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ABSTRACT

This article examines how sociology can contribute to an understanding of the work, power and impact of the pharmaceutical industry. Drawing in particular on Latour's theoretical and empirical analysis of science, in conjunction with a more explicit consideration of power, it examines the scientific 'fact making' involved in the clinical trials of drugs designed to assess their safety and effectiveness, assessments that are the basis for securing approval for their release onto the market. It also examines post-approval drug assessments and the fuller evaluation of a drug that emerges with time. It shows how the industry's control over this science, especially in the pre-approval stage, has helped to encourage extensive, and often excessive, use of pharmaceuticals.

KEY WORDS

clinical trials / drug approval / pharmaceutical industry / power / science

The pharmaceutical industry is now a major global industry dominated by multinational companies selling their products across the world. Sales of pharmaceutical products in 2003 amounted to just over $466 billion (IMS Health, 2004a), more than the GNP of many developing countries, and the consumption of prescribed medicines in advanced industrial societies is high and increasing. In England, for instance, the number of prescriptions issued by the National Health Service (excluding hospital prescriptions) has increased from an average of eight per person in 1989 to 12.5 in 2002 – an increase of 56 percent (Department of Health, 2000, 2003). This is more than one prescription per month on average for every year of a person's life.

The leading pharmaceutical companies all have head offices in advanced industrial societies, and their hold on the world market is increasing. Whereas in 1992 the top 10 companies accounted for roughly one-third of global pharmaceutical revenue (Tarabusi and Vickery, 1998), after a period of consolidation, by 2001 the top 10 accounted for nearly half (ABPI, 2003). Most of their revenue comes from patented drugs, the standard patent now lasting 20 years, although under certain circumstances patents can be extended.[1] The US is the largest market for pharmaceuticals, accounting for just under half of world revenue in 2003 (IMS Health, 2004a), and in 2004 six of the top 10 companies were based in the US: Pfizer, Merck & Co, Johnson & Johnson, Bristol-Myers Squibb, Abbott and Wyeth (IMS Health, 2004b). The other four had European headquarters: GlaxoSmithKline and AstraZeneca based in Britain; Novartis in Switzerland; and Aventis, based in France. Aventis merged with Sanofi-Synthelabo in 2004, which made the combined company the sixth largest (IMS Health, 2006) and give the top 10 over half the global revenue. All 10 are highly commercial companies, have high profit levels (Moncrieff, 2002), and are major contributors to their national economies in terms of employment and export income (Harrison, 2003), although their manufacturing is more widely distributed than their research and development (R&D) (Busfield, 2003). In order to protect the flow of new drugs crucial to profitability, the companies are also entering into alliances with the smaller biotechnology companies, which now contribute to the research that leads to marketable drugs.

In addition, there are pharmaceutical companies in developing countries; the most important are located in India, Brazil and China. These countries are increasingly being pressured to accept World Trade Organization requirements on intellectual property and the companies largely concentrate on the production of 'generic' drugs that are out of patent. Generic pharmaceutical companies are less profitable than those producing patented medicines, but can still be important to a national economy. Moreover generic drugs are of increasing importance in world markets in terms of sales *volume* (IMS Health, 2004c), partly as a result of service funders' pressure on doctors to prescribe them where possible, and their use potentially poses a threat to leading companies' profits. Consequently some have entered into partnerships with generic companies or, in some cases, taken them over.

Yet despite the importance of the industry as a productive activity to national economies and international markets and its role in patterns of consumption, it has received surprisingly little sociological attention. Sociologists of health and illness have done some research on pharmaceutical regulation (e.g. Abraham, 1995; Abraham and Lewis, 2000), on the controversies around specific preparations that draw on the sociology of science (e.g. Brown and Funk, 1986; Bury and Gabe, 1996), and rather more on medical prescribing (e.g. Britten, 2001; Weiss and Fitzpatrick, 1997), but the industry is rarely mentioned in key textbooks in the field.[2] The lack of interest in the industry (but see Conrad, 2005) may spring from the field's origins as a sociology of medicine

and, in Britain, from the focus on the experience of illness, itself perhaps a reflection of the sociological tendency to focus on the powerless rather than the powerful. Yet even if the omission of work on the industry within this field is explicable, one might expect it to feature in other sociological areas.

Rather surprisingly, notwithstanding the industry's importance to the global economy, standard sociological discussions of globalization have not used the industry as a case study (Busfield, 2003). Nor do sociological analyses of consumption discuss medicines as a major consumer good, even though they are open to many of the analyses of the construction of desires and wants as other goods. Perhaps this is because the medical prescribing that mediates between the industry and consumers makes medicines seem less obviously governed by consumer choice. Pills also belong to the category of 'inconspicuous consumption' (Warde and Shove, 1998), items that are not part of any visible display and have received less sociological examination. Nor does the use of psychotropic medication feature in Giddens' (1991) discussion of anxiety and risk and the 'reflexive project' of the self, which he sees as key features of late modernity, even though the widespread use of psychotropics could be regarded as a marker of that anxiety. Significantly, sociologists and historians of science have paid more attention to medical technologies in the form of machines such as x-rays (Howell, 1995) and newer imaging devices (Blume, 1992) than to drugs.[3]

Greater attention to the industry is crucial for several reasons. First, as I have indicated, the industry is a major power within the global economy and some national economies. In Britain, for instance, the two global pharmaceutical companies, GlaxoSmithKline and AstraZeneca, ranked fourth and sixth in the FTSE top-100 companies in terms of market capitalization in 2004 (*Observer* 1.8 04).[4] Second, the industry is a major force shaping health care in many societies, with the prescribing of medicines a dominant feature of medical care. Third and related to this, there has been a significant cultural shift in which people increasingly see medicines as a way of solving a wide range of problems, which are transformed into illnesses, instead of seeing them as a possible solution for a narrower range of physical sicknesses.[5] Pill taking has become a key feature of life in late modern society that looks set to continue into the future, even though the health of populations in such societies has generally improved – improvements that cannot largely be accounted for by the greater use of medicines (Colgrove, 2002; Lichtenberg, 2003; McKeown, 1976).[6]

I seek in this article to consider how certain sociological ideas and understandings can inform discussions of the increasing power and influence of the pharmaceutical industry. I approach the industry with a degree of scepticism, not just the usual scepticism about the industry's relation to developing countries – its reluctance to focus on their health problems and its unwillingness to sell them vital drugs at affordable prices – but a scepticism about the very widespread, and I suggest sometimes excessive, use of pharmaceuticals in advanced industrial societies. This scepticism is not grounded in any general claim that modern therapeutic drugs have little value. Many are invaluable,

especially in the treatment of severe illnesses. However, to recognize this is not incompatible with the claim that drugs are frequently used indiscriminately – antibiotics are an obvious example.

There are three aspects to this indiscriminate use. First, pills are frequently taken by those whose problems would be better dealt with by other means and for whom they have little or no benefit and may lead to unwanted side effects – an example would be the very extensive use of psychotropic medication. Second, pills are frequently produced and prescribed in dosages that are far too high. And third, even if initially necessary, pills are often prescribed for too long a period of time. My argument is that an industry in the business of meeting health needs in fact creates a culture in which the use of drugs is encouraged even when this is unhelpful, counterproductive and even harmful. This is not just a matter of the industry's promotional activities but also arises because of its contribution to the science on which judgements of the safety and effectiveness of drugs are made. Drawing on the work of sociologists of science, this article examines the science underpinning drug evaluation.

Many sociologists will be familiar with Latour's influential book, *Science in Action,* first published in 1987, in which he develops an interesting analysis of how scientific facts are constructed. Whilst the notion of social construction is now commonplace in sociology, theoretical understandings of construction vary enormously. What is important about Latour's study is that he provides an analysis of the social processes involved in the construction of facts – fact making – that goes beyond those of other writers, and is informed by empirical studies of work in scientific laboratories. His concern is not with the products of science: 'a computer, a nuclear plant, a cosmological theory, the shape of a double helix, a box of contraceptive pills, a model of the economy' (1987: 21). These are the accepted facts of science – the 'black boxes' that have been closed.[7] Instead, his concern is with examining the black boxes before they were closed: 'science in the making'. This he sees as involving a whole series of uncertainties, controversies and alliances between actors – a term he uses to embrace things as well as people. These activities include research in the laboratory, the development of networks and the production of scientific papers. He identifies a range of devices and procedures involved in fact creation, skilfully analysing the rhetorical devices used in academic papers, the use of citation, the creation of allies, as well as the 'trials of strength' between the different protagonists that can lead to the closure of a black box. He also argues that whether the box remains closed depends on the activities of others – its fate is in users' (in the broadest sense) hands: 'Buying a machine without question or believing a fact without question has the same consequence: it strengthens the case of whatever is bought or believed' (1987: 29).

Viewing pharmaceutical products as new technologies, we can draw on certain aspects of Latour's analysis to examine how the industry contributes to the construction of scientific facts about new drugs; how it helps to ensure they are judged safe and effective by drug approval agencies, so closing the black box for many people; and consequently, how once launched onto the market,

companies are in a relatively powerful position to keep the box closed and to encourage a drug's use, often well beyond its useful boundaries.

A common criticism of writers such as Latour is that they do not pay enough attention to issues of power. The point is not that power has no part in the analysis; indeed, Latour's language is redolent of power with his reference to trials of strength, actors' interests and so forth. But, as with symbolic interactionism, we are not offered much in the way of a structural analysis of power. This is essential in any consideration of the pharmaceutical industry and is not, in my view, incompatible with Latour's approach. In this article I draw on two sets of ideas about power: first, Light's (1995) notion, adapted from Galbraith (1956), of countervailing powers; and second, Mann's (1993) discussion of sources of power. The force of Light's analysis is the observation that powers stand in dynamic relation to one another: power is not monolithic and the power of one body may lead to resistance and the reassertion of power by another. In the case of health services, the focus of his work, the key powers are the state (government), commercial companies, service users, and the medical profession. The sociological question pertinent here is how the balance of power operates between these groups at the different stages of the development and use of a drug. We also need to consider the sources of power in the industry. Following Mann's analysis, we can see the industry as potentially exercising three of the four sources of power he outlines: ideological, economic and political (but not military).

Applying Latour's analysis to the development of pharmaceuticals, it is helpful to consider two stages in the making of scientific facts about drugs. The first, pre-approval stage, is that leading up to, and including, the formal approval necessary for a drug's release onto the market. The second is that of post-approval evaluation. The first aims to establish a drug's safety and effectiveness in order to secure approval; the second involves a refinement of the assessment, relating to questions such as: For what conditions more precisely is it useful? What are its side effects if used long term? What is its value in treating less serious cases? I look at fact making during both stages and, moving beyond Latour's analysis, at the operation of power during each.

Stage 1: Pre-approval Drug Development

As Latour observes, much R&D in the scientific arena is carried out in industrial contexts – his overall figure is 70 percent (1987: 170). A similar percentage of pre-approval R&D is paid for and controlled by the pharmaceutical industry (Bodenheimer, 2000), leading companies spending around 15 to 16 percent of revenue on R&D (PhRMA, 2004a). Typically, initial development is carried out by laboratory scientists, particularly pharmacologists, but also medical researchers, employed either by the pharmaceutical companies or the newer biotechnology companies. The subsequent pre-approval testing is carried out either by the pharmaceutical companies themselves or is contracted out to the

new breed of commercial companies specializing in testing. The industry's control over R&D means that it plays the dominant role in fact making in the pre-approval period, which puts it at a major advantage when seeking approval for new drugs, including the power to select information to support their case and to withhold information that might undermine it (Harrison, 2003).[8] Using Mann's framework, we can see that the industry's fact-making activities constitute a form of ideological power, grounded in the industry's economic power; power that derives from the size of the companies, the profits they make and the resources they control, which enable them to fund the expensive R&D work. Consequently the industry's economic and ideological power are intertwined, economic power underpinning ideological power and ideological power in turn contributing to economic power.

Pharmaceutical companies' control over research is clearly manifest in the selection of the substances they seek to develop and test. Commercially the ideal product is one that can be patented, is used by a large number of people over lengthy periods, and can be priced quite highly in relation to production costs. This means that leading companies' R&D typically focuses on substances that could be used to treat the health problems faced by richer countries rather than on infectious diseases in developing countries. In 2003 the best sellers globally by revenue were two cholesterol-lowering statins, an anti-psychotic and a drug to reduce blood pressure (IMS Health, 2004d).[9] The competitive environment of the industry also means that companies frequently concentrate on finding a similar product to a competitor's, but one that is sufficiently different that it can be patented – so called 'me-toos'. A study of approvals by the US Food and Drugs Administration (FDA) between 1989 and 2000 showed that approvals for new drugs constituted only a relatively small proportion of all approvals, with only 35 percent of applications related to new chemical entities. The remainder involved active ingredients already available in marketed products (NIHCM, 2002).

Once the early development of a new preparation has been carried out, testing is necessary to establish its safety and effectiveness in order to secure the necessary approval for release onto the market. The FDA is the most important regulatory body for the world market, both because of the size of the US market and because approval in the US can affect the decisions of other regulatory bodies. The agency requires four types of testing for new drugs. These constitute the requirements for the scientific evaluation of a drug prior to licensing, which in effect takes the form of a cost (the side effects)–benefit (the health improvements) analysis. The first, pre-clinical testing, involves testing on animals 'to determine if the product is reasonably safe for humans, and if the compound exhibits pharmacological activity that justifies commercial development' (FDA, 2004). The focus is on toxicity, testing ranging from six months to a year. In addition carcinogenicity tests are carried out with rodents. Human testing involves three phases. Phase 1 involves testing the drug on around 20 to 80 *healthy* volunteers, to examine its metabolic and pharmacological actions, obvious side effects, and some data on effectiveness. Phase 2 consists of the first

controlled trials of the drug on patients, usually several hundred with the specific condition it is intended to treat. Finally, Phase 3 involves randomized controlled trials using the drug and a comparator or placebo. These clinical trials involve several hundred to several thousand patients and are designed to provide additional data about effectiveness and safety in a way that can be extrapolated to the general population and used in information given to doctors. Developing a new drug is a lengthy process and the time between the first identification of an active agent with therapeutic potential and formal approval is now around 10 to 15 years (PhRMA, 2004a). Since patents are secured well before approval, the industry has been keen to speed up testing and approval so that the time between approval and patent expiry is maximized, and the FDA approval time for new priority drugs declined during the 1990s with most approved within one year instead of two.

Following Latour, we can see the requirements outlined above as constituting the procedures necessary for the acceptance of the first scientific facts about a drug, and regulatory approval as providing the first point of closure in which the initial facts about safety and effectiveness are established. Once approved, the details of the testing become for many clinicians and the lay public the black box of complexity that no longer needs to be opened. The necessary scientific evaluation has been carried out, the drug's safety and effectiveness are accepted and it can be used in routine clinical practice: a cognitive closure results. This closure is most obviously evidenced by the very rapid uptake of many new drugs and from the off-license prescribing that frequently occurs. Many clinicians feel free to prescribe new drugs very widely – a tendency often exacerbated by patients who learn about a drug and are keen to use it. [10]

However, although for many people the black box is firmly closed once a drug is officially licensed, it needs to be noted that pre-approval testing is limited and the scientific facts contained in the black box are not well established. First, the animal testing to determine toxicity and carcinogenicity is restricted in scope, and there is evidence that with attempts to harmonize requirements internationally, testing standards are being lowered (Abraham and Reed, 2002). Second, companies select certain dosage levels to test and there may be little systematic effort to identify the lowest effective dosage (Cohen, 2001). Third, the length of testing involved is usually no more than a year, and often considerably less (the FDA does not specify the necessary length of testing). The short duration of trials is a double problem: some side effects may take time to emerge, and some may arise only as a result of longer-term use. When the tranquillizer, Halcion, was submitted for approval in Britain, the longest testing was on 60 patients who used the drug for only 91 days (Abraham and Sheppard, 1999: 29). Fourth, the drug is only tested on selected groups – normally adult men. There are good reasons for this (the thalidomide tragedy highlighted the dangers of some drugs for pregnant women), but the absence of trials on women, children and the elderly is a problem since their metabolisms usually differ – a point of particular relevance to dosage levels. The lack of pre-approval testing on the elderly is an especial problem since typically they make more extensive

use of drugs. And fifth, testing relates only to the condition specified in the approval application. This is reasonable, but it means that the drug is not tested for a broader range of patients, often with less clearly defined conditions for which it may actually be used in clinical practice. The restricted nature of clinical trials is the reason why some commentators have argued that pre-approval trials test a drug's efficacy – whether it has an effect in ideal conditions – rather than its effectiveness – whether it works under real-world conditions (Streiner, 2002).

There is a further, more fundamental problem with the testing: the freedom given to companies to demonstrate a preparation's value by carrying out the studies, selecting the tests and presenting the data in ways they choose. Assessing effectiveness involves comparison. A drug is more or less effective than something else and the selection of the comparator, the strength of the tested drug, and the measures of effectiveness, are crucial to the evaluation. Yet regulatory agencies do not specify the required comparisons, do not set standards for the necessary minimal clinical difference to demonstrate effectiveness, nor the indicators to be used. The chosen comparator can be a placebo with no active ingredient, an attractive strategy to highlight a drug's effectiveness, and small differences may be heralded as showing superior effectiveness even if they only make a minimal difference to a patient's condition.[11] Where the aim is to show that the new treatment is more effective than alternatives, the company may compare the new preparation with another available drug. Decisions have to be made as to which drug serves as the comparator and about the relevant dosage levels since this affects the trial results. Choice of a low dosage of the comparator can help to make the tested preparation look more effective. Equally, selection of a high dosage of the tested drug can make it appear more effective than comparators. Cohen (2001) has argued that the pressure to demonstrate effectiveness encourages the selection and subsequent licensing of high dosage pills where frequently a lower dosage would be almost as effective and have fewer side effects. Dosage selection is also crucial to assessments of safety. Since higher dosage products are likely to generate more side effects, this might suggest the biases cancel each other out: that the pressure to select high dosages of the tested drug to show its effectiveness is counterbalanced by the need to show its side effects are not too extensive. However, a drug's effectiveness often shows up quite quickly, whereas side effects may take time to appear. Consequently, given the relatively short length of pre-approval trials, the two pressures are not likely to be balanced.

As with effectiveness there are no absolute standards of safety. Whilst a drug known to produce fatalities would not normally be deemed safe, it may be acceptable for it to produce quite severe side effects in a very small proportion of patients, on the grounds that if these emerge treatment can be stopped. This is especially the case if the benefits may be considerable as with drugs for severe, potentially fatal, illnesses.[12] The task for the company is to show that a drug is just as effective as (or preferably more effective than) alternatives but has no worse, or fewer, side effects. Here companies are considerably advantaged by

the fact that they are permitted to obtain their own data and construct their own scientific case and have not been required to include data from all the studies that have been carried out.[13] This is despite the fact that various studies show that the results of industry-funded trials tend to be more favourable to a drug than independent studies (Davidson, 1986; Kjaegard and Als-Nielson, 2002). Companies can also decide how trial withdrawals are presented, which can affect test outcomes. Yet in other contexts, scientific work carried out under these conditions is seen as suspect, as when research on the MMR vaccine and autism was criticized as 'poor science' when it emerged it had been funded by a patient group to provide evidence of a link between the two, *The Lancet's* editor stating that had he known of this interest he would not have published the paper (*Guardian* 21.2.04).

How important are these limitations, some of which are recognized by the regulatory bodies, which qualify their approval, licensing a drug for specified dosages for particular categories of patients with specific conditions, and which recognize that its safety is not adequately established and that a fuller evaluation will occur through further post-approval testing? I suggest that the limitations are serious. First, there is a risk that licensed drugs will prove either to be less effective or have more severe, sometimes life threatening, side effects than initially assessed. This has high costs for any patient who suffers these effects. For instance, the anti-inflammatory, Vioxx, licensed in 1999, was withdrawn in 2004 after a study showed an increased risk of heart attacks and strokes (some fatal) with longer-term use. Moreover, even if the side effects are not severe, it can mean that resources are wasted on relatively ineffective medicines.

Second and related to this, because drug approval provides an initial point of closure in establishing the facts about a drug's safety and effectiveness, the qualifications about a drug's use may be forgotten, notwithstanding the very limited nature of the pre-approval evaluation. It may thus be prescribed quite freely, including beyond the boundaries of the established facts, thereby changing the risk–benefit equation: potentially reducing the benefits but not the risks. Most clinicians do not have the resources, not least in terms of time, to open the scientific black box that underpins approval, particularly now there are so many drugs on the market. Moreover, they tend not to note the freedom companies have to choose the comparisons they make in seeking to establish safety and effectiveness, nor the frequently limited nature of the demonstrated differences in effectiveness. Here companies' control of the science is crucial. They make the facts and select the data that are reviewed by the approval agencies. Yet licensing serves as a badge of effectiveness and safety that colours subsequent perceptions and affects practice.

Given the limitations of pre-approval drug testing, we need to consider the extent to which drug approval agencies are independent of the industry. Do the agencies adequately protect patients' interests? In theory they act on behalf of government to mediate between the conflicting interests of public and industry. The industry is keen to ensure that approval is speedy and successful, and the public has an interest in getting some new drugs onto the market quickly.

Against this pressure for speed and successful approval, patients have to be protected from unsafe or ineffective drugs and the approval process needs to be adequate to achieve this. Approval processes reflect a compromise between these conflicting interests, and governments, on whose behalf regulatory bodies act, are open to the same conflicts. They have a clear interest in protecting the public. Yet they are usually anxious to support the industry whether because of its value to the economy, or because of their desire as health care providers or funders to have access to drugs at reasonable prices.[14] The aim is to balance the conflicting interests without fear or favour.

In practice, achieving an appropriate degree of independence is difficult and there is a real danger of 'regulatory capture' (Abraham, 1995: 22–3): that the industry manages to ensure that its concerns and ways of seeing issues shape decision making and the agencies do not serve as a countervailing power. In countries where major companies are located, capture is made more likely by the industry's control over the science submitted to the regulatory body – a control that governments have permitted. The independence of the FDA is particularly crucial, since companies outside the US often seek its approval for their products because of the global importance of the US market. Abraham (1995) argued that the FDA had managed to maintain more independence from the industry than British regulatory agencies. But there is evidence that US administrations in the 1990s and since have been particularly sympathetic to the industry and that the FDA's regulatory regime was loosened.[15] However, the withdrawal of Vioxx in 2004 has led to adverse publicity about the agency and calls for tighter regulation.

The industry's political power at the pre-approval stage lies therefore in the influence it can exert, partly by virtue of its ideological and economic power, over the regulatory processes, such as its power and influence over the licensing of new drugs. It is hard to escape the conclusion that the industry's power during this stage is currently very extensive, though the adequacy of regulation is now under discussion in the US and Europe.

Stage 2: Post-approval Evaluation

Approval by a regulatory authority is a turning point for a drug; it gives factual status to claims about safety and effectiveness, claims that tend to be accepted by many ordinary clinicians and the public without much in the way of further questioning. Latour argues, however, that although we can identify moments when a particular claim is accepted as a scientific fact and the data supporting the claim are no longer explored, this does not mean it is necessarily treated as a scientific fact for all time: that depends on the subsequent actions of others. Whilst many clinicians and patients in the post-approval stage treat the initial approval as establishing for practical purposes the safety and effectiveness of a drug, further research does take place and this, along with patients' and clinicians' experiences of the drug, can lead to questioning of the facts about a drug,

a reopening of the scientific black box and the overthrow of earlier conclusions. There are many other examples, apart from Vioxx, of licensed and widely used drugs later withdrawn on safety grounds. These include the sleeping pill, Halcion, the arthritis drug, Opren, and the statin, Baycol.

A number of factors generate further testing and create possibilities that the black box is reopened. First, the company itself may be keen to obtain data that shows the drug is useful for a wider range of conditions than those for which it is licensed and so fund further tests (though equally it may encourage wider use without further testing). Such testing is not so much designed to reopen the black box as to extend its scope. Second, since another company may be working on a competitor product and seeking to establish its superiority, the first may need to engage in further defensive testing. The aim of the competitor is to supplant the existing black box with a new one, whereas the first tries to make sure that the black box is strengthened. Third, senior doctors, especially those with academic posts alongside clinical responsibilities, may be keen to carry out research to generate further facts about a drug. For precisely which groups of patients is it useful? What are the most suitable dosage levels? Are there side effects from long-term use? If therefore they can secure funding from the industry or elsewhere, they may carry out more extensive clinical trials that may either strengthen a box's defences or threaten to undermine it. And fourth, while many ordinary clinicians and patients accept claims about safety and effectiveness relatively uncritically, they may notice problems once a drug is in use, though often they only raise questions if fairly clear-cut problems emerge. The reporting of side effects observed in clinical practice to the regulatory authorities is not mandatory. However, in Britain, as elsewhere, there is an official, non-compulsory reporting system – the yellow card system. This does not generate systematic data and there is evidence that side effects are massively underreported (Cohen, 2001: 5). It can, nonetheless, lead to major concerns about a product. If these are raised, the industry needs, if possible, to try and rebut them and may engage in further testing in an effort to do so. Post-approval testing, referred to as Phase IV research, is therefore a very different process from pre-approval testing in terms of its initiation, extent and purposes. In 2002 it amounted to only around 12.4 percent of all R&D expenditure by the leading pharmaceutical companies (PhRMA, 2004a).

Often the debates about a drug continue over many years. Currently a highly contested re-evaluation of hormone-replacement therapy is underway, especially of its value as a long-term treatment following the results of several studies indicating higher breast cancer levels for long-term users (Beral, 2003). In other cases, studies show clearly that the initial assessment needs to be more qualified and that the facts in the original black box must be modified. Nonetheless, the industry may do relatively little to publicize the new facts. There may be regulatory requirements about changing packaging leaflets, but such changes often occur slowly and revised information may not be read very carefully either by doctors or patients. Consequently, given the cognitive closure

that often results from initial approval, the additional advice may have little impact on clinical practice.

Post-approval evaluation is therefore a lengthy process – indeed, unless a drug is withdrawn, it is potentially unending – and is made more difficult by the changes introduced to the chemical composition of certain drugs as new findings emerge. The contraceptive pill, introduced in Britain in 1963, has undergone a number of changes in composition and even now, over 40 years later, its side effects are still debated.

The pharmaceutical industry's power in the post-approval stage is extensive though arguably always at risk in relation to specific preparations. Companies start with the ideological advantage that the drug in question has been approved as safe and effective, and although approval is qualified, these qualifications do not feature very heavily in the perceptions of most clinicians and patients. This ideological advantage is then backed up by major marketing activities that are dependent on the companies' economic power but strengthen the ideological impact of the scientific work. Spending on marketing by leading companies is considerable (GAO, 2002). The broad features are well known. Much is directed at doctors who are inundated with pens, pads and mugs embellished with brand names. Companies also have extensive sales forces and company reps make visits to doctors' surgeries and hospitals with product leaflets. They also fund medical conferences both large and small. And even when direct-to-consumer advertising is not permitted, press releases can be used to spread knowledge of, and demand for, a drug. These may report a drug's approval, studies of its effectiveness, or epidemiological work that emphasizes the prevalence of the illness, potentially broadening its boundaries and expanding the market for treatments.[16]

The industry's ideological advantage is compounded by the fact that doctors are often willing allies of the industry. Instead of acting as a countervailing power, as potentially they could, most doctors have a shared interest in prescribing the industry's products and not challenging its claims. Clinicians typically want to 'do something' to help their patients, and drugs provide a solution to the diverse problems they encounter. Drugs also help to maintain the aura of science crucial to medicine's professional power, are easy to prescribe, and reduce the time needed with patients (Weiss and Fitzpatrick, 1997; Wilkin et al., 1987). Indeed, the industry and profession largely stand in a symbiotic relation. The industry needs doctors to prescribe its products, and practising doctors need the industry's products to help to maintain their professional standing and power, a situation enhanced by their near monopoly over prescribing.[17] Of course doctors try to represent patients' interests, but they often share the belief that medications provide the best, easiest or most readily available solution for patients' problems. As a result they only tend to challenge the industry's claims about a preparation if they encounter marked side effects. If and when they do decide that the black box must be reopened they can be a powerful force, using adverse publicity to strengthen their hand and posing a real threat to a particular product. Yet, faced with an individual patient, it can

be difficult to determine whether the reported problem can be blamed on a specific drug since it might result from the illness. Moreover, ordinary doctors rarely challenge medicine's general reliance on the industry's products, though they may be concerned about the value of a specific drug and report side effects. Consequently, while the profession is powerful, and could use its power to challenge the activities of the industry, it only rarely acts as a countervailing power.

Although patients often value the medicines they are given, they do not have the same interest in supporting the pharmaceutical industry as many doctors and could collectively be an important countervailing power. Certainly their reporting of side effects can lead to a radical questioning of specific products. But patients have typically been deferential towards medical authority, accepting medical advice on trust and lacking the expertise to question it (though there are signs of change in this respect). Patients often, therefore, accept the culture in which drugs are viewed as the appropriate remedy for a range of ills and may be slow to identify side effects as arising from a drug they are using. Some patients and their families do become vocal about side effects, transforming themselves into user groups and deploying the media to publicize their concerns. Campaigns about the addictive properties of tranquillizers are one example. Such campaigns can be influential, though the impact is often slow, and many suffer ill-effects before a treatment is withdrawn or prescribing advice changed.

Once a drug is approved, the agencies tend not to play a very active part in considering whether a license should be revoked. If evidence is brought to them they may consider withdrawing approval but this is relatively rare. And if they request further Phase IV trials, they do not always ensure these are carried out (Cohen, 2001). Where health care is state funded, other government bodies may play a part in controlling which medicines can be prescribed and how much is paid for them, and the same role can be played by commercial health companies keen to keep costs down. In Britain, for instance, the government negotiates with the industry over drug prices, and decides whether doctors can prescribe particular patented drugs or must use generic versions. These strategies help to keep drug prices down but profit margins are arguably still quite generous to the industry (Harrison, 2003). The National Institute for Clinical Excellence (NICE) also assesses a range of medical interventions in the post-approval phase. However, such bodies are also open to capture by the industry. A recent World Health Organization report (2003) was critical of the industry's influence on NICE recommending that, while manufacturers should be able to put their views to the Appraisal Committee, they should no longer be members.

Conclusion

Whilst the boundaries of sociological endeavour are potentially extensive, the discipline has always been selective in its concerns. The absence of attention to the pharmaceutical industry is regrettable, not least because, in alliance with

medicine, the industry is shaping the ways in which society responds to a very broad range of problems. It is contributing to an extension of the territory of medical problems and the tendency to respond to problems by pill taking, as if the problem will be solved by magic. This response often fails to grapple with the sources of these problems. As many writers have noted (see Conrad and Schneider, 1992), drugs provide an individualized solution to problems that often have social and structural origins, which are not tackled by pharmaceutical remedies, as for instance, where pills are used to treat obesity. Whilst the industry's power is not unregulated, an important source of its power is the control it exerts over the scientific fact making that underpins a drug's evaluation. Given that once licensed these facts tend to be accepted, and given that the potential challenges to the drug companies face a struggle in which the cards are not equally stacked, the industry has a major advantage.

It is true that with time a fuller evaluation of a drug takes place. Yet there is little sign that this is leading to a more cautious approach to pharmaceutical use. Moreover, relying on time to produce a fuller picture of the value of particular preparations means that many people suffer adverse, sometimes even fatal, side effects that might have been avoided. Instead, what is needed is to ensure that more independent research is carried out, both pre- and post-approval, and that the uncertainties about safety and effectiveness are well publicized. Such research could be funded by the industry with companies required by government to pay a compulsory levy to fund independent, non-commercial research institutes to evaluate drugs, which would hire the researchers and control the research.[18] There is also a need for far greater openness and transparency in the availability of all trial data, whether favourable to a drug or not; an issue now receiving some publicity. Regulatory agencies also need to strengthen testing requirements, including ensuring that, where possible, drugs are tested against competitors and that data on differences in effectiveness are presented in more meaningful ways. A system of provisional licensing would also be desirable with a requirement for more extensive and lengthier testing before a full license were confirmed.

This article has focused on the producers of medicines rather than the consumers. Pharmaceutical producers use their ideological, economic and political power to play on the anxieties and discontents of life in late modern society creating a market for their products that extends well beyond obvious health needs. Health services, which are supposedly based on considerations of welfare and professionalism and a commitment to patients' interests, become the means of generating large profits for a highly commercial industry that uses scientific fact making as a tool to serve its own interests as much, if not more, than the interests of health service users.

Notes

1 A patent can be obtained if the invention is new, involves an 'inventive step' and is capable of industrial application.

2 There has been considerable interest from economists, policy analysts and journalists.
3 See Berg's (1997) work on electronic records in medicine.
4 Their market capitalizations were £65.98 and £41.16 billion (*Observer* 1.8.04).
5 Such medicalization may reduce stigma.
6 Lichtenberg (2003) found 40 percent of improvements in longevity between 1986 and 2000 were due to new chemical entities, though his findings have been contested.
7 'The word black box is used by cyberneticians whenever a piece of machinery or a set of commands is too complex. In its place they draw a little box about which they need to know nothing but its input and output' (Latour, 1987: 2–3).
8 Companies are talking of a new code of practice on transparency (PhRMA, 2004b).
9 This list changes quite rapidly.
10 Some drugs reach blockbuster status (sales of more than $1 billion a year) within a year of release (IMS Health, 2002).
11 This was highlighted in relation to Donepezil, a drug for Alzheimer's. This improved performance on a simple memory test but had little impact on clinical deterioration or the chances of hospitalization (AD2000 Collaborative Group, 2004).
12 An example would be the hair loss associated with cancer drugs.
13 When the possible suicidal impact of Seroxat on children became a public issue it emerged that GlaxoSmithKline, which secured a license for the drug for adults, had not revealed data showed suicidal tendencies in some children taking the drug.
14 The French government was strongly opposed to Aventis being taken over by the Swiss Novartis rather than the French Sanofi.
15 For example, the reduction in the time taken to secure FDA approval for which the industry pressed (Cohen, 2001).
16 Drug companies funded a Global Initiative for Asthma, publicizing an apparent worldwide increase and the need for greater awareness of the condition and treatments (*Guardian* 17.2.04).
17 In Britain, nurses' powers to prescribe are being increased.
18 Strenuous efforts would be needed to be to ensure the research was independent.

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