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Sociology of pharmaceuticals development and regulation: a realist empirical research programme

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Abstract A realist conceptualisation of interests is proposed in opposition to the fashionable view that interests, objectivity and reality are merely social constructs, and that sociological analyses should be confined to discourse, actor-networks and micro-contextual practices. The objective interests of pharmaceutical companies in profit-maximisation, and of patients/public health in the optimisation of drugs' benefit-risk ratios, can be empirically validated. The relationship between those interests and pharmaceutical regulation is best characterised by 'neo-liberal corporate bias' at the macro- and meso-levels. How such bias manifests itself at the micro-social level of science-based pharmaceutical testing and regulatory decision making is examined using a realist sociology of scientific knowledge, which appreciates that assessment of the validity of techno-scientific knowledge claims is essential for their sociological explanation. Commercial interests are shown to have biased science away from the interests of public health, in favour of industry. International comparisons of drug regulation demonstrate that drug injuries are not necessarily an inevitable by-product of pharmaceutical progress because some countries have fewer drug safety problems than others. Similarly, the lowering of techno-scientific standards for drug safety testing is not an inevitable cost of faster development of therapeutically valuable medicines, but a consequence of the internationalisation of neo-liberal corporate bias.

Keywords: interests, corporate bias, scientific knowledge, ideology, pharmaceutical innovation

Introduction

The purpose of this paper is to explain a theoretically and empirically rigorous framework within which sociology can progressively pursue searching research questions about 'pharmaceuticals and society'. In approaching the complex field of pharmaceuticals development and regulation, my strategy is first to articulate why a realist conceptualisation of interests is theoretically more coherent than apparently popular alternatives. For example, this involves the presupposition that pharmaceutical companies have objective interests in profit-maximisation, and that patients have objective interests in drugs having the maximum benefit-risk ratio possible. I then show why the necessity of that presupposition is validated by demonstrating that the rationale for the historical development of drug regulation only makes sense by appreciating that the health interests of consumers/patients cannot be reduced to their actions in the unregulated market.

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Having established the existence of objective interests, I examine their precise relationships to regulatory developments using a synthesis of archival evidence from historical sociology and established theoretical models from political sociology. I argue that this relationship is best characterised by 'neo-liberal corporate bias' at the macro- and meso-levels of sociological analysis of political organisation and representation. Such bias is suggestive of, but does not determine, the nature of the micro-social processes of testing and regulating pharmaceuticals themselves. Yet no sociological analysis of pharmaceutical development and regulation would be complete without an investigation of those processes. I contend that, to investigate such micro-level processes adequately, one needs a realist sociology of scientific knowledge, which appreciates that the assessment of the validity of techno-scientific knowledge-claims is essential for their sociological explanation. Building on that methodological insight, I then outline how commercial interests have been shown to bias the science of drug testing and regulatory review away from the interests of patients and public health, in favour of the pharmaceutical industry.

Furthermore, to establish that this bias has had real adverse effects on the health of patients, I draw on international comparisons of drug regulation to demonstrate that drug injuries are not necessarily an inevitable by-product of technological progress in pharmaceuticals because some countries have fewer drug safety problems than others. Similarly, I marshal evidence to show that the lowering of techno-scientific standards for drug safety testing across the EU, US and Japan is not an inevitable price to be paid for faster development of therapeutically valuable medicines, but more plausibly a consequence of the internationalisation of neo-liberal corporate bias in pharmaceutical regulation. Based on these various bodies of evidence, I conclude that there is compelling evidence that, overall, neo-liberal corporate bias at the macro- and meso-levels of political organisation and representation leads to biases favourable to industry's and contrary to patients' interests at the micro-social level of science-based testing and regulating of drugs. Finally, I consider how biases against the interests of public health within pharmaceutical development and regulation could be reduced.

A realist framework of interests

Since the 1980s, the concept of 'interests' has become unfashionable in social sciences, giving way to a discourse of 'stakeholders' or 'fluid' 'actor-networks' (Adam *et al.* 2000, Rappert 2007). The attack on sociological explanations using a conceptualisation of interests came from within sociology and political commentary. For some, the idea that there could be objective interests consciously or unconsciously influencing the actions of people and organisations was challenged as an authoritarian meta-narrative (Bogard 1990, Dews 1987). Woolgar (1981: 37) asserted scathingly that such explanations of social action treated people as 'interest dopes'. He contended that 'there is no sense in which the phenomenon has an existence independent of its expression . . . there is no object beyond discourse . . . the organisation of discourse is the object' (Woolgar 1988: 73, 89). In other words, whatever actions or preferences people express *are* their interests, so the concept of 'interests' is superfluous (Potter 1996). Similarly, Schwarz and Thompson (1990) suggested that people's perspectives and commitments about say, drug safety, should be regarded as expressions of group political culture (or sub-culture), rather than identifiable interests (Hancher and Moran 1989).

These perspectives of what I call 'superficiality' coincided with an emerging sympathy for Hayekian writings about the appropriateness of the market for distributing resources

and opportunities in society (Hayek 1967). The intelligibility of elevating the marketisation of society to such importance depended on the presupposition that people do not have interests beyond the preferences that they express in the market. The application of 'stakeholder' discourse reflected the application of this philosophy to the political process. Like consumers in a market, it was assumed that analysis could stop at stakeholders' expressed political preferences.[1] Indeed, rejecting 'interests' as fixed analytical categories capable of explanation, some commentators sought to define interests as nothing more than social actions and processes (Irwin 2001: 171).

I suggest that this is an impoverished view of sociological explanation. At a basic level of sociological theory, it is preferable to distinguish between actions/behaviour on the one hand, and interests on the other, because then it is possible to consider the possibility that people might behave against their own interests. That possibility cannot be discounted, in particular or in general, because a group's potential to act in its own interests is dependent on knowledge about how best to achieve particular goals – knowledge to which the group may have little or no access. In highly complex and functionally differentiated societies, such knowledge-deficits and dependencies are likely to be common, and always possible (Abraham and Davis 2007a).

Thus, it makes more sense for sociologists to employ a plausible framework of objective interests against which to examine the behaviour of various agents. Such a framework is based on the realist presupposition that there can be interests 'beyond' discourse and actions.[2] When considering the relationship between pharmaceuticals and society, I suggest that, to a first approximation, it is plausible to presuppose that an objective interest of patients and public health is that drugs released on to the market have the maximum possible benefit-risk ratio given all the scientific knowledge available at that time. Similarly, capitalist pharmaceutical companies have an objective, though not always over-riding, commercial interest in the maximisation of their profits.[3] This realist position is not merely an a priori fiat of sociological theory. It is borne out by historical sociology of the emergence of pharmaceutical regulation, which validates the plausibility of this realist theoretical framework of interests, as I show in the remainder of this section.

For many years pharmaceuticals escaped sociological scrutiny, not least because of the extremely limited conception of their links with 'society'. In late 19th and early 20th century Western industrialised countries, 'society' was little more than a market receptacle for the products of an expanding industry and profession of science and medicine. Few questioned the wisdom of doctors and scientists involved in the pharmaceutical trade. This permitted dominant producer interests to mobilise the powerful ideology[4] that the market could determine the best remedies for patients and health care (Abraham and Lewis 2002). On this view, the concept of 'interests' seemed insignificant because there was supposed to be a coincidence of interests between scientists, the medical profession and society – an ideology of coincidence of interests that was frequently promoted by drug manufacturers misinforming consumers about their products. All that mattered was that the drug trade, in collaboration with the scientific and medical professions, continued to progress with the production of more pharmaceuticals that consumers wanted to buy – because if consumers wanted to buy them then that must be in their interests. The first signs of the need to distinguish between the interests of the drug trade and consumers was when some manufacturers were accused of selling adulterated products. That is, consumers were being sold products of defective *quality* – they did not contain the ingredients they were supposed to (Abraham 1995a: 36–56).

By the early 20th century some government scientists and influential medical experts were campaigning for drug quality regulation to protect consumers' health against the dangers

of drug adulteration. They were joined by the large, technologically sophisticated pharmaceutical firms, who saw an opportunity to close out competition from other drug traders because the large companies could easily meet the expected new regulatory standards, while other drug producers could not. This coalition was successful in bringing about the introduction of drug-quality regulation. Evidently, the interests of consumers and the drug trade did not always coincide. As doctors retreated from the manufacture of drugs, the drug trade fragmented between companies concentrating on the production of drugs for prescription by doctors (known as 'ethical pharmaceuticals') and the firms who marketed their products directly to consumers (Barkan 1985, Stieb 1966).

While drug quality was subject to government regulation there continued an assumption that the techno-science of the 'ethical' pharmaceutical industry could be trusted to provide safe and effective medicines. Patients' interests were subsumed by the industry's as it was argued by industry and governments that it was not in firms' commercial interests to produce unsafe or ineffective drugs. However, pharmaceutical companies' commercial interests in the market proved a very poor barometer for drug safety or efficacy as demonstrated by drug disasters and thousands of products found to be ineffective when eventually tested independently of the industry (Abraham 1995a: 56–74). While pharmaceutical firms did not want drug disasters, their commercial interests evidently did not coincide sufficiently with those of patients to investigate thoroughly enough drugs of dubious safety.

Consequently, between the late 1920s and the mid-1970s, all the Western industrialised countries introduced government regulation of drug safety and efficacy, as well as quality. For the first time, only *government* agencies had the legal authority to determine whether a new drug was safe and effective enough to be permitted on to the market. The timing of such regulation varied from 1928 in Norway, 1935 in Sweden, 1962 in the US, and 1971 in the UK, to 1976 in (West) Germany (Abraham 1995a: 36–86, Abraham and Lewis 2000: 49–76).

Hence, governments came to regulate drug quality, safety and efficacy purportedly on behalf of patients and public health. Governments accept that it is their legal responsibility to protect the interests of patients in these respects. Evidently, therefore, the rationale for the historical emergence of pharmaceutical regulation demonstrates that the health interests of patients and the wider public reside *beyond* the preferences and desires that consumers or patients express in either the market or the political process. Moreover, the explanation for the disjuncture between patients' interests and their expressed desires in the market and clinic often resided in the ideological creation of false consciousness about pharmaceuticals, due to misleading drug promotion by companies and lack of comprehensive public access to accurate information about drug risks and benefits (Abraham and Sheppard 1997, Chetley 1990: 51–68, Collier 1989: 75–87, Medawar 1979). Thus, there are not only a priori reasons to support a realist framework of interests; there are also empirical historical ones. Indeed, as the foregoing account demonstrates, one cannot make sense of the history of drug regulation without such a framework.

Political sociology of regulation: corporate bias, neo-liberalism and capture

The previous section shows that, despite current fashions, the appreciation of the existence of objective interests is indispensable for our sociological understanding of pharmaceutical regulation. That realisation, however, conveys nothing about the *specific* relationships between interests and regulatory developments. To address this empirical matter, I turn to political sociology, which is often mistaken for a purely theoretical sub-discipline. However,

there is an empirical branch of political sociology concerned with testing theories of political actors and organisations. Here, we are particularly concerned with how theories of the regulatory state, such as capture theory, corporatism and neo-liberalism, relate to empirical findings about macro- and meso-level politics of regulatory development throughout history. Probably the best known theory of regulation is that of regulatory capture epitomised by the 'life-cycle' theory of regulatory agencies put forward by Bernstein (1955). On this view, regulatory agencies are set up by the legislature in order to protect the public interest against the excesses of industrial power. It is assumed that there exists some divergence, if not conflict, of interests between industry, seeking to maximise profits, and 'the public interest'.

Initially, regulatory agencies tend to be adversarial towards industry, but become isolated as their enthusiastic staff tire and retire. Eventually, they are progressively 'captured' by, and come to share the perspectives of, the industries they are supposed to regulate. Regulatory capture may result from direct industry lobbying of government officials, co-opting expert advisors to regulatory agencies by giving them grants or consultancies, or the 'revolving door' signalling that regulatory officials begin their careers in industry, then work for some years in the regulatory agency until they are promoted back into the higher echelons of industry (Braithwaite 1984: 298, Hancher and Moran 1989b: 288, Owen and Braeutigam 1978). According to capture theory, if regulators have trained in industry and/or they see their career development in terms of future promotion into the regulated industry, then they may be unduly concerned to maintain 'friendly relations' with industry at the expense of public interest regulation From this captured stage onwards, argues Bernstein, the regulatory agency prioritises industrial interests over consumers, unless, or until, a scandal highlighting the failures of regulation triggers a new drive for public interest regulation, in which case the regulatory agency begins a new cycle.

Theories of regulatory capture assume that, at the outset, regulation was established in order to serve the public interest (Mitnick 1980). By contrast, corporatist theory envisages a more pro-active regulatory state with its own interests. Unlike capture theory, regulatory agencies do not evolve cyclically between solely protecting the 'public interest' (before capture) and passively defending industry interests (after capture). Corporatist theories propose that the nature of regulatory systems is shaped by organised interests, together with two-way bargaining between those interests and the interests of the state (Cawson 1986). Some interests are more organised than others, and are capable of gaining exceptional influence over the regulatory state because of their (near) monopoly over resources needed for regulation. For example, in the pharmaceutical sector, regulation might be characterised as corporatist because the industry's possession of 'reservoirs of expertise' implies that its integration into the implementation of the regulatory process is virtually a pre-condition for its success, rather than a result of capture (Hancher and Moran 1989: 272). On the other hand, a neo-liberal regulatory state would be expected to be minimal and subject to the tests of 'the market' (Boreus 1997).

Extensive archival research covering the last hundred years or so has been conducted on the political sociology of pharmaceutical regulation in the US, UK, the EU and other European countries (Abraham 2007). The evidence supports what I call 'corporate bias' (a variant of corporatism consistent with some indicators of capture) up to the 1980s and subsequently 'neo-liberal corporate bias', rather than pure corporatism, capture or neo-liberalism. By 'corporate bias' I mean that the pharmaceutical industry was, and is, permitted to have privileged strategic access to, and involvement with, government regulatory policy over and above any other interest group; and more often than other factors, the industry was, and is, decisive in determining regulatory policy outcomes (or lack thereof).

The regulatory state and the pharmaceutical industry work largely in partnership and behind a cloak of secrecy.

Corporate bias is the preferred characterisation over regulatory capture because regulatory agencies and reforms were not instigated solely or largely in response to public campaigns for better drug quality, safety and testing in the public interest. Such campaigns either came to nothing in the way of regulatory reform or contributed only to belated and diluted regulatory change unless they also had support from the industry or the state itself. For example, in the UK, this is well documented with respect to: (1) the anti-adulteration campaigns of the 1880s and 1890s; (2) regulatory inaction in the aftermath of the 1914 Select Committee's recommendations for strict regulations governing the therapeutic claims made by pharmaceutical manufacturers of 'patent medicines';[5] (3) the fact that, despite clearly knowing about the 1937 Elixir Sulfanilimide drug disaster in the US, which killed 107 people and ushered in US drug safety regulation (1938), there is no trace of any reform efforts at all within the Ministry of Health to introduce government regulation of drug safety in Britain in response to this disaster, even though it could just as easily have occurred in the UK; (4) the 1941 Pharmacy and Medicines Act, which brought incidental consumer protection by putting an end to 'patent medicines', but was motivated by the changing commercial interests of the industry, rather than the protection of public health; and (5) the 10-year delay between thalidomide (1961) and the implementation of legally enforceable drug safety regulation in 1971 under the *1968 Medicines Act* (Abraham 1995a: 36–86).

While many of the socio-political indicators of a 'captured' regulatory agency are endemic within pharmaceutical regulation, they do not evolve in a progressive cycle towards industrial capture of public interest regulation. Rather, the pharmaceutical industry's privileged influence is evident at the outset of regulatory developments. For this reason also, corporate bias is a better account of pharmaceutical regulation than capture theory. In the UK, some examples of the pharmaceutical industry's privileged access to government in the *formation* of regulation are: (1) its moulding of the perspective of the Ministry of Health since the latter's inception in 1919; (2) its shaping of the voluntary Committee on Safety of Drugs (1963–68) and the *1968 Medicines Act*, especially the policy that commercial secrecy took priority over provision of information to the public and wider medical/scientific community; and (3) its effective power to veto the Department of Health's proposal in 1970 that members of the Government's expert Committee on Safety of Medicines (CSM), which advised on whether new pharmaceuticals were safe and efficacious enough to be permitted and kept on the market, should be prohibited from having personal and non-personal interests in pharmaceutical companies, such as shareholding and consultancies (Abraham 1995a: 36–86, Abraham and Lewis 2002).

Furthermore, capture theory cannot accommodate the fact that at various times the regulatory state has been concerned with its own viability to the extent of defining its own interests independent of the industry and wider public. In the UK, this is evident from: the introduction of the *1920 Dangerous Drugs Act* to discipline public order; the black-listing of NHS drugs, which lacked proof of therapeutic value, by the Joint Committee on Prescribing in the 1950s in order to rationalise the costs of pharmaceuticals to the Service; and the 'Limited List' introduced by the Government in 1984 which excluded about 1,800 pharmaceutical preparations that the NHS would no longer pay for because they were judged to be too expensive and of little therapeutic advantage to patients (Abraham 1995a, Abraham and Sheppard 1999a, Gabe and Bury 1988).

There is extensive evidence that the corporate bias of pharmaceuticals regulation has taken on a neo-liberal flavour since the 1980s. Since 1989 the funding of the UK drug regulatory agency has changed from being derived 40 per cent from direct taxation to being

Table 1 *Percentage of industry fee contribution to total EMEA budget and to FDA spending on human drug review*

Year	*Percentage of total EMEA revenues**	*Percentage of FDA spending on drug review***
1994		24
1995	28	36
1996	38	36
1997	48	36
1998	53	40
1999	70	43
2000	71	47
2001	69	50
2002	64	47
2003	67	49

Sources: *Figures for EMEA compiled from EMEA Annual Reports between 1995 and 2003. **Figures for FDA compiled from 65 Federal Register 47994 and annual financial reports to Congress from 2000.

100 per cent derived from fees from pharmaceutical companies. Subsequently, many other European countries have very substantially increased the financial dependence of their drug regulatory agencies on fees from pharmaceutical companies – fees whose payment accompanies the drugs that the companies submit to the regulatory agencies for approval (Abraham and Lewis 2000: 43–79). In the EU and the US, such funding has grown steadily from the mid-1990s to reach about 70 per cent for the European Medicines Evaluation Agency (EMEA) and 50 per cent for the Food and Drug Administration (FDA) (Table 1). Thus, the regulatory state has become increasingly minimalist, that is, its independent resource-base is shrinking.

This has created a situation in which the institutional prosperity and viability of regulatory agencies depends on their ability to attract fees from pharmaceutical firms. Consequently, regulatory agencies are encouraged to compete by making themselves attractive to drug companies, who have come to be defined as the regulators' 'customers'. In effect, the drug regulatory agencies compete with each other on a market selling their regulatory services to pharmaceutical companies. As the customers (the drug firms) want rapid drug approval, the speed of regulatory agencies' regulatory review times has become the central criterion of this competition (Abraham and Lewis 1999). In short, the drug regulatory agencies have been subjected to the 'tests of the market' – another hallmark of neo-liberalism. As shown in Table 2, regulatory review times for new patentable drugs, known as new molecular entities (NMEs) in the US have been cut by half since 1993 and these reductions are based on previous cuts since the early 1990s (Kaitin and DiMasi 2000, Kessler *et al.* 1996). Similar trends have occurred in Europe. For example, the average net in-house review times of the UK regulatory agency for new drugs fell from 154 working days in 1989 to just 44 days by 1998. The regulatory review times of Germany, Sweden and many other EU countries also fell dramatically in this period (Abraham and Lewis 2000: 20).

Such inter-agency competition is particularly acute in European countries and other small to medium-sized markets. It has always been less so in the US because, with such a large market, trans-national pharmaceutical companies are generally keen to apply to the FDA anyway. However, the international competitive pressure on the FDA to accelerate its regulatory review consequent upon increased industry funding is present by a different mechanism. The FDA was subject to severe budgetary cuts during the Reagan Administrations,

Table 2 *FDA review* and approval** times for priority and standard NMEs, 1993–2003*

	Priority			*Standard*		
Calendar year	*Number approved*	*Median FDA review time (months)*	*Median total approval time (months)*	*Number approved*	*Median FDA review time (months)*	*Median total approval time (months)*
1993	13	13.9	14.9	12	27.2	27.2
1994	12	13.9	14.0	9	22.2	23.7
1995	10	7.9	7.9	19	15.9	17.8
1996	18	7.7	9.6	35	14.6	15.1
1997	9	6.4	6.7	30	14.4	15.0
1998	16	6.2	6.2	14	12.3	13.4
1999	19	6.3	6.9	16	14.0	16.3
2000	9	6.0	6.0	18	15.4	19.9
2001	7	6.0	6.0	17	15.7	19.0
2002	7	13.8	16.3	10	12.5	15.9
2003	9	6.7	6.7	12	13.8	23.1

*Review times are defined as the total time involved while the application is with the FDA for review. **Approval time is review time plus any time waiting for the company to make revisions that are pre-conditions for approval.
Source: FDA – available at http://www.fda.gov

which reduced the number of employees from 8,200 in 1979 to 7,000 in 1987. Over the same period Congress had passed 20 new laws giving the FDA new responsibilities in both the food and drug area (Anon 1989). The Bush (senior) Administration, in its turn, continued to hold down FDA budgets (Hilts 2003: 255). To avert budgetary disaster the pharmaceutical industry agreed to part fund the agency via users' fees under the *1992 Prescription Drug Users Fee Act* (*PDUFA*) and subsequent renewals of the Act every five years, but only in exchange for explicit acceleration of regulatory review defined by industry demands.

In this context, the FDA also finds itself competing with other drug regulatory agencies for fastest review times because it is compared with them when industry and Congress review its funding every five years. Indeed, speed of regulatory review is now the primary quantitative performance indicator for the agency. It is sometimes argued that these accelerations of regulatory review in Europe and the US have been driven by patients and have then implied that this is in the interests of public health (Carpenter 2004, Daemmrich and Krucken 2000). *Sometimes*, especially in the early stages of AIDS patient activism, there is *some* truth in this.[6] However, these regulatory reforms have for the most part made no attempt to prioritise the interests of patients' health.[7] For example, the demands on the FDA to speed up its regulatory reviews apply to standard drugs, which offer little or no therapeutic advance, as well as to priority drugs, while in Europe, regulatory agencies do not even collect the requisite data to routinely distinguish between standard and priority drugs in the first place (Abraham and Davis 2007b).

Science, drug development and product regulation in the post-thalidomide era

So far I have discussed the (neo-liberal) corporate bias of political *organisation* and *representation* in pharmaceutical regulation. While this is suggestive of commercial bias

and other influences on the actual testing and regulation of drug products themselves, such micro-level processes must be empirically researched in order to establish the effects of (neo-liberal) corporate bias on regulatory science, decision making and outcomes. The pharmaceutical industry conducts all the testing of its own drugs, and government regulatory agencies review the technical data submitted by the companies before deciding whether drugs can be approved for marketing as safe and effective.

Drug testing and regulatory review is conducted by scientists, drawing on fields such as biochemistry, toxicology, pharmacology, clinical pharmacology and pharmaco-epidemiology. Typically, such scientists deny that their assessments and knowledge-claims are biased by commercial or other political interests. A challenge for sociology was, and remains, to determine how social factors, such as interests, may influence and bias scientific knowledge-claims in drug testing and regulation. In short, a sociology of scientific knowledge (SSK) was required and an understanding of this sub-discipline within sociology had to be mobilised.

The pioneers of SSK had developed a number of valuable techniques, such as the examination of scientific controversies as a way of eliciting the roles of values and interests in science (Collins 1981). However, they located their analyses within a relativist-constructivist framework, which assumed that truth-value itself was merely a social construction. On this view, knowledge-claims were not structured by a mind-independent natural world, but rather what science told us about nature was the product of the values, subcultures and interests of the scientists involved. As Collins and Yearley (1992: 310) note, the self-proclaimed effect of this relativist constructivism 'has been to show that the apparent independent power of the natural world is granted by human beings in social negotiation'.

Reflecting this perspective, relativist-constructivists promoted the methodological canon of 'symmetry' in SSK, that is, the assumption that 'true' and 'false' beliefs are held to have equivalent types of sociological explanation (Bloor 1973, Collins 1995). Scientific knowledge-claims became scientific knowledge*s* because, argued relativist-constructivists, there was no objective reality against which to test the validity of knowledge-claims. For relativist-constructivists, when there was scientific controversy, this was to be characterised as no more than a *difference* in 'world-view' or sub-cultural values. One knowledge-claim could be regarded as superior to another only by reference to the instrumental goals of the actors involved, but there was no objective basis upon which to judge between knowledge-claims *beyond* such shared goals (Knorr-Cetina and Mulkay 1983: 6). In short, for constructivists there were multiple realities and multiple knowledges, that is, knowledge became (inappropriately) collapsed into belief.

Hence, such relativism limited itself to descriptions of how scientists constructed their knowledge-claims, but permitted the validity of knowledge-claims to escape scrutiny on both epistemological and methodological grounds. Furthermore, when subjected to the relativist (and social science) principle of reflexivity, relativist-constructivists' descriptions of science become devoid of any defensible criteria of validity. As Collins and Yearley (1992: 302) put it, such relativism 'opened up new ways of knowing nothing'. Unfortunately, therefore, relativist constructivism, if faithfully applied, renders the project of knowledge-production in sociology and social science unintelligible. While this relativist-constructivist approach to SSK is clearly inadequate, it is entirely unnecessary.

By contrast, the realist empirical research programme in SSK presupposes that knowledge-claims in science are the combined product of the social organisation of scientists *and* a mind-independent natural reality. It follows from this that the truth-value of scientific knowledge-claims is not merely the result of scientists' social constructions; it is also, in part, determined by the objective structure of the natural world. Hence, the explanation for 'true' beliefs may be of a very different type from 'false' beliefs because the main explanation for the former may be that it accurately accounts for a natural mechanism (*e.g.* hydrogen combined with oxygen produces

water), while that cannot be the case for 'false' beliefs. That is to say, there is asymmetry. In addition, the realist empirical research programme in SSK is robustly reflexive because it appreciates that, just as scientists can discover truths about the natural world (with more or less accuracy), sociologists can discover truths about the social world (with more or less accuracy).

Thus, the sociological investigation of scientific knowledge needs to take into account the validity of knowledge-claims, if only to appreciate the asymmetrical nature of explanation concerning the role of social factors in producing 'true' and 'false' claims. Once it is appreciated that the validity of scientific knowledge-claims is important for SSK, then it immediately follows that the sociology of bias in science is also important. In this context, bias is defined as a consistent trend or pattern of technical inconsistencies or contradictions mapped on to a set of social interests. As demonstrated by the realist empirical programme in SSK, technical inconsistencies can take many forms. For example, contradictions between: how scientists test a drug in practice and the standards supposed to be upheld in their science at that time; what the same scientist says about a drug product in different contexts; the technical standards that regulators are supposed to be upholding and actual regulatory decisions; and contradictions between the standards applied to different scientists investigating the same drug (Abraham 1993, 1994, 1995b, Van Zwanenberg and Millstone 2000).

At any particular time in pharmaceutical development and regulation there are techno-scientific regulatory standards, whose publicly declared purpose is to protect and promote public health by ensuring that drug products are adequately safe and efficacious. Methodologically, those standards can be deployed by sociologists to investigate how well, in practice, pharmaceutical testing and regulation act in the interests of public health, and how far they are influenced by commercial or other interests. Claims and practices that are inconsistent with such standards provide a starting point for sociological investigation of whether drug testing and regulation is being biased away from the interests of patients and public health and, therefore, in contradiction to its publicly declared social function.[8] The realist empirical research programme has demonstrated that there has indeed been such a bias in modern pharmaceutical regulatory science since the 1970s – a claim yet to be contradicted by the pharmaceutical industry, government regulators, expert scientists, academic social scientists or lawyers, who have all aggressively reviewed it. Those biases are deeply embedded in complex ideologies about drug safety and pharmaceutical innovation, to which I now turn.

International comparisons and the ideology of drug safety

International comparison has also proved a valuable method in the micro-level sociology of pharmaceuticals by sharpening analyses of whose interests are served by the different socio-political arrangements that influence the approaches and outcomes of regulatory science in different countries. Two types of international difference have been scrutinised: differences in pre-market approval/evaluation of drug safety and efficacy of individual drug products; and differences in trends of post-market withdrawals of drug products on safety grounds. To date, most of these comparisons have been between the US and the UK or other European countries.

This longitudinal sociological research has shown that between 1971 and 1992 there were twice as many drug safety withdrawals in the UK as in the US because the FDA undertook more rigorous pre-market regulatory review, identified the safety problems and so never approved the drugs in the first place (Abraham and Davis 2005a). Meanwhile, the drugs were approved in the UK and caused drug injury to patients there until they were removed from the market. This realist comparative research has corrected a number of fallacious ideologies about UK drug safety regulation that had carried some sway. For example, UK

regulators, industry representatives and many media commentators had argued that the level of drug safety withdrawals in the UK was unavoidable because of the unpredictability of drug safety (Abraham and Davis 2006). They also claimed that the UK's regulatory policy of 'early licensing' (with minimal pre-market regulatory checks) was compatible with the interest of patients because the UK had such a good post-market drug safety surveillance system that drugs could be withdrawn rapidly if safety problems occurred (Abraham and Davis 2005b). These technical arguments, however, were shown to be invalid because the FDA detected many of the safety problems from pre-market data, and when there were safety problems with drugs approved in the US, the FDA typically withdrew them much faster than the UK (Abraham and Davis 2005a). That the determination of the (non-)validity of those arguments contributes to the correcting of insights into the interests of regulatory science is one example of why an examination of the validity of technical knowledge-claims must be included in sociological analysis, rather than evaded.

Sociological comparisons of case studies confirmed the extent to which the FDA had tended to demand greater assurances from pharmaceutical firms about both drug safety and efficacy than their UK counterparts in this period before marketing approval. Furthermore, they indicated that the explanations were multi-faceted. Compared with the highly secretive system of British drug regulation, there was much greater freedom of information about drug regulation in the US, so the FDA was propelled into a situation of greater public accountability; there was regular legislative oversight by the Congress to investigate the FDA's performance in regulating drugs to protect public health. Furthermore, the public health advocacy organisations specialising in pharmaceuticals are much larger and more active, and the courts are much more active in reviewing the adequacy of drug testing and regulation, especially with respect to drug injury to patients (Abraham 1995a). These socio-political arrangements militated in favour of regulation in the interests of public health and attenuated the biasing influences of commercial interests on regulatory science.

More recent case-study comparisons of EU drug regulation and the FDA suggest that between 1995 and 2005 the differences between the regulatory demands of the FDA and the UK/EU have shrunk. Significantly, in this later period, Congressional oversight of the FDA has switched to an emphasis on acceleration of drug approvals rather than protection of patients from unsafe or ineffective drugs. Moreover, the implementation of US freedom of information legislation has been allowed to deteriorate by starving it of resources so that citizens may have to wait up to a year for a substantial response. Thus, the convergence of regulatory standards on both sides of the Atlantic tends to confirm previous sociological explanations as the convergence is mainly due to the FDA's weakening demands on pharmaceutical firms, which is in turn a result of the reversal or absence of social factors that previously explained the FDA's more demanding regulatory review than its UK and European counterparts (Abraham and Davis 2007b).

Importantly, the case studies of pharmaceutical testing and regulation not only revealed international differences in the extent to which pharmaceutical companies and regulatory agencies behaved in accordance with the declared purpose of their science. They also demonstrated biases and the influence of commercial interests in drug testing and regulation *within* each of the countries researched. Even when the FDA acted to protect the interests of public health more than its UK counterparts, its regulatory decisions were not necessarily unaffected by biasing influences from commercial interests. For example, the FDA required many more regulatory checks on the safety and efficacy of the anti-arthritis drug, benoxaprofen, and approved it much later, than the UK regulatory authorities. The agency, however, still approved the drug, which was to be a disaster, despite many *evident* toxicities and problems with efficacy data *before* approval (Abraham 1995a).

Streamlining global standards and the ideology of pharmaceutical innovation

By the early 1990s, the cost of bringing a new molecular entity (NME) to the market could be as high as US$350 million and it is estimated that the time from first synthesis of a new drug to its marketing quadrupled between 1960 and 1989 (Halliday *et al.* 1997: 63, Tansey *et al.* 1994: 85). In response, the industry strove to decrease the cost and duration of R and D by reducing regulatory requirements imposed by the state, and to reach larger markets more effectively. Such transnational firms could get better returns on R and D investments if they could access international markets simultaneously (McIntyre 1999: 96). Hence, during the 1990s the pharmaceutical industry sought to persuade regulatory agencies to harmonise regulatory standards for drug testing across geographical regions and to streamline the standards demanded.

To this end the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) established the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1990. The key participants in ICH are the three pharmaceutical industry associations and the three government drug regulatory agencies of the EU, Japan and the US. With IFPMA acting as Secretariat, the ICH met regularly throughout the 1990s and 2000s to agree changes to regulatory standards across the three regions that they claimed would not undermine patient safety. However, sociological studies have shown that many of these changes reduced the standards of testing that pharmaceutical companies had previously been required to meet on chronic toxicity testing, carcinogenicity testing, patient exposure during clinical risk assessment and reporting of adverse drug reactions (Abraham and Reed 2001, 2002, 2003). In this respect, these changes were in the commercial interests of the industry, but consistently inconsistent with the interests of patients and public health because new drugs would enter the market with fewer safety checks than before. On the other hand, this biased regulatory science was justified on the grounds that such streamlining of drug testing would deliver more pharmaceutical innovation needed by patients. The secretariat of the ICH contended that 'the urgent need' for harmonisation was 'impelled' by 'the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious treatments available to patients in need', and to accelerate the development of 'life-saving treatments' and 'ground-breaking treatments of the future' (IFPMA 1998, 2000: 1).

A clear sociological problem is whether this promise of innovation is best regarded as a fallacious ideology or a reasonable account of the reality of the relationship between pharmaceutical innovation and patient need. Because the ICH's claims for innovation are futuristic and open-ended in time, one cannot provide a clear-cut answer to this problem. What can be said is that, despite the enormous neo-liberal acceleration of regulatory approval times in the last 20 years and the reductions in safety testing requirements via ICH in the last 15 years, pharmaceutical innovation has been declining over the last decade world wide, as measured by numbers of new molecular entities (NMEs) and original biologicals (*e.g.* vaccines) submitted to regulatory agencies and/or launched on to the world market (Figures 1 and 2).

Regarding the ICH's claim that it would deliver more pharmaceutical innovation *needed* by patients, the relevant measure of performance is the number of new drugs offering therapeutic advance. Remarkably, neither the UK drug regulatory authority, the Medicines and Healthcare Products Regulatory Agency (MHRA), nor the EMEA even collect data on the proportion of NMEs that offer significant therapeutic advance (House of Commons 2005). Nevertheless, the FDA does distinguish between those NMEs that offer significant

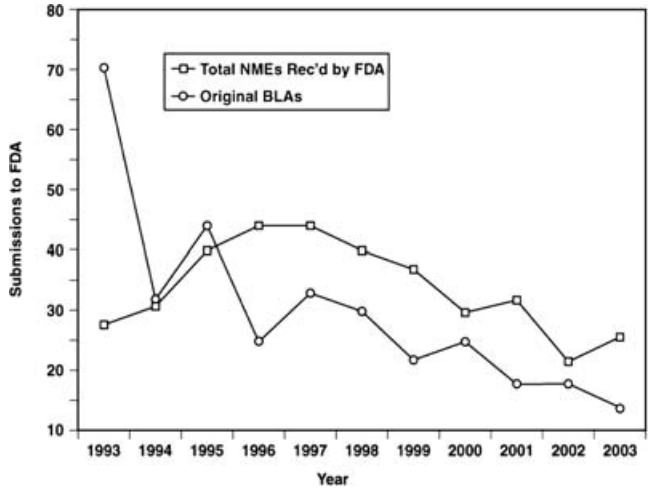

Figure 1 *10-year trends in major drug and biological product submissions to FDA.*
Source: FDA – available at http://www.fda.gov/oc/initiatives/criticalpath/nwoodcock0602.html

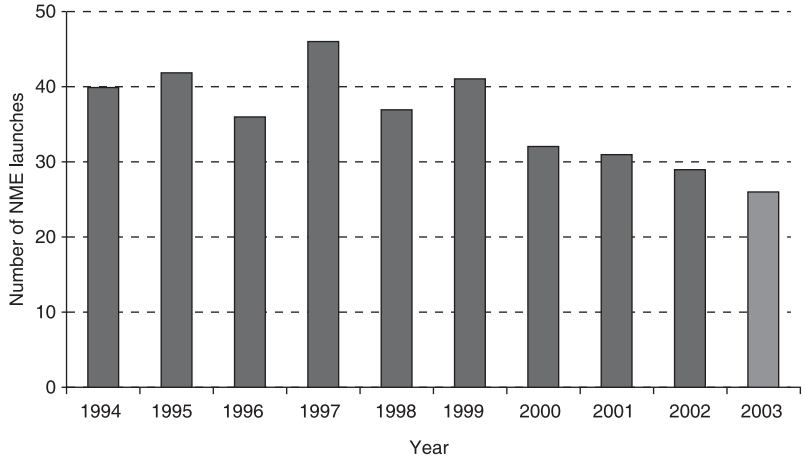

Figure 2 *Number of NMEs first launched onto the world market (1994–2003)*
NMEs = new molecular entities; BLAs = biologicals licence applications
Source: Centre for Medicines Research (2005)

therapeutic advance and those that do not. Those that do are given 'priority' review status, while the others receive 'standard' review status.[9] Most importantly, Table 2 shows that between 1993 and 2003 the number of NMEs offering significant therapeutic advance has also been declining.

Conclusion

The micro-level technical inconsistencies and contradictions found in science-based drug testing and regulatory decision making are not random rhetorical devices of isolated social

contexts/practices as relativist-constructivists would have us believe. With sustained sociological endeavour, they can be systematically linked to objective interests, whose relationship with pharmaceutical regulation may be best characterised as neo-liberal corporate bias. Such bias in political organisation at the macro- and meso-levels does indeed produce biases in regulatory science at the micro-level of decision making about individual drugs and specific technical standards for drug testing.

The consequence is that pharmaceutical development and regulation is failing to maximise the interests of patients and public health. This failure is however camouflaged by ideologies that give the impression that regulatory approaches promoting the interests of the pharmaceutical industry are also in the interests of public health, when they are, in fact, contrary to health interests. Thus, as realist sociology seeks to discover the truth about how well regulatory agencies achieve their publicly declared goal of protecting public health, it is necessary to go beyond descriptive accounts of actors' constructions of reality – constructivist accounts that might unwittingly reproduce fallacious ideologies because they shy away from a determination of the validity of actors' constructions.

Furthermore, as realist sociology exposes and explains the biases of pharmaceutical regulation, it also identifies ways in which such biases could be reduced by bringing regulatory organisation and practice closer to its declared goal to protect public health. For example, sociological research suggests that biases against the interests of public health could be counteracted by a number of measures. Comprehensive public rights of access to regulatory information and timely public accountability of regulatory decision making could be introduced. There could be state funding of regulatory agencies that is entirely independent of the pharmaceutical industry and sufficient to enforce rigorous standards of accuracy regarding industry product promotion, combined with a separation of the science of drug testing from the industry for at least some pivotal tests. Such tests could be conducted by government regulatory scientists. In addition, a prohibition of expert regulatory scientists from having any personal financial interests in pharmaceutical companies would be desirable. Then, there is the need for regular and pro-active legislative oversight which could ensure that drug regulatory agencies are progressing towards their ostensible constitutional goal to protect public health. Finally, there could be readily available access for patients to judicial review of the conduct of pharmaceutical companies to ensure their accountability to the interests of public health beyond the reviewing processes of regulatory agencies.

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Notes

1 The concept of 'stakeholders' replaced the concept of 'interest groups' in much of social science discourse in publications, grant applications and conference proceedings. That substitution implied a dis-association from a theoretical perspective committed to the view that interests

underpinned social relations and beliefs. Use of 'stakeholder discourse' by many social scientists (wittingly or unwittingly) implied that, at the very least, there was not necessarily a need to locate actors within a framework of objective interests. Typically, the role of interests is not explicitly or reflexively defined in stakeholder discourse, but implicitly it seems that interests are to be empirically recorded as (no more than) stakeholders' expression of their goals and desires. Of course, hypothetically, one could retrospectively define stakeholders as 'actors with interests', but that renders the concept of 'stakeholders' redundant because then one might just as well revert to the concept of 'interest groups'.

2 It might be argued that the 'superficiality' perspective 'brings more rather than less "reality" to the issue' because it involves empirical studies of actions (Irwin 2001: 166–67). But realists also employ empirical studies seeking to explain, as well as recount, actions. Moreover, Irwin's argument is analogous to saying that if the highway code were an impoverished document, then that flaw could be set aside so long as the authors did plenty of driving!

3 Space constraints prevent a more differentiated discussion of interests. As one moves from the macro to meso and micro levels of analysis, different interests may be specified.

4 By 'ideology' I mean a set of beliefs that distort reality.

5 'Patent medicines' were 'secret remedies', whose ingredients were not disclosed on the label to patients/consumers.

6 In some cases, patient groups press for early release of new drugs as a 'last resort', though the extent to which this is a major driver of regulatory problems and reforms has been exaggerated, compared with other factors, by the media and some social scientists (Abraham and Sheppard 1999b). If a number of patients on a drug trial in such circumstances have benefited and they wish to continue on the drug, even though the trial's overall evidence-base shows no therapeutic benefit/efficacy, then it may be in the interests of that minority of patients to have continued access to the drug. A policy response consistent with the interests of those patients is to permit continued 'compassionate' release of the drug to those *specific patients*, rather than an acceleration of the entire regulatory review system that is contrary to the interests of public health by slackening checks on safety and efficacy generally. Sometimes pharmaceutical companies refuse to co-operate with such a 'compassionate' policy because serving the small market involved is not compatible with their commercial interests – a scenario that confirms the need to distinguish industry interests even from those of patients pressing for access to drugs without a robust evidence-base of efficacy. In other cases, patient groups may press for early general market approval of a drug, whose benefit-risk ratio is unlikely to be positive because, for the (vast) majority of patients on trials, the risks outweighed the benefits. If, in this circumstance, there is no way of predicting which patients (beyond the trial) could benefit from the drug, then the patient groups would be acting against the interests of the patients *and* public health. This is because patients who take such a drug are more likely to suffer than benefit, and future patients in this, and other therapeutic fields (public health) would lose out as lower regulatory demands (of drug efficacy, as well as safety) for marketing approval come to be accepted.

7 It is not in the interests of public health or patients, in general, for the regulatory system to increase the risk-benefit ratio of the drugs approved on to the market, even if this is done, in part, as a response to the demands of some patient groups. It is, however, in the commercial interests of the industry for drug approvals to be accelerated, even if that increases the risk-benefit ratio of new drugs. Hence, insofar as regulators respond to the demands by manufacturers and some patient groups to accelerate drug approvals in ways that are inconsistent with the scientific standards of safety and efficacy established by regulators themselves, then that response is biased in favour of industry interests and away from the interests of patients and public health.

8 Thus, inconsistencies in (industrial and regulatory) scientific knowledge-claims *are necessary*, though not sufficient, to impute the operation of bias. It might be suggested that a consistent narrative of knowledge-claims about drug safety or efficacy from a pharmaceutical company or regulatory agency could also be biased. Such a suggestion should be rejected because it renders the concept of 'bias' analytically weak, if not dysfunctional, and it seems to be premised on a confusion between objectivity and truth-value, on the one hand, and 'interest-neutrality', on the

other. If a narrative of knowledge-claims is consistent, then it does not become biased merely because it is expressed by an interest group (*e.g.* a pharmaceutical company). Rather, it is an expression of knowledge-claims, undoubtedly influenced by interests, but *internally valid and unbiased*. Of course, that narrative might be shown to be biased by reference to *other* evidence, knowledge or narratives with which it is inconsistent. In that instance, however, the demonstration of bias crucially depends on, though is not established by, the identification of that inconsistency.

9 The FDA's classification system of 'priority' and 'standard' review is a less discriminating system than the (A-E) five-category classification used by the agency in the 1970s and 1980s. Compared with the earlier system, the 'priority' classification camouflages differences between new drugs of major therapeutic value and those of barely modest therapeutic significance.

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