials	21
Who controls randomised controlled trials?	21
Industry influence and bias	21
3. The medical profession and the pharmaceutical industry	25
4. The pharmaceutical industry and the public	28
Patient groups	28
The consequences	
5. The human consequences of market failure in the pharmaceutical industry	30
6. Why is the pharmaceutical industry getting away with it?	34
The Medicines and Healthcare products Regulatory Agency	34
The Pharmaceutical Price Regulation Scheme	35
The National Institute for Clinical Excellence	36
7. Policy recommendations	37
Conclusion	39
Appendix 1 Will the pharmaceutical industry leave the UK?	40
Appendix 2 Existing regulation	42
Glossary of acronyms	44

Acknowledgements

This report was written by Jon Cruddas and Zoe Gannon. We are grateful to the Barry Amiel and Norman Melburn Trust, which supported the research. We would also like to thank all those who advised us on the project, including: Martin McIvor, Meg Russell, Colin Crouch, Neal Lawson, Dan Leighton, Alan Finlayson, Jonathon Rutherford, Tony Harrison, Martin Rathfelder, Richard Wilkinson, Aubrey Blumsohn, Jack Stilgoe, James Wilsdon, Howard Reed, Ian Gibson, Richard Ashcroft, Doug Naysmith MP, Simon Reid-Henry, Nikolas Rose, Laura Biron, David Baines and Judith Wardle.

Executive summary

The pharmaceutical industry has long been regarded as one of the jewels in the crown of the British economy. It is an industry in which Britain has excelled. But like all other sectors its performance needs to be assessed. It was not long ago that the financial services sector was viewed as even more competitive and world leading. But it has crumbled because of lax regulation. We don't want to see the same fate befall the pharmaceutical industry. The danger signs are there. Profits and pay are up but productivity is down. Under the threat of flight, companies are lightly regulated in the pursuit of short-term profits driven by the bonus schemes of top executives. In a normal private sector company this would be solely the concern of the shareholders.

But this is not any ordinary sector. Just like the banks, the pharmaceutical companies are too important to fail. Their products determine whether people live or die and what quality of life they have. They are much closer to being essential utilities than they think. The argument in this report is not that the pharmaceutical industry should be nationalised but simply that it must be more effectively regulated, so that all stakeholders – the public as well as the private investors – get a better deal. Like housing, transport, gas, electricity and now financial services, some things are too important to be left to the whims of the market. The pharmaceutical industry should start to be viewed more as a utility and less as part of the casino economy which wreaked havoc with our banks. This does not mean being anti-business – far from it – but it does mean being pro-society. The current structure of high costs, high profits and a low rate of innovation is unsustainable. Regulation and intervention is required to save the pharmaceutical industry from its own worst enemy, itself.

The pharmaceutical industry grew in the 1980s to become a commanding symbol of 'the new economy' and the power of the market to innovate. But it is failing to meet our needs for safe and innovative drugs. The pharmaceutical industry is and will continue to fall short of delivering its *raison d'être* of producing drugs that improve our health.

Since 1991 the NHS drugs bill has grown by over £7.5 billion. This growing cost is not just the case in

the UK, as expenditure on pharmaceutical products has grown faster than the gross national product in all European countries.¹ At the same time, pharmaceutical companies remain incredibly profitable, with some companies seeing annual profits of between 20% and 30%. Despite these rising costs and profits, innovation is declining; if this decline continues our ability to fight increasingly complex diseases will almost certainly be reduced.

'This structure of high costs, high profits and low rates of innovation is unsustainable not just for society but also for the industry'

During the late 1980s, nearly 60 new molecular entities were released onto the market each year;² but this figure had halved to a mere 27 by 2007 (see table 1). Between 1993 and 2003 only 152 of the 359 drugs licensed, less than half, offered potential clinical improvements on already existing drugs (see table 2). Meanwhile our drugs bill is skyrocketing. Why are we paying more for less?

This structure of high costs, high profits and low rates of innovation is unsustainable not just for society but also for the industry. One city analyst said, 'For the first time in history, the industry will have negative growth in 2011.'³ Just like in banking, the market is failing for pharmaceuticals.

It has been estimated that in order to sustain current levels of growth, firms would need to introduce one new product each year that would make on average £2.7 million for each 1–1.5% share the firm has of the world pharmaceutical market. Therefore, a company the size of GlaxoSmithKline (GSK), which is one of the largest of the UK-based pharmaceutical companies, would need to release closer to seven such products each year; however, in 2008 only three of GSK's products were approved by the Food and Drugs Administration (FDA) for the US market and in the UK only four products were awarded licences by the MHRA, one of which was a Paracetamol product and all of which were me too drugs⁴ – this is less than half that needed.⁵ None of the major companies is close to reaching the necessary targets to maintain growth.

The profits that previously sustained the oligopolous pharmaceutical industry are under threat:

1. Ess, S.M., Schneeweiss, S., Szucs, T.D. (2003) 'European healthcare policies for controlling drug expenditure', *Pharmacoeconomics*, 21(2), pp.89–103.

2. Van den Haak, M.A., Sculthorpe, P.D. and McAuslane, J. (2002) *New Active Substance Activities: Submission, Authorisation and Marketing 2001*, CMR International.

3. Alexis de Rosnay, global co-head of healthcare at Lehman Brothers, quoted in L. Saigol (2008) 'A painful prognosis for big pharma', *Financial Times*, www.ft.com/cms/10/ab1b624e-1c8d-11d4-8bfc-000077b07658.html (accessed 1 September 2008).

4. In 2008 only three drugs produced by GlaxoSmithKline were approved by the FDA: Eltrombopag Olamine (on 20 November 2008) Naproxen Sodium; Sumatriptan Succinate (on 15 April 2008) and Ropinirole Hydrochloride (on 1 July 2008). Of these two were considered to be me-too drugs – drugs that appear to have therapeutic qualities similar to those of an already marketed drug; see www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu In 2008 only 4 pharmaceutical products produced by GlaxoSmithKline were granted licences by the MHRA in the UK these were Nicabate Compressed lozenges, Paracetamol compressed tablets Requip prolonged release tablets and Acwy vax – powder and solvent for solution and injection in a pre-filled syringe (a treatment for meningococcal disease); these are all me too drugs.

5. Horrobin, D.F. (2000) 'Innovation in the pharmaceutical industry', *Journal of the Royal Society of Medicine*, 93(7), pp.341–5.

- Blockbuster drugs account for 60% of the estimated £136 billion in sales of the ten leading pharmaceutical companies; many of the patents on these products will expire in the coming years.⁶
- Between 2006 and 2011 \$40 billion (circa £22 billion) in global sales by the top pharmaceutical companies will be lost.⁷
- 80 drugs that currently account for about 25% drug sales will lose their patents between 2007 and 2011.⁸

The industry is no longer innovative. Much of the innovation is found in the public sector. The majority of drugs that are therapeutic advances have their roots in publicly funded research,⁹ 70% of new molecular entities that have entered the market over the last decade were discovered in publicly funded science.¹⁰

This decline in innovation and rising costs raises further concerns as the companies try and squeeze more from less through increasingly dubious methods that bring little benefit to the patient or the taxpayer:

First, bias is created through the industry's control over clinical trials. The industry designs, manages, funds and therefore controls the majority of clinical trials. These clinical trials are used to make licensing decisions and influence prescribing practices. **Trials sponsored by the pharmaceutical**

industry have been shown to contain bias in favour of the industry sponsor.

Second, there is a significant degree of contact between the pharmaceutical industry and medical professionals. The pharmaceutical industry invests heavily to influence doctors. While the Department of Health invests nearly £4.95 million in postgraduate education for doctors, **the pharmaceutical industry spend over 300 times as much: £1.65 billion.** Influence by the pharmaceutical industry can alter the prescribing habits of doctors, which can result in increased costs to the NHS and unnecessary risks to the patient; it demands effective regulation.

Third, pharmaceutical companies are increasingly seeking to exert influence through patient or advocacy groups in the UK. For the company the 'strong ties can advance corporate goals and brand objectives,'¹¹ but for the patient group they can limit independence and objectivity. This degree of influence is rife in patient groups. In a study of patient groups that disclosed financial information, 83% had received funding from the industry.

Without appropriate intervention the pharmaceutical markets will continue to fail not just the taxpayer and the patients but their shareholders too.

Effective regulation must now be a priority. This report supports **five priority policy proposals**, which are described below.

6. Herper, M. (2006) 'Nagging doubts for big pharma', *Forbes*, www.forbes.com/2006/07/25/pharma-profits-dangers-cz_mh_0726drug.html (accessed 20 July 2008).

7. Forbes (2006) 'Drug patent expiration', www.forbes.com/2006/06/22/cz_mh_0623genericdrugslide_6.html?thisSpeed=20000 (accessed 1 September 2008).

8. Herper, M. (2006) 'Nagging doubts for big pharma'.

9. Gozner, M. (2004) *The \$800 Million Pill: The Truth Behind the Costs of New Drugs*, California University, Berkeley.

10. United Nations Development Programme (1999) *Human Development Report*, Oxford University Press.

11. Durand, M. (2006) *Pharma's Advocacy Dance*, <http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=377999&searchString=Pharma's%2520Advocacy%2520Dance> (accessed 8 January 2009).

12. BBC (2008) 'NHS drug costs to be renegotiated', <http://news.bbc.co.uk/1/hi/health/6927814.stm>.

Policy I: Make a greater investment in publicly funded science.

Hypothecate savings made through introducing greater value-based drugs pricing for an additional £1 billion of funding for publicly supported science research by 2010-11, increasing the total funding for publicly funded science from £1.7 billion to £2.7 billion. Some of this money has already been raised through changes in the pricing system announced in 2007. These changes should now go further.

Money could be raised through the savings made from introducing a value-based pricing system, which are estimated to be £500 million per annum. Although much can be made of Alan Johnson's¹² achievements in regards to price cutting, this report argues that this still fails to incentivise therapeutic innovation actively. Therefore the report argues that beyond the obvious arguments for price cuts, the most pressing issue at this time is the cost of drugs in relation to their relative therapeutic efficacy. This report supports the Office of Fair Trading's proposals for reforming the Pharmaceutical Price Regulation Scheme (PPRS). This would link therapeutic efficacy to price; in the short term it would reduce the NHS bill, and in the long term it would provide the right incentive for drug companies' research and development (R&D) investments. This would be a step towards ensuring efficacy and therapeutic innovation.

In recent years the government has taken steps to ensure the UK remains at the forefront of drug development. This has included increasing funding on health research, which is estimated to stand at £1.7 billion by 2010-11. This report supports using the estimated saving made through the introduction of a value-based

pricing system, which by 2011 could be £1 billion, based on estimated savings of £500 million per annum assuming the scheme was introduced in 2009. This would effectively increase funding by 60% and put total government spending on health research at £2.7 billion – nearly equal to the industry's estimated investments in R&D. The government must now take action to guarantee that therapeutic innovation will continue, through investing in publicly sponsored research. This not only improves the scientific base, and our potential to make therapeutic breakthroughs, but also can encourage investment in the UK by the drugs industry.

Policy 2: Make clinical trials open to public scrutiny

Independent scientific information is essential for the future of modern healthcare and the future of the pharmaceutical industry. For this reason it is essential that all phase 3 trials be carried out independent from the industry. These could be funded through an industry levy. This proposal was initially put forward by Professor John Abraham from Sussex University in his book *Science, Politics and the Pharmaceutical Industry*,¹³ as it would ensure independence and allow greater scrutiny and accessibility to the necessary clinical trial data. Further, any trial used for licensing must have been registered before it was started, as is currently done in the US. This could also be combined with a 'guilty until proven innocent' approach on all industry-sponsored clinical trials.

Policy 3: Educate doctors through public funding

For doctors, independence, transparency and freedom from bias are essential. This report has highlighted how through industry funding and influence this is impossible. This report would therefore support greater investment in independent education for doctors and other medical professionals. The current spending by government on information for doctors stands at about £5 million. This report argues that this needs to increase to £10 million, as doctors currently struggle to deal with often conflicting advice. The report would also support other measures to limit industry influence, such as banning or limiting industry contact with doctors. As of July 2009, Massachusetts and Vermont have introduced new legislation banning pharmaceutical companies from lobbying doctors, through providing free lunch and gifts; this report supports similar legislation in the UK.

Policy 4: Review progress made since 2005 Health Select Committee report

The 2005 Health Select Committee report was the largest of its kind. Enacted over eight months, it explored the reality of the pharmaceutical industry and proposed a series of sensible policy proposals, including strengthening the power of the Medicines and Healthcare Products Regulatory Agency (MHRA), curbing intensive marketing by the industry, and adopting a national drugs policy. However, for this report to be most effective we believe that a review of the progress that has been made since its publication is essential and would therefore lend support to such a review.

Policy 5: Control pay and bonuses

Control pay and bonuses so that executive rewards and share options do not disfigure the product market as they did in financial services. Compass will be calling on the government to establish a pay commission to adjudicate on pay in key industries such as the pharmaceutical industry and the financial sector.

13. Abraham, J. (1995) *Science, Politics and the Pharmaceutical Industry*, UCL.

Introduction

Pharmaceutical products are an integral part of our modern healthcare system; from statins to antibiotics to painkillers, the way we manage our bodies, treat disease and alleviate pain is increasingly through commercially produced pharmaceuticals. These pharmaceuticals are designed, produced, priced and distributed by an industry, which is frequently failing to meet public expectations and its own potential for improved therapeutic efficacy.

The pharmaceutical industry grew in the 1980s to become a commanding symbol of new capitalism and the power of the market to innovate, yet in these changing times it is increasingly clear that innovation within the industry is declining, and its practices must come under increased scrutiny. No longer meeting our needs for safe and innovative drugs, the pharmaceutical industry is falling short of delivering its *raison d'être* of producing drugs that improve health, and will continue to do so.

Over the last 50 years the development of medicines produced by the pharmaceutical industry has contributed significantly to the welfare of individuals and society in terms of disease management, pain control and quality of life. Not only this, the pharmaceutical industry has also made huge socio-economic contributions in the UK. It:

- employs 73,000 people directly¹⁴
- accounts for 65% R&D investment in the UK¹⁵
- is the third largest industry in the UK after tourism and finance.¹⁶

The report argues that although the socio-economic contributions of the pharmaceutical industry should not be forgotten, they should not be used to defend or legitimise the issues this report highlights in regard to the actions of some pharmaceutical companies or the declining rates of therapeutic innovation. This report will go on to discuss these problematic practices, which include influencing the medical profession and patient groups, biasing science through clinical trial design, and investing excessively in marketing and advertising.

The overriding concern for society will always be the health improvements gleaned from drug and medical technology; however, within the pharmaceutical industry each firm's legal responsibility is not to the public, but to its shareholders, whose overriding concern is for the company to maximise shareholder value and make a profit. It is this internal contradiction which must be resolved. These are companies not charities. The profit motive can encourage a company to innovate, streamline and work flexibly; however, it can also encourage pharmaceutical companies to spend excessively on marketing and advertising, or research into areas with an existing market, rather than on areas of high need unless they are regulated and supervised effectively.

Expecting pharmaceutical firms to act like charities, and not like the companies they are legally obliged to be, is a delusion on our part, but it is an image that has been fostered by the industry and its representatives. This misguided perspective accounts for many of the inherent problems that can be seen in the way the industry is treated by regulators and government. In failing to see the industry as a business, society fails to recognise the need for more stringent regulation, often expecting it to act in our best interest, not its own. The consequence of this is a declining rate of therapeutic innovation accompanied by a plethora of practices designed to maximise market share and profit margins at the cost of true therapeutic innovation.

The pharmaceutical industry understands the usefulness of fostering this image and therefore actively presents itself as the archetype of a caring, science-based free enterprise. It pushes the image that it is the neo-liberal dream of an innovative market, which through competition will undertake risky and costly R&D, dedicated to the treatment of disease, and alleviation of suffering. With attractive phrases like Johnson & Johnson's 'our caring transforms', Pfizer's 'life is our life's work' or GlaxoSmithKline's 'enabling people to do more, feel better, live longer', pharmaceutical companies seek to portray themselves not as profit-seeking companies, but as the Good Samaritan. The trade group in the UK that represents the industry is the Association of the British Pharmaceutical Industry (ABPI), which actively seeks to present this image with the strap line 'Medicines for a healthy future'.

14. Association of British Pharmaceuticals (2007) Annual Report 2007, www.abpi.org.uk/publications/pdfs/AnnualReview07.pdf (accessed 9 February 2008).

15. House of Commons Health Select Committee (2005) *The Influence of the Pharmaceutical Industry*, Stationery Office.

16. Ibid.

The ABPI represents 72 companies. It is based in Whitehall, employs 60 full-time members of staff and has considerable influence on and a close relationship with government. The then President of the ABPI, Nigel Brooksby, stated in the ABPI's 2007 annual report:

(I am the) envy of my colleagues in Europe for the strong and mutually supportive relationship the industry has enjoyed with government and the NHS in the UK.¹⁷

The current President of the ABPI, Chris Brinsmead, stated in the ABPI's 2008 annual report:

I believe the year will be seen as one in which we laid the groundwork for significantly better relationships with the Government.¹⁸

The ABPI, like its equivalents in the US and across Europe, often opposes changes to legislation, arguing consistently that prices are high because R&D costs are high, and that any restraint on charges – or changes to the regulatory structure – could damage the pipeline and ensure that medicines which were needed would not make it through. It argues that the profit margins it enjoys are the necessary incentive to ensure innovation. Generally this body is most concerned with medicines and medical technologies currently under patent and is less concerned with the generic drugs market.

What is the pipeline?

Pipeline is a term commonly used to describe the potential drugs each company is currently developing. When a pipeline is described as lost, this means that the drug they were developing has failed in a clinical trial. This can be through lack of efficacy of the drug or through lack of safety; however, lack of efficacy is by far the most common cause of a lost pipeline.

There is no doubt that the arguments against regulation put forward by the industry and by its trade group are powerful rhetoric, but the reality is less clear, as this report will explore. Although much of the pharmaceutical industry often fights

against regulation, this report will highlight where better regulation could actually save the industry, and enable greater therapeutic advances. These are the key areas affecting the industry's ability to make greater therapeutic innovation:

- **The structure of the industry, the cost of drugs and declining innovation.** The NHS has a drugs bill of £11 billion and faces regular scandals over the availability of increasingly expensive drugs. This section looks at why the prices are so high, why innovation is declining, what this means for the future of healthcare and the industry, and, more importantly, what can be done about it.
- **Biased science – the gold standard of evidence-based medicine.** Closer scrutiny of randomised controlled trials shows that evidence-based medicine is increasingly subject to bias. This section explores how, why and what this means.
- **The medical profession.** Much of the controversy surrounding the pharmaceutical industry centres on prescription medicine; this section looks at the relationship between doctors and the industry.
- **Patient groups.** There are numerous groups to represent individuals who are affected by most illnesses, disabilities and other medical conditions; these groups lobby government and provide information and support. This section discusses the relationship between these groups and the industry.

What is the difference between a patented drug and a generic drug?

A patented drug is a drug for which a specific company owns exclusive rights. When a company develops a new drug it is patented by that company and monopoly rights are granted, which last 20 years. Once a patent expires, generic copies of the drug can be produced by other companies. Thus a generic drug is one that is no longer controlled by a patent. After the monopoly rights are lost numerous generic drug manufacturers will produce the drug, which can push the cost down by as much as 90%.

17. Association of British Pharmaceuticals (2007) *Annual Report 2007*, www.abpi.org.uk/publications/pdfs/AnnualReview07.pdf (accessed 2 September 2008).

18. Association of British Pharmaceuticals (2008) *Annual Report 2008*, www.abpi.org.uk/Details.asp?ProductID=344 (accessed 4 May 2009).

This report will focus on these four areas within the UK, but will draw comparisons with other countries, especially the US, which is the largest market for and producer of pharmaceuticals. It has a very different and in many ways more relaxed regulatory structure than that in the UK. However, with the election of Barack Obama this is expected to change over the coming months and years, as he promised greater regulation of pricing for drugs, and healthcare reform.

What this report seeks to do is highlight the rise and subsequent fall of the pharmaceutical industry. It tracks the changes in medical development and regulation and concludes that regulating the pharmaceutical industry effectively must now be a priority if we hope to continue to find the medical interventions we desire.

What is a randomised controlled trial?

A randomised controlled trial (RCT) is a type of scientific experiment most commonly used in testing the efficacy of a pharmaceutical product. They are seen as the best way to prove the efficacy of a drug or medical intervention. In a RCT people are allocated at random to receive one of several possible treatments. One of these interventions is the standard of comparison, also called the control. The control is most commonly a placebo ('sugar pill').

It is vital to ask the right questions now: where are new drugs coming from and how much do they really cost to create? Who is innovating and who profiting? And how can we ensure health needs are met? The market has proved wanting as a method of encouraging the right sort of drugs at a price that society can afford, making the pharmaceutical industry – like the financial sector before it – another example of market failure. A way forward must be sought towards innovative, productive and humane drug development.

The growth of the pharmaceutical industry

The pharmaceutical industry came into its own in the 1980s with high profits and high levels of innovation and development. However, most of

the large firms seen today – such as Allen and Hanbury, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Squibb and Wyeth Laboratories – have their roots in the last century before they bloomed into large public corporations and rapidly expanded in the middle of the 20th century.

In the early 1900s the UK and the US introduced regulations to ensure the quality of pharmaceutical products. However, in 1911 the US and the UK took very different paths. In the UK the National Health Insurance Act – which provided 'medical benefit' to people on low income – made the UK government the first mass purchaser of drugs.¹⁹ This gave the government a vested interest in regulation, specifically cost control and the efficacy of pharmaceutical drugs. Its equivalent has only happened relatively recently in the US with the creation of Medicare and Medicaid, which has resulted in an increased interest in regulation.²⁰

During the 1940s and 1950s a series of major pharmacological breakthroughs, each offering new and exciting possibilities for the treatment of disease, offered potential growth in pharmaceutical companies. This ushered in an age of antibiotics; Penicillin is perhaps the best known, but this was rapidly followed by Streptomycin, (to treat tuberculosis) and Chloramphenicol (the first antibiotic to be manufactured synthetically on a large scale). This period also saw pharmaceutical companies begin to transform into the companies that exist today where research, development, manufacture and marketing are all controlled and managed within the same company. As a result of the creation of mass markets in Europe and the US, these companies become increasingly global.

The birth of the NHS in 1948 further separated the regulatory paths of the UK and the US. The UK became increasingly concerned with the control of the cost of drugs, fearing wasteful expenditure and unsafe use. In the US trade associations were set up, as there was less incentive for centrally managed regulation. This resulted in the pharmaceutical industry intensifying the promotion of drugs directly to doctors, especially where drug companies were marketing patentable, but molecularly similar, drugs with what appeared to be similar therapeutic effects.²¹ It is not surprising therefore that the pharmaceu-

19. Public Records Office (1921) MH58/241B Committee on the supply of drugs for insured persons report.

20. Herper, M. (2006) 'Nagging doubts for big pharma'.

21. These are commonly referred to as me-too drugs and are discussed later. For further discussion see Temin, P. (1980) *Taking Your Medicine: Drug Regulation and the United States*, Harvard University Press.

tical products are far more expensive in the US than anywhere in the rest of the world.

There was an increased focus on regulation in the UK in the 1960s after the public outcry over Thalidomide. From the late 1950s to the early 1960s Thalidomide was prescribed to women in the first few months of pregnancy to relieve morning sickness, until it was later recognised that it had caused serious unforeseen birth defects. In a bid to avoid another occurrence and in response to the public outcry the Committee on Safety of Drugs was formed in 1963 in the UK. This later became the Committee on Safety of Medicines (CSM) under the Medicines Act of 1968. The Medicines Act of 1968 became law in 1971 and since then has provided a comprehensive legal framework for the control of medicines in the UK.

It is apparent that this regulation was enacted reluctantly. Legislators were optimistic about the benefits and promises of new drugs and much like today were committed to protecting the industry.²² Even after the Thalidomide disaster, the then UK Conservative Health Minister Enoch Powell argued that it was in the commercial interests of a drugs company to test its products appropriately and ensure that they were safe and beneficial – intimating that regulation was, in consequence, unnecessary.²³

Until the late 1970s the industry was driven less through an understanding of biology and more through the mass random screening of chemical compounds. By the 1980s this had begun to change. The 1980s and 1990s were a period of huge success and growth for the industry as a series of blockbuster drugs, including medicines such as Prozac, made it to market, creating huge profits. Under Margaret Thatcher in the UK and Ronald Reagan in the US a period of effective deregulation and a pro-business legislation ensured these companies grew to become immensely profitable. In recent years the oligopolous structure has remained, with the industry still dominated by the few super firms, such as GlaxoSmithKline and AstraZeneca in the UK.

It is apparent that these companies are recognising that the current model of drug development is unsustainable. Those within the industry such as Richard Sykes, former chairman of GlaxoSmithKline (previously GlaxoWellcome), argue that advances in areas such as genomics will

eventually identify new targets for the industry to act on.²⁴ However, it will be years if not decades before this basic research can be transformed into drug development and it is increasingly apparent that the industry may not last that long. The pharmaceutical industry was and still is going through a very painful transition period with the approaching end of patents for all the large companies. During this period there have been a number of super-mergers designed to shore up economic stability and future competitiveness. However, mergers have proved insufficient and with the approaching end to the patent life on past blockbusters it is thought that a lot of the earnings are coming from temporary gains, like a good allergy season, and cost controls.²⁵ For example, in the US the share value of Pfizer rose as it announced more cost cuts in 2008; it has removed \$1.2 billion off its 2006 cost levels and expects cuts to reach \$2 billion by the end of 2009.²⁶ This is being echoed across the industry, with most of the larger firms cutting staff and costs.

Running concurrent to these changes in the global pharmaceutical industry since the 1980s there has also been a growth of small bio-tech firms at a national level in the UK, the US and across some of Europe. These firms are commonly located in and around the universities. They are highly active and very innovative; these smaller firms are appearing to take the lead in terms of innovative drugs as the larger firms' innovation declines and they are seen by many as key to the future of the industry.²⁷

There are three main bodies that supervise and regulate the industry and the distribution of drugs in the UK:²⁸

- The pharmaceutical industry is regulated by a licensing system to ensure safety, quality and efficacy of drugs. **The Medicines and Healthcare Products Regulatory Agency (MHRA)** oversee this. The MHRA is also responsible for monitoring medicines post licensing.
- The **National Institute for Clinical Excellence (NICE)** was created to explore and offer guidance on the relative efficacy and cost efficiency of drugs – this provides essential information to doctors, health professionals and the general public.
- **The Pharmaceutical Price Regulation**

22. Abraham, J. and Davis, C. (2006) 'Testing times: the emergence of the prazolol disaster and its challenge to British drug regulation in the modern period', *Social History of Medicine Advance Access*, available at <http://shm.oxfordjournals.org/cgi/content/abstract/hk005v1> (accessed 1 September 2008).

23. Medwar, C. (1992) *Power and Dependence: Social Audit on the Safety of Medicines*, Social Audit.

24. Sykes, R.B. (2000) *New Medicines: The Practice of Medicine and Public Policy*, Stationery Office.

25. Herper, M. (2006) 'Nagging doubts for big pharma'.

26. FiercePharma (2008) 'Pfizer: \$800m in cuts to hit 4Q', editorial, www.fiercepharma.com/story/pfizer-800m-cuts-hit-4q/2008-09-23?utm_medium=rss&utm_source=rss&cmpid=OTC-RSS-FP0 (accessed 1 September 2008).

27. BMJ (2003) 'Fewer new drugs from the pharmaceutical industry: a better understanding of the economic challenges facing research based companies is needed', editorial, *British Medical Journal*, 326, pp.408–9.

28. See appendix 2 for further information.

Scheme (PPRS) regulates pricing through price cuts and profit controls.

Although the regulation of the industry can in some ways be seen to be relatively stringent, over the past decade, a decade of New Labour, it is argued that drug regulation in the UK, Europe and the US has been restructured in response both to a neo-liberal agenda and to claims by the pharmaceutical industry that over-regulation was stifling innovation.²⁹

Yet if you trace the history of modern

“New Labour seemed to struggle to regulate the industry effectively, never seeming to realise the impact that this was having on the NHS, the pharmaceutical industry and on public health”

medicine you see the role of government regulation in many forms designed to bolster medical expertise: peer reviews, RCTs and post-marketing surveillance were introduced as a protective barrier against the encroachment of false beliefs and business interests into medicine.³⁰

An awareness of the issues inherent in the modern pharmaceutical industry has existed for some time within academia; however, it is only recently that these discussions have reached Westminster. In 2005 the Health Select Committee conducted the largest analysis by Parliament of the pharmaceutical industry ever carried out. This review was only the second select committee report on the industry – the first was carried out in 1914. The review conducted in 2005 took eight months and collected information from key stakeholders; including pharmaceutical companies, doctors, MPs, academics and patient groups, this report was highly comprehensive in its analysis and presented 44 decisive policy proposals.

In February 2007 this was followed by an Office of Fair Trading (OFT) report, which analysed the PPRS. It looked at the current system of profit controls and price cuts and argued that instead we should implement a value-based system, where price is based on ther-

apeutic efficacy.

Despite this growing awareness in political spheres New Labour seemed to struggle to regulate the industry effectively, never seeming to realise the impact that this was having on the NHS, the pharmaceutical industry and on public health. The comprehensive findings of the 2005 Health Select Committee report, and the OFT report in 2007, have not been implemented.

Tony Blair promised to protect the pharmaceutical industry:

We must work together to ensure that the future of the UK pharmaceutical industry is even brighter.³¹

Yet the Blair government seemed to accept unquestioningly the industry’s own short-term definition of what a brighter future was. For public health, for science, and for the medical profession it certainly was not the route defined by the industry. In fact, it now looks as if this was not the best route for the industry either. The industry itself is seeking new ways forward; it is trying to adapt, but it is now a huge clunking machine and seems unable to make the necessary changes to ensure that public health needs are met.

Now is the time to reassess the current state of regulatory surveillance structures of the pharmaceutical industry and put into place appropriate measures to protect medical expertise and public health from the encroaching interests of big business.

This report will focus on four key areas:

- the drugs industry – costs of drugs and declining innovation
- biased science
- the medical profession and the industry
- patient groups, the public and the industry.

29. Abraham, J. (2005) ‘Regulating the drugs industry transparently’, *British Medical Journal*, 331, pp.528–9.

30. Petryna, A. et al. (2007) *Global Pharmaceuticals: Ethics Markets, Practices*. Duke University Press.

31. ‘Foreword by the Prime Minister’, Pharmaceutical Industry Competitiveness Taskforce, available at www.advisorybodies.doh.gov.uk/pictf/ (accessed 11 March 2008).

The problem

I. The cost of drugs and declining innovation

The drugs industry

The cost of drugs is increasing. This is worrying in itself but when placed alongside the declining rate of innovation in the pharmaceutical industry a case of market failure is clear. It is essential that this trend is reversed.

There is a crisis in productivity and therapeutic advancement in the pharmaceutical industry. Globally the number of medicines containing new molecular entities (NMEs) has dramatically declined from the average of over 60 per annum during the late 1980s³² to a mere

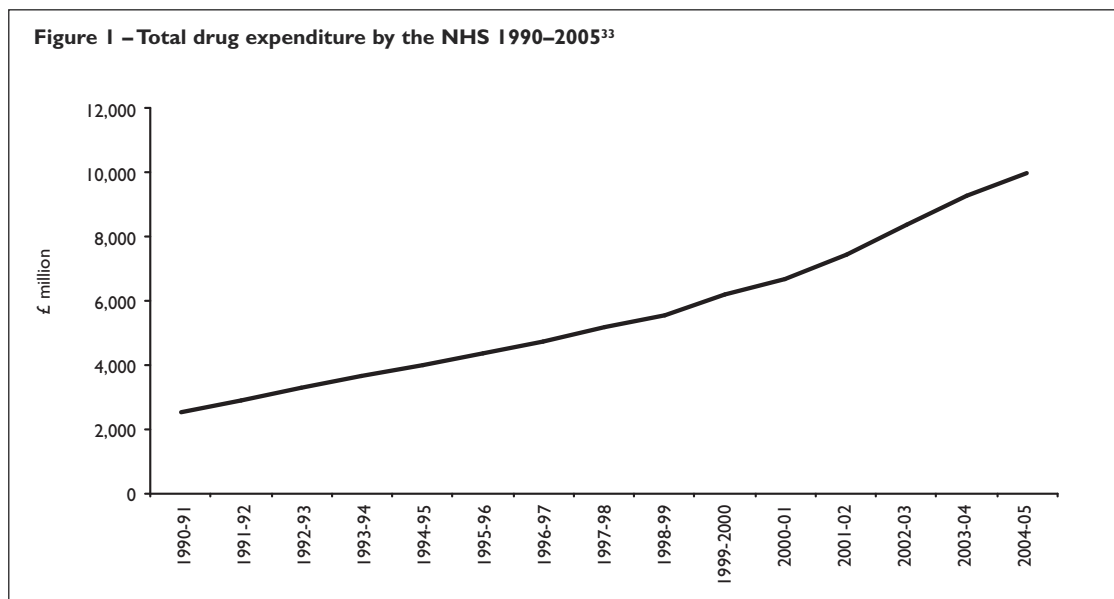
What is a new molecular entity?

A new molecular entity is an active ingredient that has shown some biological activity, which has not been marketed before. The number of new molecular entities coming onto market each year is often recognised as a measure of the rate of innovation. Therefore, if there are fewer new molecular entities making it onto the market this is seen as demonstrative of a declining rate of product innovation.

27 in 2007 (see table 1); meanwhile our drugs bill is skyrocketing. In 1991 the drugs bill for the NHS (see figure 1) was £2.5 billion, a decade later it was £7.5 billion and it now stands close to £11 billion. Since 1991 the drugs bill has grown by nearly £7.5 billion. Ess, Schneeweiss and

32. Van den Haak, M.A., Sculthorpe, P.D. and McAuslane, J. (2002) *New Active Substance Activities: Submission, Authorisation and Marketing 2001*, CMR International.

33. Sources: Prescription Pricing Division of the NHS Business Services Authority, England, and Department of Health Finance Division. 2. Figures are net which include Pharmaceutical Price Regulation Scheme (PPRS) receipt savings. 3. The total drugs spend include drugs expenditure in primary care and the HCHS. The primary care expenditure reflects amounts paid to pharmacy and appliance contractors and amounts authorised for dispensing doctors and personal administration in England. HCHS expenditure includes drugs and medical gases. 4. From 2000-01 figures are in resource terms; prior to this figures are in cash terms. Cash figures relate to February to January prescribing due to delay in prescription processing and payment calculations. Resource figures represent the actual cost between April and March.



Szucs (2003) highlight that this is not just the case in the UK but that expenditure on drugs has grown faster than the gross domestic product in all European countries and in the US.³⁴ Yet at the same time these companies remain incredibly profitable, with some companies seeing annual profits of 20–30%.³⁵

Table 1 Number of new molecular entities brought to market internationally, based on IMS figures³⁶

Year	Average number of NMEs released onto the market each year
1995–2000	44
2001–2006	33
2007	27

Source: <http://us.imshealth.com/i360/>

It is clear that the rate of product advancement is declining (see table 1), however, there is limited information on the rate of therapeutic innovation. The MHRA and the European Medicines Evaluation Agency (EMA) do not even collect data on the therapeutic advances of medicines

licensed. This can be seen as problematic as while product advancements – which are patented as they can also be classed as NMEs – ensure that commercial interests are met, it is largely through therapeutic innovation that health and societal needs are met.

However, looking at figures from the US (the FDA in the US does distinguish between NMEs and therapeutic innovation) it is clear that therapeutic innovation is declining. The FDA figures show that between 1993 and 2003 only 129 of the 321 drugs licensed, less than half, offered clinical improvements (see table 2). Based on these figures it is fair to argue that we are simultaneously seeing a decline in the number of drugs, the number of new molecular entities and the therapeutic innovation of drugs making it to the market. Thus while costs and profits increase, actual product innovation and – more importantly for society – therapeutic innovation appear to be declining.

If this pattern of declining innovation – in therapeutic and product innovation terms – continues, we will increasingly struggle to fight the disease burden through a pharmaceutical model. Steps must be taken, both to improve the therapeutic innovative potential of the industry and to explore alternative routes towards innova-

How does a drug reach the market?

For a drug to reach the market place a 'lead compound' must first be found; this can be a NME or an existing molecular entity presented for an alternative condition. This lead compound will have been found to have interesting biological activity with therapeutic potential. Once found, it will be taken through a series of tests, which begins with non-clinical testing in a lab and continues through three phases of clinical trials designed to ensure its efficacy and safety:

- Phase I: trials in 20–100 healthy adults to test the safety of the drug
- Phase II: trials in 100–300 patient volunteers to determine the safety and efficacy of the drug
- Phase III: trials on larger groups of patients (typically 1,000–3,000), to gain further data on safety and efficacy.

These trials are normally undertaken by the producer and submitted to a regulatory agency, such as the MHRA in the UK, to establish quality, efficacy and safety. If the drug is approved it is licensed and becomes publicly available. Throughout this process, decisions are made on whether or not to continue, based on projected profitability of the product, but not necessarily on its projected therapeutic advantage. In the EU, US and Australasia there has never been a requirement on companies to produce drugs with a therapeutic advantage. If such a requirement were put in place it is likely that we would see a change in the focus of pharmaceutical research carried out by the industry, with a greater emphasis placed on therapeutic advance rather than on predicted profitability.

34. Ess, S.M., Schneeweiss, S., Szucs, T.D. (2003) 'European healthcare policies for controlling drug expenditure', *Pharmacoeconomics*, 21 (2), pp.89–103.

35. Angell, M. (2004) 'Excess in the pharmaceutical industry', *Canadian Medical Association Journal*, www.cmaj.ca/cgi/content/full/171/12/1451 (accessed 20 March 2009).

36. IMS is a world leading strategic consultancy for health-care and pharmaceuticals; see www.imshealth.com/web/home/0,3153,64576068_63872702,00.htm (accessed 1 October 2008).

tion. This must in part be through increased investment in publicly funded scientific research and the science infrastructure as a whole.

What is the difference between therapeutic innovation and product innovation?

Therapeutic innovation should not be confused with product innovation. Therapeutic innovation provides the most benefit to patients, whereas product innovation may not improve therapeutically on previously available therapies but it may be of commercial advantage to the companies – for example it may extend the patent life of an existing product. However, a degree of product innovation can also be useful to patients; for example, a product innovation may mean that the drug needs only to be taken once a week rather than daily – this can be of considerable benefit to patients.

Table 2 FDA review and approval times for priority (with therapeutic innovation potential) and standard NMEs, 1993–2003³⁷

	Total priority NMEs approved	Total standard NMEs approved
1993	13	12
1994	12	9
1995	10	19
1996	18	35
1997	9	30
1998	16	14
1999	19	16
2000	9	18
2001	7	17
2002	7	10
2003	9	12
Total	129	192
Total drugs approved by FDA 1993-2003		321

Source: www.fda.gov

With this apparent declining innovation, both product and therapeutic, it is clear that we must also look to alternative methods of disease

management. Although we may hope that changes can be made to improve innovation if we are entering an age where there is not a ‘pill for every ill’, we must look to life-style changes, to early intervention and for example in the case of cancer to a greater investment in supplementary technologies such as radiotherapy and surgical techniques. If the pills are no longer being produced we must look to the alternatives.

The current industry structure appears unsustainable

The structure of high costs, high profits and low rates of innovation is unsustainable. The pharmaceutical industry asserts that the costs are high because drug development is expensive, and expands on this to argue that only if we continue to pay marked-up prices for drugs can it continue to develop. However, this argument does not hold up. **Insufficient investment in R&D** is accompanied by an unproductive search for the ‘one size fits all’ **blockbuster** drug, and an inefficient use of resources to search for more **me-too drugs** has resulted in fewer therapeutic innovations making it onto the market. A greater degree of innovation is possible if the necessary checks and balances are in place to encourage a greater engagement in therapeutic innovation.

What is a blockbuster drug?

A blockbuster drug is one that grosses over \$1 billion. These are often seen as the drugs that sustain the largest of the pharmaceutical companies, including Pfizer’s Lipitor, which grossed \$12 billion in 2007, and AstraZeneca’s Nexium, which grossed over \$5 billion in 2007.

The industry’s own attempts to revive its fortunes – in the form of super-mergers, acquisitions and most recently cost cutting, which it has pursued with vigour – have not improved the industry’s ability to innovate. To name a few: GlaxoSmithKline resulted from a £120 billion deal in 2001 between SmithKline and GlaxoWellcome. AstraZeneca was created in a \$102 billion (circa £52 billion) deal in 1999. Sanofi-Aventis was formed from a \$64 billion (circa £34 billion) merger in 2004 and Pfizer completed a \$53 billion (circa £29 billion) takeover of Pharmacia in 2003.³⁸ This

37. NMEs are given priority in the US if they are considered to be a therapeutic innovation.

38. Saigol, L. (2008) ‘A painful prognosis for big pharma’, *Financial Times*.

strategy shored up the industry in the short-term, creating a degree of financial stability; costs were cut and value was added for shareholders. Yet the hoped-for hothouse of new drug development never materialised. In fact it is now argued that, despite the increase in size, merging R&D operations actually reduces innovation and freethinking potential. It is now recognised that stability and quality of research deliver the best results.³⁹ It is very clear that these mergers have not been enough, and now we should consider how best we can encourage the industry to engage in therapeutic innovation.

Increase investment in research and development

Those who advise the industry argue that investment in R&D must increase. PriceWaterhouseCoopers states that:

To flourish, companies will need to invest more in research, understand and demonstrate the value of their products... Though these and other changes that lie ahead are daunting, we believe that the rewards both in terms of human health and business success are enormous.⁴⁰

For the industry to flourish, for it to produce the drugs we need at prices which can be afforded, change has to happen.

The industry constantly reasserts that it invests heavily in R&D, and that costs of drugs are rising because R&D is expensive. Although there is no doubt that drug development is expensive, the industry's assertions on just how expensive it is have been challenged.

An industry-sponsored study placed the bill for each new drug in the US at \$800 million (circa £444 million).⁴¹ However, this industry-sponsored estimate can be disputed for a number of reasons, which would place a more accurate figure for the cost of each new drug at \$240 million or closer to £130 million:⁴²

- The industry counts the opportunity cost of capital, not actual cash outlays, which it is argued by *Public Citizens* inflates the estimate by about 50%.
- The industry analysis does not account for the amount that is tax deductible, which in the US is 34%. In the UK an equivalent scheme allows

companies to claim back R&D expenditure in the form of tax credits. This allows large companies to deduct 125% of expenditure on R&D activities when calculating their profit for tax purposes.⁴³

- The industry-sponsored analysis only looks at a selection of drugs and it coincidentally seems to have selected ones which were the most expensive to develop.

In the UK the pharmaceutical industry estimates it spends £3.2 billion on R&D,⁴⁴ yet this estimate has also been challenged. Goozner argues that as much as half of this expenditure should rightly be considered marketing rather than R&D.⁴⁵ If accurate this would place R&D total expenditure by the industry at closer to £1.5 billion. By 2010 this will be exceeded by public spending on health research in the UK, which will stand at £1.7 billion.⁴⁶

On top of this the industry spends heavily on marketing and advertising. Marcia Angell – former editor in chief of the *New England Journal of Medicine* – points out that the industry spends less than half as much on R&D as on marketing and administration.⁴⁷ Individual estimates of the pharmaceutical industry's expenditure on marketing vary – and the limited information publicly available through the annual accounts of the industry means that information is scarce. However, Gagnon and Lexchin estimate expenditures for marketing drugs in the US in 2004 was at \$57.5 billion (circa £32 billion) and it is fair to assume that over the last few years this will only have increased.⁴⁸

Executive pay

As in banking, pay and executive remuneration packages have now reached excessive levels in the pharmaceutical industry. As table 3 shows, despite apparent declining rates of innovation the top pharmaceutical executives are awarding themselves huge financial rewards. In February 2009 Alistair Darling promised to launch a probe into excessive remuneration packages in the City – this investigation must be extended to the pharmaceutical industry. Controlling pay and bonuses is essential so that executive rewards and share options do not disfigure the product market as they did in financial services.

39. PharmaDeals (2007) *Synergy or Vanity*, http://files.pharmaventures.com/mega_mergers.pdf (accessed 1 October 2008).

40. PriceWaterhouseCoopers (2008) *Pharma 2020: The Vision: Which Path Will You Take?*, www.pwc.com/extweb/pwcpublications.nsf/docid/91BF330647FFA402852572F2005ECC22 (accessed 3 September 2008).

41. Tufts Center for the Study of Drug Development (2001) 'Tufts Center for the Study of Drug Development pegs costs of a new prescription medicine at \$802 million', <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6> (accessed 1 September 2008).

42. Public Citizen (n.d.) 'Would lower prescription drug prices curb drug company research & development?', www.citizen.org/congress/reform/drug_industry/r_d/articles.cfm?ID=7909 (accessed 1 September 2008).

43. HM Revenue and Customs, 'Research and Development Tax Credits', www.hmrc.gov.uk/randd/ (accessed 1 September 2008).

44. Kyle, M. (2007) *Innovation in the Pharmaceutical Industry*, www.wvz.unibas.ch/wifor/vorlesungen/H507/Stutzer/Kyle_Innovation_Pharmaceutical_Industry_2007.pdf (accessed 3 September 2008).

45. Goozner, M. (2004) *The \$800 Million Pill*.

46. OSCHR (2007) *Major Boost for UK Health Research Funding*, Office for Strategic Coordination of Health Research, www.nihr.ac.uk/files/pdfs/OSCHR%20Press%20release.pdf.

47. Angell, M. (2004) *The Truth About the Drug Companies: How They Deceive Us and What To Do About It*, Random House.

48. Gagnon, M.A. and Lexchin, J. (2008) 'The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States', *PLoS Medicine*, p.5.

Table 3 Top ten executive pay and remuneration packages in the pharmaceutical industry, 2008⁴⁹

CEO	Pharmaceutical company	Pay (\$m)	Pay (circa £m)
Miles White	Abbott	33.4	16.366
Fred Hassan	Schering-Plough	30.1	14.749
Bill Weldon	Johnson & Johnson	25.1	12.299
Bob Essner	Wyeth	24.1	11.809
Robert Parkinson	Baxter	17.6	8.624
Daniel Vasella	Novartis	15.5	7.595
Richard Clark	Merck	14.5	7.105
Frank Baldino	Cephalon	13.5	6.615
Sidney Taurel	Eli Lilly	13.0	6.370
Jeff Kindler	Pfizer	12.6	6.174

Blockbuster drugs

Increased investment is vital but it must be designed to produce therapeutic innovation; the old model of blockbuster drugs is broken. Despite this the industry maintains its focus on finding the next big blockbuster – a drug which grosses over \$1 billion. Even those within the industry accept that this model of blockbusters is unsustainable. A city analyst argued that ‘For the first time in history, the industry will have negative growth in 2011’⁵⁰ and Bain & Co. consultant Preston Henske stated that ‘the blockbuster business model is irreparably broken.’⁵¹ This search for the cash cow to carry them through the next decade is no longer a sustainable model: to move forward the industry must become more flexible.

The blockbusters that are currently sustaining these large companies are being lost as their patent life expires. When a drug loses patent, sales of blockbuster drugs can often fall by up to 90% within a year through competition from cheaper generic versions. Blockbuster drugs account for 60% of the \$245 billion (circa £136 billion) in sales of the ten leading pharmaceutical companies.⁵² The majority of top earning drugs that were patented in the 1990s face expiration within the next few years, and 80 drugs that currently account for about 25% of drug sales will lose their patent between 2007 and 2011.⁵³ Between 2008 and 2011 \$40 billion (circa £22 billion) in global sales by the top pharmaceutical companies will be lost.⁵⁴ See table 4.

It is estimated that to continue as we are, firms would on average need to introduce one

Table 4 Major patents that expired in 2008⁵⁵

Drug	Company	Indication	Predicted loss of sales (\$) ⁵⁶	Predicted loss of sales (circa £)	Patent loss date
Fosamax,	Merck	osteoporosis	3 billion	1.5 billion	6 Feb.
Advair	GlaxoSmithKline	asthma	6 billion	3 billion	12 Feb.
Serevent	GlaxoSmithKline	asthma	500 million	251 million	12 Feb.
Sonata	Wyeth	insomnia	85 million	42.6 million	6 June
Effexor XR	Wyeth	depression	3.7 billion	1.86 billion	13 June
Lamictal	GlaxoSmithKline	bipolar disorder	2 billion	1 billion	22 July
Topamax	Ortho McNeil	epilepsy and migraine	2.5 billion	1.25 billion	26 Sept.
Casodex	AstraZeneca	prostate cancer	1.2 billion	600 million	1 Oct.
Trusopt	Merck	glaucoma	700 million	353 million	28 Oct.

49. Fierce Pharma (2009) ‘Top 15 Big Pharma paychecks of 2008’, www.fiercepharma.com/special-reports/top-paychecks-big-pharma (accessed 1 January 2009).

50. Alexis de Rosnay, global co-head of healthcare at Lehman Brothers, quoted in Saigol, L. (2008) ‘A painful prognosis for big pharma’.

51. Arnst, C. (2004) ‘The waning of the blockbuster drug’, *BusinessWeek*, 18 October, www.businessweek.com/magazine/content/04_42/b3904034_mz011.htm.

52. Herper, M. (2006) ‘Nagging doubts for big pharma’.

53. *Ibid.*

54. Forbes (2006) ‘Drug patent expiration’.

55. ‘Generics to soothe your drug budget’ (2008) *BusinessWeek*, http://images.businessweek.com/ss/2008/02/0206_generic_drugs/index_01.htm (accessed 1 September 2008).

56. Predicted loss of sales is based on total annual sales in 2007.

new product each year that would sell \$4.9 million (circa £2.7 million) for each 1–1.5% it has of the world pharmaceutical market in order to sustain current levels of growth. Therefore, a company the size of GlaxoSmithKline would need three to seven new products each year. Thus the real problem becomes ever more apparent, namely that research productivity is failing and none of the major companies is close to the target.⁵⁷

This loss of patents will affect all companies as none seem free of it.

The ideal product to become a blockbuster drug is one that can be patented, is used by a large number of people over a lengthy period of time, can be priced high in relation to production costs and has a large western market. It is in the interests of business to create drugs that must be taken over an extended period of time and it should not be a surprise that anti-psychotics and statins are consistently the best-selling drugs.⁵⁸ These are the ideal blockbuster drugs and have dominated R&D trends in most large pharmaceutical companies. However, with the declining success of this blockbuster model we will need to see a decrease in spending on marketing and advertising and an increase in spending in R&D, looking not just at traditional development models, but being much more flexible.

Me too, me again and me as well

Half of R&D spending by the industry is spent on drugs that add little to the physician's armamentarium; they are so-called me too drugs.⁵⁹ Although these have limited therapeutic advancement they do provide product innovations that have commercial advantages to the companies that produce them. There are those who defend me-too drugs, as providing more therapeutic options and enhancing competition.⁶⁰ Up to a point they are right; product innovation can improve drugs and provide a degree of choice. However, this must ultimately be about balance, as while to a certain level product innovation can be positive, if taken too far it consumes R&D investment to the detriment of therapeutic innovation; it increases the number of drugs on the market

and ensures that new more expensive drugs are always being prescribed, regardless of the efficacy of cheaper alternatives. It should not surprise us that since 1996 less than half of the drug innovations (NMEs) licensed and produced in the US have offered therapeutic advances (see table 2).

What is a me-too drug?

Me-too drugs – also called ‘follow on’ drugs – are products that largely duplicate the action of existing drugs.⁶¹ Defined as drugs that have almost identical clinical outcomes to existing drugs, me-too drugs provide little additional value in therapeutic terms. For example, we now have at least eight different statins, including Mevacor, Lipitor, Zocor, Pravachol, Lesco, Vytorin, Simcor and Crestor.

The production of me-too drugs takes up vast amounts of R&D investment, and is also using up large amounts of public money. A recent extensive study by Morgan et al. in 2005 found that in British Columbia 80% of the increase in drug expenditure between 1996 and 2003 was spent on the use of new, patented drug products that did not offer substantial improvements on cheaper alternatives available before 1990. The report concluded that:

The rising cost of using these me-too drugs at prices far exceeding those of time tested competitors deserves careful scrutiny.⁶²

Morgan et al. went on to argue that because the list of top 20 drugs in global sales includes newly patented versions of drugs in long-established categories – namely drugs that were marketed before 1990, such as angiotensin-converting enzyme inhibitors, statins, selective serotonin reuptake inhibitors, and proton pump inhibitors – ‘me-too drugs doubtless dominate spending trends in most developed countries.’⁶³ The investment decisions of the pharmaceutical industry are influencing the costs of drugs to the government and society. The decisions made by the industry affect not only the shareholders, but also society as a whole.

57. Horrobin, D.F. (2000) ‘Innovation in the pharmaceutical industry’, *Journal of the Royal Society of Medicine*, 93, pp.341–5.

58. IMS Health (2004).

59. Gozner, M. (2004) *The \$800 Million Pill*.

60. See Calfee, J.E. (2000) *Prices, Markets and the Pharmaceutical Revolution*, American Enterprise Institute Press; diMasi, J. and Paquette, C. (2004) ‘The economics of follow-on drug research and development trends in entry rates and the timing of development’, *Pharmacoeconomics*, 22 (Suppl. 2), pp.1–14.

61. Hollis, A. (2004) *Me-too Drugs: Is There A Problem?*, World Health Organisation, www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf (accessed 15 March 2008).

62. Morgan, S.G. et al. (2005) ‘“Breakthrough” drugs and growth in expenditure on prescription drugs in Canada’, *British Medical Journal*, 331, pp.815–16.

63. Ibid.

Where is innovation actually coming from?

The pharmaceutical industry argues that it is the only body capable of innovation. However, this argument should be challenged as the current model of innovation is shifting; innovative breakthroughs are not coming from the giants of the industry but are starting in publicly funded research and small bio-tech firms.

The majority of drugs that are therapeutically innovative have their roots in publicly funded research; 70% of NMEs that have entered the market over the last decade were discovered in publicly funded science.⁶⁴ \$27 billion (circa £16 billion) is spent on publicly funded R&D in the US each year, this is nearly equal to what the pharmaceutical industry claims it spends on R&D.⁶⁵ However, UK public investment lags slightly behind; currently £1.5 billion is invested annually on publicly funded R&D, while the industry estimates its own spending is £3.2 billion.

Innovation and drug development is taking place very successfully in publicly funded institutions in the UK, the US and across Europe. This research is often used subsequently by the industry to make vast sums in profit.

Key points

- The cost of drugs is growing in the UK, Europe and the US at a faster rate than that of GDP.
- Innovation is declining in terms of product innovation and therapeutic innovation.
- The current industry model is unsustainable.
- To ensure useful therapeutic drugs continue to be developed greater investment in R&D is needed by the industry.
- Increased public investment in therapeutic innovation and drug development is also necessary.
- Supervision and regulation should be put in place to ensure therapeutic innovation is prioritised.

Possible solutions

In February 2007 the Office of Fair Trading (OFT) released a comprehensive review of the Pharmaceutical Price Regulation Scheme and called for essential reform of the price controls of

drugs, which would begin to address the issue of escalating drug prices as well as incentivising the production of therapeutic advancement over product advancement.

The OFT report identified a number of drugs where prices are significantly out of line with patient benefits, including treatments for cholesterol, blood pressure and stomach acid. It recommended that the current 'profit-cap- and price-cut' scheme be replaced with a patient-focussed, value-based pricing scheme, in which the prices the NHS pays for medicines reflect the therapeutic benefits they bring to patients.

This would offer greater value for money for patients and encourage the right sort of investment for pharmaceutical companies. The OFT estimates that this would free up £500 million per year of public money, which could be invested elsewhere.

The UK government has recently pushed a similar, if less radical, proposal, where the industry has agreed to reduce prices for less effective drugs in the short term with the promise of prices rising if the drugs' efficacy is shown to be greater than previously expected. It is hoped that this scheme will reduce spending on drugs by £390 million in 2009, which is certainly a step in the right direction. However, the proposal does not go nearly far enough, as it still focuses on commercial interests over public health interests. The government should also be looking now at how its pricing system could encourage therapeutic innovation.

This is not the only method of regulation. Alternatives are:

- to consider regulating more stringently through the MHRA, as suggested later in this report
- to consider suggestions made in 2003 by Anthony Harrison, from the health think-tank the King's Fund, who argued that government should take a more active role in relation to the research agendas of pharmaceutical companies by setting up a health research and healthcare taskforce, which would identify key areas of need.⁶⁶

As the colossus that is the pharmaceutical industry struggles and its innovation and drug development grinds to a slow and painful halt it is hard to see any other future beyond a dramatic

64. Gozner, M. (2004) *The \$800 Million Pill*; United Nations Development Programme (1999) *Human Development Report*, Oxford University Press.

65. McClellan, M.B. (2003) 'Technology and innovation: their effects on cost growth of health-care', Statement before the Joint Economic Committee US Congress, 9 July, www.fda.gov/ola/2003/healthcare0709.html (accessed 1 September 2008).

66. Harrison, A. (2003) *Getting the Right Medicines? Putting Public Interests at the Heart of Health-related Research*, King's Fund.

decline in drug development. However, to ensure that drug development and innovation continues it is necessary to facilitate the growth of academic research and small bio-tech firms supported by government-funded clinical trials. This is why it is vital that any saving made through price cuts should be hypothecated to support our science infrastructure – this would encourage a mixed economy where innovation could happen and the dependence on the big pharmaceutical companies and the market could be mitigated.

The pharmaceutical industry is too important to fail. We cannot allow what could be one of the greatest of the UK's achievements to collapse. We must learn the lessons of the banking crisis and step in now, before it is too late.

2. Bias in industry-sponsored clinical trials

Evidence suggests that industry influence over clinical trials has resulted in biased science. When a drug is sold it is not sold alone but as part of a package of science. The efficacy of the drug is believed in because of the science that supports it. However, through systematic bias created in clinical trials inaccurate information is published and used as evidence when it comes to licensing decisions on the safety, efficacy and quality of drugs, and this in turn affects prescribing practices of doctors.

The gold standard of science: randomised controlled trials

Randomised controlled trials

The randomised controlled trial (RCT) is the gold standard of evidence-based medicine and the best route to ensure that unbiased knowledge is available to judge the safety and efficacy of a drug.⁶⁷ In consequence it is no surprise that RCTs are a vital aspect of scientific analysis of the efficacy and safety of a drug.⁶⁸ After the thalidomide disaster in the 1960s, regulation was introduced requiring producers of a drug to provide the necessary RCT for licensing. The body that currently regulates this in the UK is the MHRA. Additionally, RCTs affect how doctors practise medicine and as a result impact directly on our health.⁶⁹

Who controls randomised controlled trials?

The vast majority of RCTs are commissioned, conducted and in consequence controlled by pharmaceutical companies, which make higher profits if the trial reaches favourable conclusions. Trials are often managed by contract research

organisations (CROs). These are often considerably cheaper for the company and can also mean that concealing unfavourable data is easier than if research is conducted through a university. In partnership with the sponsoring company, CROs design, write and carry out clinical trials. Indeed it should not surprise us when it is said that 'Companies may design studies likely to favor their products.'⁷⁰ The drug companies or CROs also then assess the data, 'providing the spin... that favors them.'⁷¹

Industry influence and bias

Why bias a drugs trial?

A lot rides on the results of a company's drug trials; a large trial published in a major journal has the journal's 'stamp of approval' and is therefore a highly valuable commodity. In turn these trials also affect licensing decisions.⁷² A negative result can pose a financial risk to the company. In the worst cases, the failure of a drug to show efficacy, or to raise safety concerns, can cancel the pipeline. Thus pressure may be exerted by the company to show a favourable outcome and this can result in a bias in the design, outcome and reporting of industry-sponsored research.⁷³

The failure of drug companies to adhere to ethical and clinical principles governing how they conduct trials and subsequently publish them could have adverse effects on patients if they overestimate the benefits and underestimate potential harm. Coultas identifies that fabrication, falsification and plagiarism are the traditional criteria for research misconduct, but that other more subtle behaviour, such as withholding relevant clinical trial data, may cause greater threats to public safety and trust in the research enterprise.⁷⁴

Industry influence creates bias

Within the scientific community it is increasingly recognised that the industry's influence is creating a bias in RCTs. Richard Horton, editor of the *Lancet*, and Richard Smith, previous editor of the *British Medical Journal*, argue that 'deliberate slicing and manipulations of trial data can provide a seriously misleading picture.'⁷⁵

In the 1980s Elina Hemminki⁷⁶ revealed biased under-publication of industry-sponsored studies

67. Lachin, J.M. (1998) 'RCTs are considered the most reliable form of scientific evidence in healthcare because they eliminate spurious causality and bias'; Lachin, J.M., Matts, J.P. and Wei, L.J. (1988) 'Randomization in clinical trials: conclusions and recommendations', *Controlled Clinical Trials*, 9(4), 365–74.

68. See also: Jüni, P., Altman, D.G. and Egger, M. (2001) 'Systematic reviews in healthcare: assessing the quality of controlled clinical trials', *British Medical Journal*, 323, pp.42–6; Schulz, K.F., Chalmers, I., Hayes, R.J. and Altman, D.G. (1995) 'Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials', *Journal of the American Medical Association*, 273, pp.408–12; Chalmers, T., Celano, P., Sacks, H. and Smith, H. (1983) 'Bias in treatment assignment in controlled clinical trials', *New England Journal of Medicine*, 309, pp.1358–61; Emerson, J.D., Burdick, E., Hoaglin, D.C., Mosteller, F. and Chalmers, T.C. (1990) 'An empirical study of the possible relation of treatment differences to quality scores in controlled randomized clinical trials', *Control Clinical Trials*, 11, pp.339–52.

69. Wyatt, J. (1991) 'Use and sources of medical knowledge', *Lancet*, 338, pp.1368–73.

70. Bodenheimer, T. (2000) 'Uneasy alliance – clinical investigators and the pharmaceutical industry', *New England Journal of Medicine*, 342, pp.1284–6.

71. Ibid.

72. Smith, R. (2005) 'Medical journals are an extension of the marketing arm of pharmaceutical companies', *PLoS Medicine*, 2(5), www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020138 (accessed 6 July 2009)

73. Bero, L.A. and Rennie, D. (1996) 'Influences on the quality of published drug studies', *International Journal of Technology Assessment in Healthcare*, 12, pp.209–37.

74. Coultas, D. (2007) 'Ethical considerations in the interpretation and communication of clinical trial results', *Proceedings of the ATS*, 1 May, 4(2), pp.194–9; Sleight, P. (2004) 'Where are clinical trials going?: society and clinical trials', *Journal of Internal Medicine*, 255, pp.151–8.

75. Horton, R. and Smith, R. (1999) 'Time to register randomised trials', *Lancet*, 354, pp.1138–9.

76. Hemminki, E. (1980) 'Study of information submitted by drug companies to licensing authorities', *British Medical Journal*, 280, p.833–836.

as a particular concern. Hemminki found that if a clinical trial had been designed to look for adverse effects of drugs it was far less likely to be published than studies that had not looked for adverse drug reaction. This could suggest the adverse drug reactions caused by drugs were being covered up in industry-sponsored trials by withholding them from publication. In 1994 Rochon and colleagues studied 57 industry-sponsored trials of non-steroidal anti-inflammatory drugs for the treatment of arthritis pain and found that not one of these published trials showed unfavourable results to the industry.⁷⁷ Again this is highly suggestive of an industry bias. In 1997 a study by Stern and Simes stated that:

This study confirms the evidence of publication bias found in other studies and identifies delay in publication as an additional important factor.⁷⁸

This shows that where unfavourable results were found, delays in publication were very common; these delays could be seen to be a method of damage control by the industry. A further study in 1997 into the relative efficacy of a treatment for post-operative vomiting and nausea concluded that:

A false impression of... efficacy may arise because a quarter of all relevant published reports are duplicates, and reporting of study results is uncritical.⁷⁹

This suggests that not only are we seeing a biased under-publication of unfavourable trials, but also interestingly what appears to be a biased over-publication of favourable trials and uncritical reporting of the trials methodology and results.

In 1999 Friedberg and colleagues found that studies funded by the pharmaceutical industry were eight times less likely than independently funded research to reach unfavourable qualitative conclusions and that one in five contained qualitative over-statements of quantitative results – namely the conclusions were not supported by their evidence.⁸⁰ A further study by Jørgensen et al. in 2006 found:

Industry supported reviews of drugs should be read with caution as they were less transparent, had few reservations about methodological limita-

tions of the included trials, and had more favourable conclusions than the corresponding Cochrane reviews.⁸¹

What are Cochrane reviews?

A Cochrane review is a review carried out by the Cochrane Collaboration, which is a not-for-profit, independent organisation formed in 1993. It consists of more than 11,500 healthcare specialists in over 90 countries. They carry out rigorous, systematic reviews of high-quality clinical trials on the use of conventional and alternative treatments. Their reviews are deemed to be independent and of a very high quality as they attempt to evaluate and interpret all the research evidence on a topic to help health professionals and others make informed decisions about healthcare. Cochrane reviews are therefore often used as a point of reference or a comparison to other trials or reviews, which are deemed less scientifically rigorous.

A further study in 2007 into the relationship between the conclusions of meta-analysis and the financial sponsorship of the study concluded that:

Meta-analyses on antihypertensive drugs and with financial ties to one drug company are... associated with favourable conclusions.⁸²

Epstein (2007) also concludes that differences in interpretation of results between meta-analyses funded by drug companies and those that are not raise concerns about the reliability of studies funded by the industry.⁸³

What is meta-analysis?

Meta-analysis is a statistical method of combining the results of numerous individual trials. In combining numerous studies meta-analysis is thought to show the overall efficacy and safety of a drug or medical intervention.

This assessment of the methodological quality of a trial is intricately intertwined with the quality of the reporting of trials – the extent to which a report provides information about the design, conduct and analysis of the trial. In 2001 Jüni et al. argued:

77. Rochon, P.A. et al. (1994) 'A study of manufacturer-supported trials of non steroidal anti-inflammatory drugs in the treatment of arthritis', *Archives of Internal Medicine*, 154, pp.157–63.

78. Stern, J.M. and Simes, R.J. (1997) 'Publication bias: evidence of delayed publication in a cohort study of clinical research projects', *British Medical Journal*, 315, pp.640–5.

79. Tramer, M.R., Moore, R.A., Reynolds, D.J.M. and McQuay, H.J. (1997) 'A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting', *British Medical Journal*, 314, p.1008.

80. Friedberg, M. et al. (1999) 'Evaluation of conflict of interest in eco analysis of new drugs used in oncology', *Journal of the American Medical Association*, 282(15), pp.1453–7.

81. Jørgensen, A.W. et al. (2006) 'Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review', *British Medical Journal*, 333, p.782.

82. Yank, V., Rennie, D. and Bero, L.A. (2007). 'Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study', *British Medical Journal*, 335, pp.1202–5.

83. Epstein, R.A. (2007). 'Influence of pharmaceutical funding on the conclusions of meta-analyses', *British Medical Journal*, 335, p.1167.

There is ample evidence that many trials are methodologically weak and increasing evidence that deficiencies translate into biased findings of systematic reviews.⁸⁴

Fiona Godlee, current editor of the *British Medical Journal*, stated in 2008:

The evidence that industry funding biases the design and reporting of clinical research is overwhelming.⁸⁵

The government must step in to create the necessary regulatory structure to ensure that this is no longer allowed to continue.

Key points

- 1 The industry designs, manages, funds and controls the majority of clinical trials.
- 2 These clinical trials are used to make licensing decisions and influence prescribing practices.

- 3 Trials sponsored by the industry have been shown to contain significant bias in favour of the industry sponsor.

Possible solutions

- This report recommends a mandatory disclosure of the results from the drug trials similar to the disclosure that is now mandatory in the US as a result of legislation passed in 2007; infringement of this legislation results in fines, with naming and shaming of repeat rule breakers. It covers all trials, which must be registered with an ethics committee, and demands that all data must be made available within one year of the end of a trial.⁸⁷ This report recommends that a similar scheme should be operated in the UK.
- This report also recommends that a national standards committee should be set up, which would assess the quality of drug trials and aim to put in place a national set of standards to which all clinical trials need to attain before

84. Juni, P., Altman, D.G. and Egger, M. (2001) 'Systematic reviews in healthcare'.

85. Godlee, F. (2008) 'Doctors and the drug industry', *British Medical Journal*, 336, www.bmj.com/cgi/content/full/336/7634/0 (accessed 7 July 2009).

86. Feinstein, A.R. (1995) 'Meta-analysis: statistical alchemy for the 21st century', *Journal of Clinical Epidemiology*, 48, pp.71–9.

87. Groves, T. (2008) 'Mandatory disclosure of trial results for drugs and devices', *British Medical Journal*, 336, www.bmj.com/cgi/content/extract/336/7637/170 (accessed 7 July 2009).

88. This is an imaginary step-by-step guide on how bias can be and on occasion has been created in a clinical drugs trial.

89. Manning, M. (2006) 'Pharmaceutical businessmen branch out to start contract research firm', *Tampa Bay Business Journal*, www.bizjournals.com/tampabay/stories/2006/2008/21/story4.html (accessed 1 September 2008).

90. Press Association (2004) 'SSRI dangers for children suppressed', *Guardian*, www.guardian.co.uk/society/2004/apr/23/mentalhealth.medicineandhealth (accessed 1 September 2008).

91. Henderson, L. (2000) 'More AMCs finding growth from reform', *CenterWatch Newsletter*, 7(6), pp.1, 10–13.

92. In the case of Vioxx there is a growing body of evidence that highlights an early awareness of the risk it increases the chances of uneven arrhythmia; the trials were deliberately designed to conceal this; see Krumholz et al. (2007) 'What have we learnt from Vioxx?', *British Medical Journal*, 334, pp.120–3.

93. Krumholz et al. (2007) 'What have we learnt from Vioxx?'

94. Tierney, J.F. and Stewart, L.A. (1999) 'Investigating patient exclusion bias in meta analysis', *International Journal of Epidemiology*, 34, pp.79–87; Hollis, S. and Campbell, F. (1999) 'What is meant by intention to treat analysis? Survey of published randomised controlled trials', *British Medical Journal*, 319, pp.670–4; Fergusson, D., Aaron, S.D., Guyatt, G. and Hebert, P. (2002) 'Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis', *British Medical Journal*, 325, pp.652–4.

95. Tramer, M.R. et al. (1997) 'A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting', *British Medical Journal*, 314, p.1088.

96. Wazana, A. (2000) 'Physicians and the pharmaceutical industry: is a gift ever just a gift?', *Journal of the American Medical Association*, 283, pp.373–80.

How to bias a drugs trial... and not get caught!⁸⁸

1. Always contract out your clinical trials to a CRO – they have the added bonus of being cheaper⁸⁹ and any negative results can be more easily covered up if the conclusions are not what you wanted them to be.⁹⁰ CROs have received the lion's share of clinical trial revenue. In 2000 in the US CROs received 60% of research grants from the industry, compared with 40% for academics.⁹¹
2. To make sure that your drugs trial comes up with favourable results ensure a subtle bias in selection, detection or attrition:
 - Selection bias – make sure you have an uneven allocation of participants in each of your comparison groups. Perhaps you could screen out any individuals with a history of a disease that means that even if your drug increases the risk it is much less likely to show up and can therefore easily be understated in your conclusion!⁹²
 - Detection bias – make sure you have a biased assessment of outcome, for example, if you are worried that your new drug may cause arrhythmia, simply make sure you don't have a cardiologist on hand.⁹³
 - Attrition bias – biased occurrences and handling of deviations from protocol. In all trials a certain number of patients will not complete a trial; if this number is less than 5% there is little to worry about, however, if it is more than 20% we should be concerned. This drop-out rate is often ignored or underestimated in reporting of trials this can give a more favourable result for the trial than is entirely accurate.⁹⁴
3. Even once your trial has been completed you can still act to create bias. If the results don't say what you want, you have two options: cover-up the results to ensure the report does not get published⁹⁵ If it says only mediocre things, have a conclusion that says nice things and get it published anyway.⁹⁶
4. Once this process is completed try and get your study published in a major journal and ensure that this publication is reprinted and sent out to GPs and other opinion leaders. That way the maximum number of people will hear about it. Also fingers crossed your study will be included multiple times in any meta-analysis!

licensing or publication. Truly independent trials are only possible post-licensing as a result of the right to commercial secrecy. However, the costs of post-licensing trials are massively prohibitive unless they are supported by the company. Therefore, steps should be made to allow post-licensing clinical trials by independent bodies, but also greater transparency in industry-sponsored ones. To do this, academic involvement in the design and assessment of trials is paramount.

- This report would also support proposals such as those put forward by John Abraham for independently conducted research trials. Such trials could be paid for by an industry levy and would be transparent and available for scientific scrutiny throughout.⁹⁷ By the time a drug or pharmaceutical product has reached phase 3 trials it has already been granted patent rights, as such independent phase 3 trials would not be commercially damaging for the industry, but they would allow a greater degree of transparency.

97. Abraham, J. and Lawton Smith, H., eds (2003) *Regulation of the Pharmaceutical Industry*, Palgrave; Abraham, J. and Sheppard, J. (1999) *The Therapeutic Nightmare: the Battle Over the World's most Controversial Sleeping Pill*, Earthscan

3. The medical profession and the pharmaceutical industry

Because of the shareholder structure of most pharmaceutical companies they are required to increase their market share. One obvious way of doing this is by influencing the prescribers of medicine: doctors, nurses and pharmacists. However, the prescribers of medicine's main priority is to improve the health of their patients; this can result in a conflict of interests. As a result the relationship between health professionals, particularly doctors, and the industry can be problematic for the independence of the medical profession. Also attempts to influence prescribing practices are diverting attention and investment away from therapeutic innovation and towards increasing market share through biasing prescribing practices.

The drugs that each of us takes are trusted, not because we as individuals know or understand the complex chemical processes that are involved as we swallow the pill, but often because we simply trust in the independent and unbiased information provided to us by our doctor, nurse or pharmacist. Years of medical training and continuing postgraduate education are designed to ensure that these professional groups of people can provide us with the information and treatment that we need. In this paradigm the individual depends on the medical profession, and any publicly available information through the NHS, for unbiased information on treatments. However, within this dependency a different story is also apparent, a story in which the information the doctors have is actually biased, and the growing influence of the industry over doctors has resulted in non-rational prescribing practices, which are potentially damaging the curative potential of our health service.

The industry influence can be either subtle and discreet, or explicit. The higher level of independence for doctors in the US in prescribing practices makes industry influence more explicit there. In the UK the mass purchasing power of the NHS

has empowered society, and as a result industry influence, although still apparent, is certainly less explicit.

In the UK and the US doctors' interaction with pharmaceutical representatives begins in medical school. According to a study in the US in 2000 by Wazana, this contact continues at a rate of about four times per month for the rest of their career.⁹⁸ In a study by Campbell et al. in 2007, 94% of physicians in the US reported having a relationship with the industry: more than a third received reimbursement for costs associated with meetings or continuing medical education, and more than a quarter (28%) received payments for consulting, giving lectures or enrolling patients in trials.⁹⁹ These meetings, attendance at lunches, and even gifts of free pens are associated with increased prescription rates of the sponsor's medication. This degree of contact led Wazana to conclude:

The present extent of physician-industry interactions appears to affect prescribing and professional behaviour and should be further addressed at the level of policy and education.¹⁰⁰

In his book *Overdosed America* John Abramson¹⁰¹ points to the dominance of the industry in relation to prescribing practices and its role in the current crisis in the medical system. Indeed the growing body of evidence on the impact of the pharmaceutical industry on the medical profession led Jerry Kassirer, former editor of the *New England Journal of Medicine*, to argue that the pharmaceutical industry has 'deflected the moral compasses' of many doctors and health professionals.¹⁰²

It is clear that the industry recognises the sales potential gained through contact with doctors. An internal study carried out by Merck & Co. in the US estimated that the 'return on investment' especially from doctor-led discussion groups was significant. The study goes on to show that doctors who attended a lecture given by another doctor wrote an additional \$623.55 (circa £353) worth of prescriptions for the painkiller Vioxx over a 12-month period compared with doctors who didn't attend. Doctors who participated in the more intimate discussions wrote an additional \$717.53 (circa £405) worth of prescriptions for Vioxx.¹⁰³

It is fair to suggest that industry influence in the UK is less significant than in the US, yet we

98. Wazana, A. (2000) 'Physicians and the pharmaceutical industry: is a gift ever just a gift?', *Journal of the American Medical Association*, 283, pp.373-80.

99. Campbell, E.G. et al. (2007) 'A national survey of physician-industry relationships', *New England Journal of Medicine*, 356, pp.1742-50.

98. Wazana, A. (2000) 'Physicians and the pharmaceutical industry: is a gift ever just a gift?'

101. Abramson, J (2004) *Overdosed America: The Broken Promise of American Medicine* Harper Collins

102. Kassirer, J.P. (2004) *On the Take: How Medicine's Complicity With Big Business Can Endanger Your Health*. Oxford University Press.

103. Hensley, S. and Martinez, B. (2005) 'To sell their drugs, companies increasingly rely on doctors', *Wall Street Journal*, http://online.wsj.com/article/SB112138815452186385.html?mod=today_us_us_page_one (accessed 1 September 2008).

104. Dobson, R. (2003) 'Pharmaceutical industry is the main influence in GP prescribing', *British Medical Journal*, 326, p.301.

105. National Audit Office (2007) *Prescribing Costs in Primary Care*, www.nao.org.uk/pn/06-07/0607454.htm (accessed 8 September 2008).

106. Moynihan, R. et al. (2002) 'Selling sickness', *British Medical Journal*, 324, pp.886–91.

107. BMJ (2005) 'The influence of big pharma', editorial, *British Medical Journal*, 330, pp.855–6, www.bmj.com/cgi/content/full/bmj%3B330/749/6/855 (accessed 8 January 2009).

108. Mansfield, P.R. (2007) 'Is it insulting to suggest that health professionals are influenced by drug promotion?', www.healthyskepticism.org/news/2007/May.php (accessed 3 September 2008).

109. Moynihan, R. (2008) 'Doctors' education: the invisible influence of drug company sponsorship', *British Medical Journal*, 336, pp.416–17.

110. For further information see Brennan, T.A. et al. (2006) 'Health industry practices that create conflicts of interest: a policy proposal for academic medical centers', *Journal of the American Medical Association*, 295, pp.429–33; Chren, M.M. and Landefeld, C.S. (1994) 'Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary', *Journal of the American Medical Association*, 271, pp.684–9; Steinman, M.A. et al. (2007) 'Characteristics and impact of drug detailing for gabapentin', *PLoS Medicine*, 4, p.e134; Bekelman, J.E., Li, Y. and Gross, C.P. (2003) 'Scope and impact of financial conflicts of interest in biomedical research: a systematic review', *Journal of the American Medical Association*, 289, pp.454–65; Zipkin, D.A. and Steinman, M.A. (2005) 'Interactions between pharmaceutical representatives and doctors in training: a thematic review', *Journal of General Internal Medicine*, 20, pp.777–86; Steinman, M.A., Shlipak, M.G. and McPhee, S.J. (2001) 'Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical industry promotions', *American Journal of Medicine*, 110, pp.551–7; Katz, D., Caplan, A.L. and Merz, J.F. (2003) 'All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving', *American Journal of Bioethics*, 3, pp.39–46.

111. For further information on No Free Lunch see www.nofreelunch.org/.

112. See www.healthyskepticism.org/fora/index.php?s=b8b779d63ad2f05e3d149f9dc69694a (accessed 1 September 2008).

should see the situation in the US as a warning of the potential route if regulation in this area relaxes.

However, this does not mean that the UK is free from industry bias. The pharmaceutical industry is heavily relied upon for information by GPs and is argued to be the first port of call in decision making; while GPs are aware of the possible bias they generally considered information provided by the drugs industry factually accurate.¹⁰⁴ The 2007 National Audit Office report found that 'it was difficult for GPs to assimilate all the information they received on prescribing'.¹⁰⁵ This difficulty could in turn exacerbate industry influence.

In the UK the pharmaceutical industry sponsors over two-thirds of all medical postgraduate education and information.¹⁰⁶ The annual marketing budget by the industry for medical education is estimated to be £1.65 billion in the UK; this is just under half the total amount spent by the industry on R&D in the UK. The Department of Health spends the equivalent of just 0.3% (£4.95 million) of this on publishing independent information on prescribing practices.¹⁰⁷ In an increasingly complex health-care system we must recognise the potentially damaging influence and power of a few pharmaceutical companies, which encourage increased spending on drugs that may have a cheaper generic alternative and on drug therapies over alternative therapies.

At this stage it is important to mention that although society depends on the industry for drugs and the information on them, increasingly there are alternative sources of information. In the UK, for example, we now have the 'map of medicines', which provides guidance for doctors on best prescribing practice. We also have a body of NICE guidelines, which can assist doctors in prescribing decisions. These are vital sources of information; however, they are not enough to combat the influence of the pharmaceutical industry and we should therefore think seriously about how we can limit this influence.

It is not inaccurate to suggest that doctors and other medical professionals are influenced by the industry. Intelligence and education do not protect people from being misled. Invisible bias affects us all, and marketing and advertising are powerful tools.¹⁰⁸ But with the apparent decline in

innovation and the growing cost of drugs we should certainly ask whether it is right that such an industry rather than an independent education is influencing our health decisions.

There are many possibilities in terms of policy solutions, but what is not in doubt is the reality that there is a conflict of interests between doctors' commitment to patient care and the desire of pharmaceutical companies and their representatives to sell their products. Indeed as international expert Harvard professor David Blumenthal asks, 'Why would for-profit companies... pour more than a billion dollars a year into continuing medical education without the expectation of gaining anything from it?'¹⁰⁹ This poses a significant challenge and government must work with the medical profession to limit it.¹¹⁰

Key points

- 1 There is a significant degree of contact between the pharmaceutical industry and medical professionals.
- 2 The pharmaceutical industry invests heavily in influencing doctors.
- 3 There is a conflict of interest between doctors' need to treat patients, and the pharmaceutical industry's desire to sell their drugs.
- 4 Influence by the pharmaceutical industry can alter the prescribing habits of doctors; this could result in increased costs to the NHS and unnecessary risks to the patient.

Possible solutions

These are some alternative methods of ensuring non-biased prescribing practices:

- The 'no free lunch pledge'¹¹¹ states: 'I am committed to practising medicine in the interests of my patients and on the basis of the best available evidence, rather than on the basis of promotion.' This is an interesting scheme and has huge potential; it is being taken seriously by many doctors in the UK as many doctors' surgeries no longer allow pharmaceutical representatives to visit.
- Peter Mansfield from HealthySkepticism, a group critical of pharmaceutical marketing, suggests that medical education could be funded by the taxpayer through a system of competitive grants.¹¹²

- Doctors could also be encouraged to make publicly available information on all visits and gifts from the industry – on the internet and at doctors' surgeries – to ensure patients are aware of any possible bias.
- Doctors could be encouraged to seek out alternative sources of information and be given a budget to purchase it.
- Finally, trainee doctors should receive information and training on pharmaceutical company representatives and how they exert influence. Further to this point steps could be made to keep pharmaceutical representatives out of training hospitals and universities.

4. The pharmaceutical industry and the public

The pharmaceutical industry's influence within the public sphere does not end with doctors; pharmaceutical companies are also highly active in influencing the general public. Each company's focus varies internationally and depending on the classification of the drug. In the US, direct to consumer advertising (DTCA) is allowed for all drugs and expenditure by the pharmaceutical industry on marketing, and advertising is much higher than in the UK. In the UK, DTCA is only legal for over the counter medicines – which do not require a prescription – and as a result there is a significant focus by the industry on targeting patient groups.

This influence could create a bias in favour of specific patented drug treatments over other cheaper and even safer alternatives; it could also encourage drug treatment over other perhaps lower risk treatments, with fewer side effects, and could result in bias towards drugs which are more expensive or untested. This can be costly for patients and society; it can be unsafe for those encouraged to take unnecessary risk on drugs which may not have been rigorously tested – as is shown in the discussion on clinical trials – and it creates intense tension between patient groups and the government.

Marketing to the general public is big business for the industry and can prove highly lucrative. If you take the example of Schering Plough's blockbuster Claritin – a hayfever remedy – you can see the appeal of marketing for the companies. In 1998 Schering Plough spent \$186 million (circa £109 million) promoting Claritin, and as a result realised a half a billion dollar increase in sales year on year to achieve annual sales of \$1.9 billion (circa £1.14 billion) in 1999.¹¹³ Further, after DTCA regulation was relaxed in the US at the end of the 1980s, pharmaceutical companies' spending on DTCA grew rapidly during the 1990s, reaching \$2.47 billion (circa £1.7 billion) in 2000.¹¹⁴ The level of investment by the US pharmaceutical industry suggests they have a considerable effect on sales.¹¹⁵ Information on the efficacy of DTCA and its role in pharmaceutical

marketing is limited. However, in a survey of US executives from pharmaceutical and biotechnology firms, 75% of respondents cited patient education as the top ranked marketing activity necessary to improve sales figure of any drug.¹¹⁶ It is important for patients to be informed of potential efficacy of drugs. However, the bias created through what can be described as excessive influence can create, or exacerbate, bias in favour of certain drugs and drug treatments more generally, and may not be in patients' best interest.

Patient groups

In the UK, because of the relatively stringent regulation of DTCA, the focus of pharmaceutical marketing rests with patient groups. There are over 2,000 patient or advocacy groups in the UK, and they provide invaluable information and support for their members. They are in some cases the only voices for vulnerable people in the face of illness, disability and discrimination. However, worryingly, these groups, whose existence in some cases is very hard to mouth, desperate for funding in order to continue to exist and support their members, are accepting pharmaceutical industry funding. For the company these 'strong ties can advance corporate goals and brand objectives'¹¹⁷ and for the patient group they can limit both perceived and actual independence and objectivity.

Pharmaceutical industry sponsorship of patient groups is widespread. Ball et al. examined websites of 69 patient groups for ten chronic conditions; 37 (54%) disclosed funding sources, 31 of which received industry funding.¹¹⁸ Of the groups that disclosed financial information, 83% had received funding from the industry. This suggests that a large proportion of patient groups are receiving some funding from the industry. This funding can in some cases be a small proportion of their budget. However, Paul Flynn MP, in evidence given to the Health Select Committee, argued that for some patient groups pharmaceutical company funding actually represents much larger percentages of their funding, up to 80% in some cases.¹¹⁹ For example, in 2007 GlaxoSmithKline, one of the largest UK phar-

113. Maguire, P. (1999) 'How direct to consumer advertising is putting the squeeze on physicians', *American Society of Internal Medicine Observer*, March.

114. Fairfield, C.T. (2001) 'US leading products by DTC spend, January 2000–December 2000', IMS Health, www.imshealth.com/public/structure/discontentment/1.2779,12031203143221,00.html (accessed 1 September 2008).

115. Mintzes, B. et al. (2002) 'Influence of direct to consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey', *British Medical Journal*, 324, pp.278–9.

116. Abraham, J. and Davis, C. (2007) 'Interpellative sociology of pharmaceuticals: problems and challenges for innovation and regulation in the 21st century', *Technology Analysis and Strategic Management*, 19, pp.387–402.

117. Durand, M. (2006) *Pharma's Advocacy Dance*.

118. Ball, D.E., Tisocki, K. and Herxheimer, A. (2006) 'Advertising and disclosure of funding on patient organisation websites: a cross-sectional survey', *BMC Public Health*, 6, p.201.

119. Health – Minutes of Evidence, www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/4112501.htm (accessed 1 September 2008); Evidence from Paul Flynn given to House of Commons Health Select Committee, www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/4112505.htm (accessed 1 September 2008).

maceutical companies, provided financial support to 55 patient groups in the UK, with a total investment of £2.36 million.¹²⁰ For some organisations this was a very minimal amount of their total budget, but in some cases it equalled up to 25% of an organisation's budget. This influence could be seen to affect such organisations' behaviour directly or indirectly.

This bias can create tension between government bodies such as NICE and patient groups, as a report by the *Independent* argued.¹²¹ The report stated that key organisations which have been active in attacking NICE had been sponsored by the pharmaceutical industry.

The case is similar in Europe. A study by Kirsten Schubert and Gerd Glaeske at Bremen University showed the influence of the pharmaceutical industry over patient groups. The report showed that in 2005 health insurance companies were the main sponsors of patients' groups in Germany, spending a total of €28 million (circa £19 million). However, the report argues that pharmaceutical companies are increasingly moving in to the area. Schubert stated, 'Pharmaceutical firms have recognized that patient groups have a large influence' and that 'members are often not aware of the involvement of the pharmaceutical industry'. The authors of the study recommend that all sponsorship be made transparent.¹²²

Key points

- 1 Pharmaceutical companies invest large amounts of money in influencing the general public.
- 2 This can be done in a number of ways, the most concerning of which in the UK is the sponsoring of patient groups.
- 3 This can at worst create bias or at best the impression of bias and can limit the independence of the group.

Possible solutions

- Independent monitoring bodies could be established to police marketing codes of practice and award real penalties.
- Increased attention could be paid to the sponsorship of patient groups, with a focus on decreasing pharmaceutical company funding.
- Additional funding could be provided to patient groups from the government for

educational purposes and to gain independent information. This would provide a great opportunity to encourage a closer engagement between patient groups and the NHS as a form of co-production.¹²³

- Pharmaceutical industry funding could be pooled in the form of a Blind Trust and this funding could then be provided to organisations independent of industry influence.

120. GlaxoSmithKline, www.gsk.com/responsibility/cr_issues/patient-groups/uk-patient-organisations.htm (accessed 1 September 2008).

121. Laurence, J. (2008) 'Drug firms bankroll attacks on NHS', *Independent*, www.independent.co.uk/life-style/health-and-wellbeing/health-news/drug-firms-bankroll-attacks-on-nhs-947316.html (accessed 1 September 2008).

122. Quoted in Tuffs, A. (2006) 'Sponsorship of patients' groups by drug companies should be made transparent', *British Medical Journal*, 333, p.1238; Abraham, J. and Davis, C. (2007) 'Interpellative sociology of pharmaceuticals'.

123. Gannon, Z. and Lawson, N. (2008) *Co-production*, Compass.

The consequences

5. The human consequences of market failure in the pharmaceutical industry

This report so far has looked at the behaviour of the pharmaceutical industry in what is in many ways a largely theoretical stance; what follows are four case studies where bias in science and ineffective regulation have had human consequences. These are intended to illustrate the issues that insufficient regulation can contribute towards creating.

The happy pill – SSRI drugs

The first of the selective serotonin reuptake inhibitors – SSRI drugs – was Zimeldine. Zimeldine was developed in the early 1980s for the Swedish company Astra AB. It was first sold in 1982, by 1983 it had been banned worldwide due to serious and fatal cases of central and peripheral neuropathy known as Guillain-Barré syndrome and suicide ideation, particularly in younger people.¹²⁴

This was not the end of SSRI drugs, as they are now prescribed to 54 million people worldwide. SSRIs include Cipmil, Dutonin, Efexor, Faverin, Lustral, Seroxat and – perhaps the most famous – Prozac. Prozac was first marketed by Eli Lilly in 1987 as a new, safe anti-depressant, and by 1999 it was providing Eli Lilly with more than 25% of its \$10 billion revenue.

Eli Lilly cranked up its marketing machine at almost the perfect moment, as previous treatments for depression had been deemed

dangerous and addictive; Prozac was marketed as a safe alternative. It was seen as the wonder drug, and appeared across the media and even featured on programmes like the *The Jerry Springer Show* as the answer to our prayers. The day it was launched, patients were already asking for it by name.¹²⁵ It was, if not a medical miracle, certainly a marketing one.

During the 1990s and into this century the prescribing rates for Prozac and other SSRIs have grown. In the UK between 1992 and 2001 the number of prescriptions of SSRIs for under-18s increased tenfold, although no SSRIs were licensed for use in children. In 2003, the NHS warned against using all SSRIs in under-18s except Prozac, after studies showed they performed no better than a placebo, and came with disturbing side effects, the most worrying of which is suicide ideation.

While the number of prescriptions for SSRIs including Prozac booms, the science behind this wonder drug is increasingly challenged. Prozac is based on a theory that emotions are governed by serotonin levels. Thus the basic principle of Prozac is that by targeting serotonin levels emotions could be managed. This view of emotions is at best highly simplistic and at worst wrong, as numerous competing factors contribute to depression, including family history, life experience, hormone levels and diet.

The science may be dubious but the side effects are increasingly becoming clear and on 2 February 2004 a panel of scientific advisers of the US Food and Drug Administration urged the agency to warn that new anti-depressants may increase the risk of suicidal thinking or behaviour among children and teenagers.¹²⁶

124. NCBI Zimeldine – Substance Summary, <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=182628> (accessed 6 July 2009).

125. Moore, A. (2007) 'Eternal Sunshine', *Guardian*, www.guardian.co.uk/society/2007/may/13/socialcare.medicinelandhealth (accessed 1 September 2008).

126. Moynihan, R. (2004) 'FDA advisory panel calls for suicide warnings over new anti-depressants', *British Medical Journal*, 328, p.30, www.bmj.com/cgi/content/full/328/7435/303-a?maxtoshow=&HITS=60&hits=60&RESULTFORMAT=&fulltext=prozac&searchid=1&FIRSTINDEX=20&resourcetype=HWCIT (accessed 1 September 2008).

By 2008 it was increasingly recognised that SSRI drugs not only were potentially damaging individually through adverse side effects, but that SSRIs are not in most cases any better than a placebo. In a meta-analysis of all trials published and previously unpublished by the industry, which compared the effect on patients taking the drugs with those given a placebo or sugar pill, it showed all patients improved but that, except in cases of severe clinical depression, those on a placebo improved just as much as those taking the drug.¹²⁷

Prozac brought depression out of the closet and many people would swear that it helped them through difficult times, but this step forward for societal acceptance of depression was not the only story in town. It is now thought that although Prozac and other SSRIs are heralded by many as wonder drugs this should be questioned, first, because of the dubious scientific theory behind them, second, because of the adverse reactions they cause and finally because it is increasingly clear that, except in the most severe cases of depression, taking an SSRI is no better than taking a sugar pill. Not only is prescribing SSRIs hugely costly, but it also has serious human implications.

Vioxx – a drug disaster

Vioxx (Rofecoxib) was introduced and marketed by the drugs company Merck in 1999¹²⁸ as an effective and safer alternative to previous non-steroidal anti-inflammatory drugs for the treatment of the pain associated with osteoarthritis.¹²⁹ Six years later it was removed from the market worldwide when it was recognised that it significantly increased the risk of cardiovascular incidents. It was described by Dr David Graham in the US Senate as the ‘single greatest drug safety catastrophe in the history of this country or the history of the world’.¹³⁰

Prior to approval, none of Merck’s clinical trials looked specifically into cardiovascular risk, yet Dr Gurkupal Singh, adjunct clinical professor of medicine at Stanford University, testified that as early as November 1996 Merck scientists ‘were seriously discussing a potential [heart attack] risk of Vioxx’.¹³¹

The subsequent trials that were conducted were arguably designed to ensure that this risk of cardiovascular events was not evaluated. All initial nine studies that were used when Merck

applied for licensing of Vioxx to the Food and Drug Administration (FDA) in 1998 were carried out over short periods of time and enrolled patients with an already low risk of cardiovascular disease, offering further potential to conceal the potential risk.¹³²

In January 1999 Merck launched its biggest study on Vioxx, using 8,000 patients. Merck hoped to prove that there were fewer gastro-intestinal effects in Vioxx than in its closest competitor Naproxen;¹³³ this study was known as VIGOR. The first results were disclosed in November 1999: one group of patients was 79% more likely to be at risk of ‘death or serious cardiovascular event’;¹³⁴ however, the study had omitted three heart attacks and so the risk of cardiovascular problems to patients taking Vioxx was five times, not four times, that of Naproxen.¹³⁵ Furthermore, data from an interim analysis had different termination dates for cardiovascular and gastrointestinal events and missed out three more myocardial infarctions, distorting the cardiovascular data further still.¹³⁶

Following the findings, in 2001 the FDA in the US warned Merck in a letter that the promotion of minimised cardiovascular risks ‘misrepresents the safety profile of Vioxx’.¹³⁷ This was then followed with the FDA updating warning labels to include the VIGOR results in 2002.

Merck’s next study, ‘APPROVe’, finally brought the end of Vioxx in September 2004. The report found that if patients took the drug for longer than 18 months, risk of cardiovascular problems including heart attack were doubled.¹³⁸ The inadequacies of methodology, peer review and critical review of data, and biased presentation of the results, allowed Vioxx not just to make it to market but subsequently to stay on the market for five years.¹³⁹ From launch to being taken off the market 107 million prescriptions for the drug were made and ‘88 000 to 139 000 Americans had heart attacks and strokes as a result of taking rofecoxib (Vioxx)’.¹⁴⁰ The subsequent 27,000 claims, representing 47,000 plaintiffs, were originally all contested by Merck, which feared a potential \$25 billion liability.¹⁴¹ However, it eventually settled in 2007 on a \$4.85 billion payout. In the process it also worked up \$1.2 billion in legal costs.¹⁴² More recently Florida’s Attorney General has filed a lawsuit against Merck & Co., this time for deceptive marketing and promotion of Vioxx.

127. Kirsch, I. et al. (2008) ‘Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drugs administration’, *PLoS Medicine*, <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0050045> (accessed 1 September 2008).

128. MSNBC (n.d.) ‘The rise and fall of Vioxx’, www.msnbc.msn.com/id/9911524/ (accessed 31 July 2008).

129. Harlan et al. (2007) ‘What have we learnt from Vioxx?’, 334, pp. 120–3, *British Medical Journal*, www.bmj.com/cgi/reprint/334/7585/120?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=vioxx+story&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT (accessed 8 January 2009).

130. Lenzer, J. (2004) ‘FDA is incapable of protecting US “against another Vioxx”’, *British Medical Journal*, 329, p. 1253, <http://bmj.com/cgi/content/full/329/7477/1253> (accessed 1 September 2008).

131. Quoted in Harlan et al. (2007) ‘What have we learnt from Vioxx?’

132. Ibid.

133. Ibid.

134. Ibid.

135. Tanne, J. (2005) ‘Journal criticises Vioxx study for omitting three heart attacks’, *British Medical Journal*, 331, p. 1423, www.bmj.com/cgi/reprint/331/7530/1423.pdf (accessed 1 September 2008).

136. Harlan et al. (2007) ‘What have we learnt from Vioxx?’

137. MSNBC (n.d.) ‘The rise and fall of Vioxx’.

138. Ibid.

139. Harlan et al. (2007) ‘What have we learnt from Vioxx?’

140. Lenzer, J. (2004) ‘FDA is incapable of protecting US “against another Vioxx”’.

141. Harlan et al. (2007) ‘What have we learnt from Vioxx?’

142. Fiercepharma (2007) ‘Merck settling Vioxx case for \$4.85 billion’, www.fiercepharma.com/story/merck-settling-vioxx-claims-4-85b/2007-11-09?utm_medium=nl&utm_source=internal&cmp-id=EMC-NL-FH&dest=FP (accessed 9 January 2009).

The suit claims that Merck failed repeatedly to disclose the drug's adverse effects, while offering it to the state's Medicaid program as a safe painkiller; this was in direct violation of the state's Deceptive and Unfair Practices Act.¹⁴³

The most recent suit also alleges that Merck tried to intimidate physicians and researchers who questioned the safety of Vioxx, and may have misrepresented or concealed published evidence, including its own, showing possible harmful effects. In the UK, under pressure from US lobbying firms government ministers have backed down from supporting UK citizens who took Vioxx from filing law suits against Merck, despite an earlier pledge of support, and despite the conclusion of the trial in US.¹⁴⁴ This is suggestive of bias created in science through overt industry influence, which subsequently had significant effects in terms of human health – these claims continue to be denied by the drugmaker.

Baycol – avoidable casualties?

Baycol, also known as Lipobay, was first licensed in 1998 as an anti-cholesterol drug produced by the German drugs firm Bayer. It was seen as an immediate success as millions of people worldwide switched from using other statin drugs to Baycol. However, Baycol users soon began to complain of adverse effects, including rhabdomyolysis, a deterioration in muscle tissue, which can lead to kidney failure, paralysis and death.

Bayer rejected these complaints and claimed that patients were taking Baycol in doses not consistent with Baycol's product labelling and sent out a letter to doctors recommending that they monitor their patients' doses more closely, and Baycol labels were changed to reflect the dangers of mixing Baycol with other drugs.¹⁴⁵ However, by August 2001 it was overwhelmingly clear that muscle deterioration or rhabdomyolysis occurred ten times more often with Baycol than with other statins.¹⁴⁶ In August 2001 Bayer announced the Baycol had been linked to 52 deaths.¹⁴⁷ This resulted in a recall of the drug worldwide.

This has not only been damaging for public health but also for the company as in response to this recall more than 12,000 Baycol lawsuits were filed. The company approached the litigation by settling the most serious cases; so far, Bayer has settled 2,312 Baycol cases for \$872 million.¹⁴⁸

With a more rigorous clinical trial and more effective regulation of adverse effects post-licensing this problem could have been avoided; instead the drug stayed on the market for three years. The potentially devastating impact of this on the company that brought Aspirin to the market over 100 years ago is part of the worrying story – the impact that poor regulation can have on companies.

Ritalin and Concerta – drugs for children

Ritalin and Concerta are amphetamines whose active ingredient is methylphenidate. These two drugs are prescribed to millions of children across the globe to treat a condition known as Attention Deficit Hyperactivity Disorder (ADHD).

Initially the drug was welcomed by scientists who were carrying out an extensive trial known as the 'Multimodal Treatment Study of Children with ADHD'. They concluded in 1999 that, after one year, medication worked better than behavioural therapy for ADHD. This finding influenced medical practice on both sides of the Atlantic and prescription rates in the UK have since tripled. Ritalin and Concerta were prescribed to around 55,000 children in 2006 (nearly 1% of children) – at a cost of £28 million to the NHS.¹⁴⁹ In the US the figures are much higher, with an estimated 10% of children on Ritalin.¹⁵⁰

However, in 2007 the study's co-author, Professor William Pelham of the University of Buffalo, stated that the beneficial impact of the medications were exaggerated in the first study and the idea that if children were medicated longer they would have better outcomes was not the case. Professor Pelham, who led the study, stated that in the long run there are 'no beneficial effects' of medication.¹⁵¹ This raises again the concerns of opponents about the incomplete understanding of the biological basis for prescribing products containing methylphenidate.

It is also increasingly clear that there are side effects associated with a prolonged use of the drug, particularly stunted growth; children who take Ritalin for more than three years can be up to an inch shorter than their counterparts and 4.4 pounds lighter.¹⁵² More worrying is that Ritalin and other products containing the active ingredient have now also been linked to eight deaths in

143. SFBJ (2008) 'State sues Merck for deceptive marketing of Vioxx', editorial, *SOUTH Florida Business Journal*, www.bizjournals.com/southflorida/stories/2008/09/29/daily21.html?b=1222660800^1709231&brthrs=1 (accessed 1 September 2008).

144. Evans, R. and Bosely, S. (2009) 'Ministers dropped Vioxx protest after lobbying from US drug firm', *Guardian*, www.guardian.co.uk/business/2009/may/04/merck-vioxx-campaign-parliament (accessed 8 May 2009).

145. Baycol FYI (n.d.) 'The Baycol recall – how a lawyer can help with a baycol lawsuit', www.baycolfyi.com/ (accessed 1 September 2008).

146. *Ibid.*

147. CNN.com (2001) 'Baycol linked to 52 deaths', <http://edition.cnn.com/2001/BUSINESS/2008/13/bayer/> (accessed 1 September 2008).

148. Defective Drugs (2004) 'Bayer's Baycol problems continue', www.adrugrecall.com/newsletter/jun04/bayer-baycol.html (accessed 1 September 2008).

149. Stratton, A. (2007) 'Ritalin of no long-term benefit, study finds', *Guardian*, www.guardian.co.uk/news/2007/nov/12/uknews.health (accessed 1 September 2008)

150. Laurance, J. (2008) 'Ritalin over-prescribed to children', *Independent*, www.independent.co.uk/life-style/health-and-wellbeing/health-news/ritalin-overprescribed-to-children-940308.html

151. News-Medical.Net (2008) 'Long term use of Ritalin ineffective and may stunt children's growth', editorial, www.news-medical.net/?id=32452 (accessed 1 September 2008).

152. DeNoon, D. (2007) 'Study: Ritalin stunts growth', CBS News, www.cbsnews.com/stories/2007/07/20/health/webmd/main3082458.shtml (accessed 1 September 2008).

children in the UK.¹⁵³ Although these represent a tiny percentage of the actual number of children prescribed Ritalin, it must be questioned whether we wish to continue prescribing to 1 in 100 of our children a drug with questioned levels of efficacy and significant potential side effects, especially given there are safer alternatives in the form of talking therapy, diet and exercise.

153. See MHRA (2006), www.mhra.gov.uk/home/groups/es-foi/documents/oidisclosure/con2023292.pdf (accessed 1 September 2008).

6. Why is the pharmaceutical industry getting away with it?

It is no coincidence that the growth of the colossus that is the pharmaceutical industry coincided with the election of Margaret Thatcher in 1979 in the UK, and Ronald Reagan in 1980 in the US. With these two uniquely determined and ideologically neo-liberal administrations came a new pro-market belief. Vast wealth and profit were symbols of an industry functioning effectively, almost irrespective of therapeutic or product innovation.

‘This government accepted unchallenged the perspective that markets could solve our ills; regulatory reform was never deemed a priority and discussion on it fell silent’

The Thatcherite neo-liberalism that dominated UK and international politics in the 1980s continued under New Labour in regard to its treatment and regulation of a number of key sectors – most notably finance, public services and pharmaceuticals. While progress was made early on under the Labour government with interventions like NICE – providing guidance and information – the underlying principle that markets serve the public interest held sway. The pharmaceutical industry has benefited, in terms of market growth, from this political ideology and as a result it has dominated discourses of medicine; however, it is now failing. This government accepted unchallenged the perspective that markets could solve our ills; regulatory reform was never deemed a priority and discussion on it fell silent. Blair promised to protect the industry and he seemed happy to allow market forces to determine health. The checks and balances that are necessary to ensure that the profit motive also encourages therapeutic innovation are not there, allowing the situation to continue, relatively unrestrained.

When looking at this regulatory structure there are a number of issues to consider, most notably within the MHRA (for a discussion on the current regulation see appendix 2).

The Medicines and Healthcare products Regulatory Agency

Bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA) are commonly set up in response to a public outcry. When such a regulatory group is created to defend the interests of the public against the excesses of an industry this is the start of a life cycle. At this point the regulatory authority is commonly adversarial towards the industry it is regulating. However, over time the regulatory authority becomes more closely aligned to the industry and begins to represent industry desires over the needs of the public.

While efforts have been made to ensure its transparency in the MHRA – for example most recently through ensuring employees’ families do not have shares in or relations with companies regulated by the MHRA – these efforts have failed to address inherent problems in the original structure of the agency.

First, the MHRA is funded through licensing fees from the pharmaceutical industry. It is arguable that this is common in other industries, but what is unusual is that the MHRA is also in competition for licensing fees with other bodies across Europe, specifically the European Medicines Agency (EMA), which offers pan-European licensing. This has created a situation where the prosperity and institutional viability of the regulatory agency depends on its ability to attract fees from the pharmaceutical industry, not on its ability to meet public needs for safe, effective medicines.

As it is the role of the MHRA to act in the public interest this pressure from the industry could be seen as damaging to its independence and integrity. This can be demonstrated in the pressure placed on the MHRA to speed up the licensing process. In 2003 the time from application to the granting of a licence of a new molecular entity was approximately 70 working days, by 2005 a response could usually be expected in approximately 30 working days.¹⁵⁴

Second, the information seen by the MHRA is almost wholly industry-sponsored trials, so it

¹⁵⁴House of Commons Health Committee (2005) *The Influence of the Pharmaceutical Industry*.

could be argued that the information that is assessed by the regulator is already biased, as has been demonstrated in the discussion of clinical trials. The MHRA has rigorous standards for ensuring that the trials it assesses are of a high quality, however, it is argued that irrespective of the quality of the trial bias is still very apparent.¹⁵⁵

Third, there is no pressure from the MHRA or requirement for the companies to demonstrate that their drug is therapeutically more effective than medicines currently available. Companies are not required to undertake comparative drugs testing nor are they required to demonstrate medical need. This could be seen to be contributing to the growth of me-too drugs.

Fourth, it is also the role of the MHRA to regulate medicines post-licence. However, as funding for the MHRA comes from licensing fees, the MHRA has limited incentive and limited funds to regulate post-licensed medicines effectively. Post-licensing surveillance of drugs is notoriously problematic, with the widely recognised gross under-reporting in the yellow card system (see appendix 2).

With a more rigorous regulatory structure these problems could be reduced or eliminated.

The MHRA in recent years has made significant progress; however, there are still issues to address and pitfalls to be avoided. This report advocates a number of steps necessary to ensure safe and effective medicines make it to market:

- The MHRA should carry out random testing of the raw data provided by the industry.
- All clinical trials for any drug licensed globally should be registered before the trials start, ideally on an international register, but a register could also work on a national level. This report would also argue that on registration the design of the trial should be made available to the scientific community for scrutiny. Although this report is aware that this may be seen as commercially problematic, most drugs have already completed a patenting process by phase 2 clinical trials, so transparency in phase 3 clinical trials would not be commercially difficult.
- The clinical trials necessary for licensing should include information on comparative efficacy. This would need to be a mandatory requirement on drug companies applying for

a licence to continue testing into phase 4 clinical trials looking for efficacy of drugs and long-term effects of drugs in communities.

- Additional funding could be provided for the MHRA from the Department of Health; this money should be ring fenced for post-licensing surveillance. We could consider increasing government funding of the MHRA to at least 60% of the total money it receives to reduce industry influence.
- Competition between regulatory bodies in Europe should be reduced, for example through greater engagement in pan-European regulation and licensing.

The Pharmaceutical Price Regulation Scheme

The current Pharmaceutical Price Regulation Scheme (PPRS) is recognised internationally as a method of ensuring a fairer price, but in a recent Office of Fair Trading report it came under fire; the report argued that there is a major question as to whether value for money is being secured.¹⁵⁶

There are a series of inherent problems in the scheme:

- The effect of the price cut secured every five years reduces over time as drugs that have been subject to a cut are replaced by new drugs at uncontrolled prices.
- The effect of the cut on hospital prices is not clear, as the PPRS affects list prices rather than the transaction prices at which hospitals purchase.
- The PPRS does not provide the incentives for cost in relation to therapeutic efficacy.
- The PPRS is linked to the profits of a drug not its efficacy.

Although this report welcomes the price cuts guaranteed through the PPRS we would support the OFT's proposals to replace the PPRS with a value-based system. This would cut costs in the short term but more importantly incentivise therapeutic innovation in the pharmaceutical industry in the longer term. With appropriate investment of the estimated £500 million per annum savings there could be much greater support for public research.

155. Smith, R. (2005) 'Medical journals are an extension of the marketing arm of pharmaceutical companies', *PLoS Medicine*, 2(5). www.aliveandwell.org/docs/richard_smith_medical_journals.pdf (accessed 7 July 2009).

156. Office of Fair Trading (2007) *The Pharmaceutical Price Regulation Scheme: An OFT Market Study*, www.of.gov.uk/shared_of/report_s/comp_policy/oft885.pdf (accessed 20 July 2008).

The National Institute for Clinical Excellence

For the NHS, as with any healthcare system, independent information on efficacy is essential, and the National Institute for Clinical Excellence (NICE) has provided this to a high standard over the last ten years. It has ensured that the best knowledge on medical technologies and procedures is available to the general public and medical professionals. This is not to say it is perfect, but despite the problems discussed below it must be recognised that NICE has had an essential role in improving the body of knowledge available.

The major obstacle for NICE is that in practice its guidelines are not always instigated quickly enough or universally. This has caused serious acrimony between NICE and patient groups keen to see a specific medicine available on the NHS. More worryingly, however, it has no power to enforce its suggestions and even lacks the power to be allowed to see all the relevant information.

Increasingly there is criticism of NICE's decisions by patient and professional groups as well as the industry, specifically because of the slow release of data and the perceived unfairness of its decisions.¹⁵⁷ Furthermore, NICE's decision-making process is often far from transparent.

Perhaps the most important function for NICE is its ability to assess efficacy and cost. It is the last barrier against the industry crippling the NHS through excessive prices, yet it is also crippled by lack of funding and lack of power to enforce its decisions.

This report therefore recommends that:

- there should be an increase in NICE funding to support its research into public health guidelines
- NICE should be granted access to all data given to the MHRA for licensing; currently NICE often struggles to make accurate decisions because it does not have access to all the relevant information
- NICE should assess the quality of information it receives, specifically the clinical trial data
- there should be far greater transparency of its decision-making process.

The current model is not sustainable; industry and government, nationally and internationally,

should engage a new model of innovation. Drug development can be more effective through improved supervision, the creation of a more mixed economy and additional funding for independently supported research, and we can hope that health innovations will follow.

157. House of Commons Health Select Committee (2007) *National Institute for Health and Clinical Excellence*, first report of session 2007-08, vol. 1, Stationery Office.

7. Policy recommendations

To make drug development innovative and humane, and improve the productivity of the pharmaceutical industry, there can be no doubt in anyone's mind that – as in the banking sector – reforms and regulations must be enacted on an international level. These companies are truly international entities, with markets and production lines that stretch across the globe. Diseases and disabilities that plague one country are not limited by national borders. Our response to these diseases and our regulation of these companies must be international.

The nation state is in many ways victim to the whims of these firms, dependent on them for the valuable export trade and in Britain for the knowledge economy. The ever apparent threat of a company moving abroad is commonly seen as a reason to retain light regulation (see appendix 1). This report would therefore strongly lend its support to an improved regulatory and supervision structure on an international level and would encourage a harmonisation of the European regulatory systems.

There are obstacles and powerful resistance to any reform of pharmaceutical industry practices – most notably from the trade bodies and the industry itself – but if it is the fundamental purpose of the pharmaceutical industry to produce therapeutic innovation and improve health, then action is clearly needed. Western governments and healthcare systems across the world risk bankruptcy with the escalating cost of drugs. The drugs the industry is creating offer increasingly minimal therapeutic rewards, and the industry is facing decline and perhaps even collapse. To ensure drug development continues and is successful in the future, effective regulation of the industry must focus on effective incentivisation for therapeutic innovation. However, this must go hand in hand with greater support for publicly funded independent research.

Throughout this report policy solutions have been suggested for long and short term reform. Further to these suggestions this report advocates **five priority proposals** essential for an improved national system, as discussed below.

Policy 1: Make a greater investment in publicly funded science

Hypothecate any savings made on the UK drugs bill with an additional £1 billion of funding for publicly supported science research by 2010-11, increasing the total funding from £1.7 billion to £2.7 billion each year. This money could be raised through the savings made from introducing a value-based pricing system, estimated to be £500 million per annum. While much can be made of Alan Johnson's achievements in price cutting,¹⁵⁸ this report argues that this still fails to incentivise therapeutic innovation actively. Therefore the report suggests that beyond the obvious arguments for price cuts the most pressing issue at this time is the cost of drugs in relation to their relative therapeutic efficacy. This report supports the Office of Fair Trading's proposals for reforming the PPRS. This would link therapeutic efficacy to price; in the short term it would reduce the NHS bill, and in the long term it would provide the right incentive for drug company's R&D investments. This would be a step towards ensuring efficacy and therapeutic innovation.

'This report would support ring-fencing the estimated saving made through the introduction of a value-based pricing system'

In recent years the government has taken steps to ensure that the UK remains at the forefront of drug development by increasing funding on health research; this funding is estimated to stand at £1.7 billion by 2010-11. This report would support ring-fencing the estimated saving made through the introduction of a value-based pricing system, which by 2010 could be £1 billion, based on estimated savings of £500 million per annum, assuming the scheme was introduced in 2009. These ring-fenced savings could be invested in greater publicly funded health research. This would effectively increase public funding for health research by 60% and put total government spending on health research at £2.7 billion – nearly equal to the industry's estimated investments in R&D. The government must now take action to guarantee that therapeutic innovation

158. BBC (2008) 'NHS drug costs to be renegotiated', <http://news.bbc.co.uk/1/hi/health/6927814.stm> (accessed 6 July 2009).

continues by investing in publicly sponsored research. This not only improves the scientific base, and our potential to make therapeutic breakthroughs, but can encourage the pharmaceutical industry to invest in the UK.

Policy 2: Make clinical trials open to public scrutiny

Independent scientific information is essential for the future of modern healthcare and the future of the pharmaceutical industry. For this reason it is essential that all phase 3 trials be carried out independent from the industry. These could be funded through an industry levy. This proposal was initially put forward by Professor John Abraham from Sussex University and Helen Lawton Smith in their book *Regulation of the Pharmaceutical Industry*,¹⁵⁹ as it would ensure independence and allow greater scrutiny and accessibility to the necessary clinical trial data. Further, any trial used for licensing must have been registered before it was started, as is currently the case in the US.

Policy 3: Educate doctors through public funding

For doctors, independence, transparency and freedom from bias are essential. This report has highlighted how this is impossible because of industry funding and influence. This report would therefore support there being greater investment in independent education for doctors and other medical professionals. The current spending by government on information for doctors stands at about £5 million. This report argues that this figure needs to increase to £10 million, as doctors currently struggle to deal with often conflicting advice. The report would also support other measures to limit industry influence, such as banning or limiting industry contact with doctors.

Policy 4: Review progress made since 2005 Health Select Committee report

The 2005 Health Select Committee report was the largest of its kind.¹⁶⁰ Enacted over eight months it

explored the reality of the pharmaceutical industry and proposed a series of sensible policy proposals, including strengthening the power of the MHRA, a curb on the intensive marketing by the industry, and an adoption of a national drugs policy. However, for this report to be most effective a review of the progress that has been made since its publication is essential and therefore this report would lend support to such a review.

Policy 5: Control pay and bonuses

Control pay and bonuses so that executive rewards and share options do not disfigure the product market as they did in financial services. Compass will be calling on the government to establish a pay commission to adjudicate on pay in key industries such as the pharmaceutical industry and the financial sector.

¹⁵⁹. Abraham, J. and Lawton Smith, H., eds (2003) *Regulation of the Pharmaceutical Industry*.

¹⁶⁰. House of Commons Health Select Committee (2005) *The Influence of the Pharmaceutical Industry*.

Conclusion

This report has traced the history of the pharmaceutical industry. It tracked its rise as a symbol of new capitalism, and the power of the market to innovate. It looked at its successes and failures. The report is a story of an industry and a story of changing times in which the truths of the past are called into question. While the report is in no way conclusive, or definitive it has challenged our understanding of the industry and shown that although its socioeconomic contribution to our economy remains strong, its contribution to our ability to fight disease and disability is shrinking. It is clear that if this story continues unchecked it will not have a happy ending.

The products sold by the industry are an essential part of modern day healthcare, but what we really need now are essential drugs and therapeutic innovations at prices we can afford. This is within the industry's and society's capabilities but the industry is failing to produce them. The government hoped to enlist the powerful force of the quest for profit to improve drugs development, but failed to regulate it effectively to ensure that health needs were met. The industry's legal responsibility to maximise shareholder value, to compete on the stock exchange, in the short term will eventually be its downfall, unless appropriate regulation is put in place. Declining trust and innovation show that this model is unsustainable. Simultaneously, the rising costs will damage the healthcare potential of the NHS and other systems across the globe – evidence of this can already be seen in the impending collapse of Medicare and Medicaid in the US.

The picture the industry painted of itself was one of innovation, science and the promotion of health – certainly at a cost, but that cost was deemed to be necessary. What this report has shown is that the industry's image should be challenged.

In expecting these companies, this industry, to act charitably we fail to grasp the fact that we have created a market in health where investment is not decided by need, but by profitability. This report explored where this has led us, it looked at the current state of the industry and proposed a number of policy solutions to a number of

concerning problems. What is overwhelmingly clear is that the current situation cannot be allowed to continue. It must now be a priority to put in place the necessary structures, incentives and regulations to ensure that it is not just profit that determines the actions of this industry but therapeutic innovation.

'Just like financial services, if markets are left too free for too long then eventually they self destruct. This cannot be allowed to happen in the market for the creation of drugs'

In the midst of a recession, with many areas of our economy struggling, the pharmaceutical industry needs to be saved from itself. Just like financial services, if markets are left too free for too long then eventually they self destruct. This cannot be allowed to happen in the market for the creation of drugs. Indeed, the myth of the free market – given the levels of public investment – needs to be quashed. If Britain is to have a strong pharmaceutical industry that delivers social benefit in the future, it is incumbent on politicians and the regulatory regimes to intervene now to ensure productivity and innovation accelerate at least as fast as pay and profits.

Appendix I

Will the pharmaceutical industry leave the UK?

Talk of altering regulatory structure is commonly followed by threats that the industry will jump ship and move its valuable R&D investments elsewhere. The Office of Fair Trading report in 2007 suggested that this threat is unlikely to be carried out and that there were five key factors that affect location of R&D investment:

- a highly skilled workforce with relevant scientific qualifications
- the presence of opinion leaders in the medical field
- access to high-quality clinical trials infrastructure
- existing R&D activity, including public sector R&D
- historical and cultural factors.¹⁶¹

Based on these key areas it is clear that the UK is and will remain a very favourable environment for investment, for the following reasons.

First, the UK has a highly skilled workforce. Britain, geographically and logistically, is well positioned to attract the right employees and to access its key markets, the US and the EU.¹⁶² With a strong university structure it is a highly competitive environment. For example, AstraZeneca has over 2,000 highly qualified UK staff working in its eight key sites dedicated to research, clinical trials and manufacturing. This represents not only a significant supply of highly skilled workers but also billions in sunk costs.¹⁶³ The other large investor in UK pharmaceutical R&D is GlaxoSmithKline, which employs almost 8,000 highly qualified research staff.¹⁶⁴

With the growth of the emerging markets of India and China it is increasingly feared that the pharmaceutical industry will move abroad, and indeed in terms of clinical trials India is attractive. GlaxoSmithKline has already moved a third of its trials there. However, it is argued that any full-scale move is highly unlikely given that

spending on science is too low and any innovation is unorganised.¹⁶⁵ Further, as only 10% of Indian graduates are qualified to the same level as their western counterparts,¹⁶⁶ there are significant issues with the economic and business set-up, so India is not as attractive as the west. The World Bank states that India is only the 134th 'easiest' country in the world to do business in,¹⁶⁷ and according to Bound (2007) corruption is still rife and the infrastructure is the burden of the private sector¹⁶⁸ rather than centrally funded by public spending. All of this ensures that the UK will remain a highly preferable space for investment.

Second, the presence of opinion leaders in the medical field. The UK has a strong history of pharmaceutical R&D and a strong history of scientific innovation. It has world-leading universities, including Oxford, Cambridge, LSE and Imperial College London. With these world-leading universities are world-leading experts in pharmacology and medicine.

Third, access to high-quality clinical trials infrastructure. Perhaps one of the first areas to move out of the UK if R&D investment is located elsewhere would be clinical trials; the UK is second only to the US for the cost of R&D. Although the US previously had relatively low levels of regulations, which would attract drug makers, regulation of the US industry is changing the appeal of conducting clinical trials there. Following the errors of Vioxx, found to increase cardio-vascular risks to users,¹⁶⁹ the FDA has strengthened the standards of research presented to adjudicate a drug's suitability.¹⁷⁰ High levels of regulation in clinical trials are essential and costly, but this is balanced in the UK by greater access for the pharmaceutical industry to NHS patients for clinical trials.

Fourth, existing R&D activity, including public sector R&D. Casper and Mataves argue that institutional start-ups, including the small biotech firms we see growing in and around British universities and research, foster innovation and 'encourage rapid responses to changes in the competitive environment'.¹⁷¹ These start-ups are making 'radical innovations'¹⁷² and this existing R&D activity is highly attractive to the pharmaceutical industry. Furthermore, any

161. Office of Fair Trading (2007) *The Pharmaceutical Price Regulation Scheme: An OFT Market Study*.

162. Hawkes, A. (2008) 'Companies leaving the UK: what will we lose?', *Accountancy Age*, www.accountancyage.com/accountancyage/comment/2216638/companies-leaving-uk-lose (accessed 19 August 2008).

163. AstraZeneca (2006) *The Economic Contribution of AstraZeneca to the UK and its Regions*, www.astrazeneca.co.uk/documents/AstraZeneca-Ecoal-09-08-06.pdf (accessed 19 August 2008).

164. GlaxoSmithKline (2004) press release, 14 March, www.gsk.com/press_archive/press_2004/press_03162004.htm (accessed 28 August 2008).

165. Bound, K. (2007) *India: The Uneven Innovator*, Demos.

166. *Ibid.*, p.21

167. *Ibid.*, p.57.

168. *Ibid.*, p.58.

169. MSNBC (n.d.) *The rise and fall of Vioxx*.

170. FDA (2008) *Federal Register*, 73(82), 28 April, Rules and Regulations, www.fda.gov/Cber/rules/forclinstud.pdf (accessed 1 September 2008).

171. Casper, S. and Mataves, C. (2003) 'Institution frameworks and innovation in the German and UK pharmaceutical industry', *Research Policy*, 32, p.1872.

172. *Ibid.*, p.1867.

perceived damage done to the industry through changes in regulation would be more than offset by investments into publicly funded research.

Again, the difference between western markets and the emerging markets is clear; China is expanding its R&D spending and we are also seeing the return of students with valuable links to Europe and the US.¹⁷³ However, in China western companies often 'exist more on paper than in reality', as Chinese authorities, cautious over their presence, are not friendly to any full-scale moves.¹⁷⁴ That said, investment in specific areas is taking place. In 2007 GlaxoSmithKline established its first 'fully integrated research institute in China'¹⁷⁵ and Novartis has spent \$100 million in biomedical science research units.¹⁷⁶

However, the lack of democratic ownership over innovation presents massive risks to corporations that have to stay onside with the Chinese government. As in India, basic issues remain with the quality of China's graduates, scientists, infrastructure and universities, while leading research centres are becoming established seeing investment by giants such as Novartis going beyond these centres 'standards plummet'.¹⁷⁷

Fifth, historical and cultural factors. The companies that currently invest in the UK have their roots here and are intimately connected with UK institutions. For example, GlaxoSmithKline is well entrenched, and champions its involvement with Imperial College London and works with them on '450 PhD studentships and more than 200 postdoctoral research collaborations'. GlaxoSmithKline describes the importance of being able to work with Imperial, and sees the University as 'a world leading science-based university whose reputation for excellence in teaching and research... [is] underpinned by a dynamic enterprise culture'.

No one can know ultimately whether a company or industry will stay or go. Each company will always weigh up the positives and negatives; it will decide whether or not one area is more favourable than another. However, as this section has shown, in terms of leading experts, skilled workers and existing R&D infrastructures the UK remains a favourable environment for R&D. Furthermore, the suggested reforms that this report has put forward can only improve the UK as a site of investment. But also it makes clear

that for regulation to be effective, because of the geographic mobility of the pharmaceutical industry it must ultimately be internationally harmonised.

173. Wilsdon, J. and Keeley, J. (2007) *China: The Next Science Superpower*, 174. *Ibid.*, p.39.

175. GlaxoSmithKline (2007) *Annual Report 2007*, www.gsk.com/investors/rep07/annual-report-2007.pdf (accessed 19 August 2008).

176. Science (2006) 'Novartis invests \$100 million in Shanghai', editorial, *Science*, 314, p.1064.

177. Wilsdon, J. and Keeley, J. (2007) *China*, p.60.

Appendix 2

Existing regulation

Pharmaceutical regulation is complex and there are numerous policies and bodies that can influence the behaviour of the pharmaceutical industry. To assist in the understanding of this report here is a short discussion on the three central ones; the MHRA, NICE and the PPRS.

The Medicines and Healthcare Products Regulatory Agency

Created in April 2003 the MHRA replaced the Medicines Control Agency (MCA) as the UK's licensing authority. The MHRA is an executive agency of the Department of Health and responsible for regulating and licensing pharmaceutical products in the UK. Since 1989 licensing and post-licensing monitoring of medicines has increasingly been funded through licensing fees from individual pharmaceutical companies as part of a Thatcherite move to privatise the civil service. Licensing decisions are based on clinical trial data provided by the manufacturers of the drug on the safety, quality and efficacy of their product under the Medicines Act 1968. The MHRA is also responsible for regulating medicines post-licensing; this is carried out through the yellow card system in which adverse reactions to medicines are reported to the MHRA by doctors, nurses, pharmacists and most recently patients themselves.

The MHRA was originally dogged with controversy over its lack of transparency and an overly close relationship with the pharmaceutical industry. However, over the last few years it has striven to increase transparency and openness. For example, since November 2005 staff and immediate members of their families have no longer been allowed any financial or other interests in the industry to ensure unbiased evaluations. The MHRA is aware that there are limits to its current framework and has announced a review, which will be reported in 2009. Yet with the international nature of the industry, the MHRA's ability to regulate appropriately is limited by the European context.

Regulation in the UK always sits within a European regulatory context and for pharmaceuticals this is controlled by the Commissioner for Enterprise and the Commissioner for Health and Consumer Behaviour. Although these two departments rarely see eye to eye, the most interesting feature of this is the European Medicines Evaluation Agency (EMA). The EMA offered the possibility of a pan-European drug product licence from January 1995. This meant that for a drug to be licensed in the UK it is not always necessary to go through the MHRA. When a pharmaceutical product gets a pan-European product licence; the UK government has less ability to manage which products can come onto the UK market. NICE has partially counteracted this through its role in reviewing the merits of drugs on clinical and economic grounds and helps decide whether or not the product should be available to patients through the NHS.

The National Institute of Clinical Excellence

In 2009 NICE has been the subject of much controversy; it is increasingly presented as a rationing body and attacked by its opponents. However, at its inauguration in 1999 NICE was generally welcomed as a highly positive intervention.¹⁷⁸ Globally healthcare systems have struggled with a deficit of clear advice about cost and clinical effectiveness.¹⁷⁹ The NHS is perpetually confronted with numerous, and often contradictory, pieces of advice on the use of drugs and other medical technologies. Before NICE there was no consensus, advice or guidance on new drugs that entered the market other than that provided by the industry.¹⁸⁰ There was also a significant deficit of independent information on the relative efficacy of drugs – how effective a drug is in relation to other available drugs.

The Pharmaceutical Price Regulation Scheme

The PPRS was introduced in 1957 and is generally reassessed every five years. It was designed to limit the cost of drugs through profit and price controls. It was originally constructed

178. Walley, T., Earl-Slater, A., Haycox, A. and Bagust, A. (2000) 'An integrated national pharmaceutical policy for the United Kingdom?', *British Medical Journal*, 321, pp.1523–6.

179. House of Commons Health Select Committee (2007) *National Institute for Health and Clinical Excellence*.

180. Dent, T.H.S. and Adler, M. (2002) 'From guidance to practice: why NICE is not enough', *British Medical Journal*, 324, pp.842–5.

to ensure value for money for the NHS as well as providing the necessary long-term incentives for the pharmaceutical industry to invest in new and useful drugs for the future.

Without this sort of price regulation drug companies can increase the price of their drugs unchecked. An example in the US is that the price of Schering-Plough's top-selling allergy pill Claritin was raised 13 times over five years before its patent ran out; this was a cumulative increase of more than 50% and was over four times the rate of general inflation.¹⁸¹

Price controls are necessary to ensure value for money and that the cost of drugs does not bankrupt the NHS. Annually the NHS spends nearly £11 billion a year on pharmaceutical treatments, £8 billion of which is on branded drugs.¹⁸² The PPRS is currently the only effective method of ensuring price controls on the money spent on branded drugs in the UK.

At a basic level the PPRS has always functioned in two ways:¹⁸³

- **Through price controls:** these allow companies to set the initial price for any new active substances but impose restrictions on subsequent price increases. Price controls are combined with price cuts, which are agreed through renegotiations with the Department of Health. Once price cuts are negotiated each company is given flexibility in deciding which of its products to target in cutting prices; this system is called price modulation.
- **Through profit controls:** these set out a maximum level of profits that a company may earn from supplying branded drugs to the NHS. When this level is exceeded companies are required to repay any excess profits to the Department of Health. The profit controls also allow companies to increase prices if their profits fall below a given minimum.

The Department has published data on the profits repaid for the period 1992 to 1999 in its departmental reports to parliament (table 5).

In 1999 the basic structure of the PPRS changed: companies were allowed a greater margin for error in the profit controls so less money was refunded for excessive profits. At the same time the Department of Health introduced price cuts to the amount it was paying for certain

drugs from the industry. This changed the main focus of the PPRS to price reductions; in 1999 it made a reduction of 4.5% and in 2005 a reduction of 7%. It is argued that these reductions have delivered a greater level of saving than repayments of excess profits. For the NHS, PPRS price cuts have delivered savings in primary care; these amounted to about £450 million in the UK in 2005.¹⁸⁴ However, year on year these savings are lost as the medicines covered by the price cuts are replaced by newer, more expensive medicines.

Table 5 Total refunds from profit controls to the NHS, 1992–1999

Year	Total refunded (£m)
1992	£25.4
1993	£15.8
1994	£34.3
1995	£14.5
1996	£15.5
1997	£12.2
1998	£7.2
1999	£16.6

181. For further information on the burden of rising drug prices, see Families USA (2003) 'Out-of-bounds: rising prescription drug prices for seniors', www.familiesusa.org/site/PageServer?pagename=Publications_Reports (accessed 1 September 2008).

182. Office of Fair Trading (2007) *The Pharmaceutical Price Regulation Scheme: An OFT Market Study*.

183. Ibid.

184. Ibid.

Glossary of acronyms

ABPI	Association of the British Pharmaceutical Industry
ADHD	Attention Deficit Hyper Activity Disorder
BMJ	British Medical Journal
CRO	contract research organisations
CSM	Committee on the Safety of Medicines
DTCA	direct to consumer advertising
EMA	European Medicines Agency
FDA	Food and Drugs Administration
MHRA	Medicines and Healthcare products Regulatory Authority
NHS	National Health Service
NME	new molecular entity
NICE	National Institute of Clinical Excellence
OFT	Office of Fair Trading
PPRS	Pharmaceutical Price Regulation Scheme
RCT	randomised controlled trial
R&D	research and development
SSRI	selective serotonin reuptake inhibitor

“The Compass report is a timely and important critical examination of the appropriate role for the pharmaceutical industry in our society and in contributing to public health. It poses significant challenges to the industry, the UK government, the medical profession and patient organizations about how pharmaceuticals can meet the needs of UK citizens and the NHS more effectively.”

Professor John Abraham, University of Sussex, and Expert Advisor to the House of Commons Health Select Committee.

“This is an impressive report, which addresses high priority issues for the British pharmaceutical industry, the NHS, and government policy for health and industrial development. It asks hard questions and puts forward challenging policy proposals which deserve serious consideration.”

Professor Richard Ashcroft, Queen Mary University London

“This sober and well documented report must be read by all health policy makers, medical practitioners, persons working in the pharmaceuticals industry, public policy commentators - and indeed anyone who cares about their own health. While over-reliance on pharmaceuticals is one of the problems produced by the power of the industry, we still need a growing supply of effective, safe, properly tested, and innovative medicines. This report shows that, as the sector is currently structured and regulated, it is under-achieving on all these points. Action is urgent needed before we have a full crisis on our hands.”

Professor Colin Crouch, University of Warwick Business School

“Free markets work well for shoes and toothbrushes, but for life saving drugs we need people to come before profits. But the deregulation of the pharmaceutical market is failing not just people but profitability too. Something has to be done. Jon Cruddas and Zoe Gannon’s report tells us what is wrong and more importantly tells us how we can start to put it right. This is an area where government intervention would be timely, productive and popular. Otherwise the pharmaceutical industry could drag down the economy just like the deregulated banks did.”

Neal Lawson, Chair of Compass