

BIAS IN SCIENCE AND MEDICAL KNOWLEDGE: THE OPREN CONTROVERSY

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Abstract Analysis of the scientific evaluation of medicine safety has been neglected in sociology. This article examines the influence of interests and values on scientists' safety evaluation of the medical drug *Opren* in industrial and government contexts. By systematically identifying inconsistencies in the technical justifications of industrial and government scientists it is argued that the concept of interest-based bias is crucial for explaining the development of medical knowledge. Specifically, evidence is adduced to suggest that industrial interests biased scientists' production and interpretation of medical knowledge about *Opren* with potentially adverse consequences for patients' interests in safe medication. The Mertonian 'ethos' of science is seen to have very little application to the work of scientists in the context of drug regulation, giving way to institutional instrumentalism. The paper concludes by proposing an alternative system for the clinical testing and regulation of drugs which could discourage such industrial bias and provide greater patient protection.

Key words: bias in science, medical controversy, *Opren* safety, drug regulation, pharmaceutical industry, interests.

Introduction

Classic concerns of sociologists, such as the operation of values and interests, are not readily identifiable in science. Scientists are often presented as disinterested agents in pursuit of truth. This applies to medical scientists in government and industry as well as in academia. Regarding the regulation of the drug *Opren* by the British government's expert advisory Committee on the Safety of Medicines (CSM) Kenneth Clarke, then Minister of Health, pronounced:

the Committee on the Safety of Medicines acted in October 1981 as it must always act – rationally, based on the scientific data that were then available (House of Commons 1983:582).

According to many scientists in the pharmaceutical industry the marketing of medicines is based on scientific testing that ensures patients receive valuable therapy. For example, Bruce Peck, Director of Regulatory Affairs at Eli Lilly (Lilly) has declared:

Lilly does not market a drug nor request government approval for its use until extensive and well-controlled scientific studies prove that its benefits far outweigh the risks (Peck 1983:127).

Values and social interests, it is implied, play no part in the therapeutic evaluation of medicines.

This view of science tended to be reflected in sociology by the Mertonian conviction that scientists formed a 'community' operating according to a set of prescribed norms: the open and free exchange of ideas and findings ('communism'); openness to treating any knowledge claims on their merits ('universalism'); freedom from economic or political motivations (disinterestedness); and the tendency to treat any knowledge claim with caution and subject it to close scrutiny ('organized scepticism') (Merton 1942). According to Merton values and interests entered science solely from outside the scientific community as pollutants:

The ethos of science involves the functionally necessary demand that theories be evaluated in terms of their logical consistency and consonance with the facts. . . . In some instances scientists are required to accept the judgements of scientifically incompetent political leaders concerning matters of science. But such politically advisable tactics run counter to the institutionalised norms of science (Merton 1938:258–59).

Since the post-Kuhnian era of the 1970s, sociologists have begun to document the role of values and interests in the development of scientific knowledge. Yet, as many commentators point out, the sociology of scientific knowledge remains largely 'internalist' (Cozzens and Gieryn 1990:1; Knorr-Cetina and Mulkay 1983:6; Restivo 1987:13–14). Frequently attention is restricted to 'local accounting procedures' at particular laboratories, or to professional interests *within* the academic scientific community (Collins 1983a; Latour and Woolgar 1979, 1986; Krohn 1980). As Nelkin (1989:305) puts it:

. . . the field is still turned inward, into itself, creating its own language with too little reference to the outside world. . . . Rare are the studies that focus on the ideologies embedded in science because of its political and economic relationships, and its proximity to centres of power.

The sociological literature available on contemporary medical knowledge, such as McCrea and Markle (1984), Nicolson and McLaughlin (1988) and Richards (1991), are mainly concerned with the medical profession and its patient clientele, rather than with the scientific activity conducted by the pharmaceutical industry and the government authorities responsible for regulating the industry.¹ This paper seeks to redress the balance by concentrating on the work of industrial and government scientists, although their interactions with academic scientists form a significant part of the research. By examining the possible ways in which values and interests may bias medical knowledge, I shall address *both* Mertonian concerns about the 'ethos' of science and modern sociological inquiries into how scientific knowledge is produced.

Methodology

The approach in this paper is derived from a synthesis of Wynne (1984), who analysed the *technical inconsistencies* in a scientific institution's account of itself in order to probe its underlying values, and of Irwin (1984; 1987), who used technical *controversies* in risk assessment to elicit the interests and commitments that framed 'expert' decisions about new technology. Focussing on technical inconsistencies is important because it precludes a purely rationalist defence of the scientific claims involved that could be mounted to deny bias. That is, it excludes the possibility that those claims have been adopted by scientists simply because they are 'objectively more sound' than alternatives (Mazur 1973:244). To be confident of the operation of bias one must *at least* identify conditions of technical inconsistency, and not merely the presence of values or interests.

Such inconsistencies may be, for example, between claims of the same scientists in different social contexts (Chubin 1981:432), or between the claims of a particular scientific institution/individual scientist and the established knowledge of the scientific field in question (Barnes 1974: 41–2, 136–8). Equally, the study of controversies is valuable because it can elucidate 'what is hidden in ordinary science' (Collins 1981: 4) and provides a fruitful context for discovering specific norms and interests of scientists (Brante and Elzinga 1990:44).

The 'interests approach' adopted here takes account of the macro-level of social structures which influence scientific research direction and the micro-level agency of individual scientists (Hagendijk 1990; Martin 1988; Giddens 1984). Pharmaceutical companies have basic commercial interests in sales of their drug products, but that does not necessarily imply that all individual scientists employed by a particular company will construct those interests in the same way. Patients' interests in the safety and efficacy of medicines can sometimes converge with those of the pharmaceutical industry because safe and effective products are likely to be successful on the market. However, there is scope for divergence and even conflict of interests between patients, who desire maximally therapeutic products, and pharmaceutical companies, who want their drugs to reach the largest market rapidly and at low research and development cost. Within this context it is the responsibility of the government's regulatory authorities to determine whether the scientific evidence generated by the clinical testing and experience of a drug implies that it is sufficiently safe and effective to be put, or to remain, on the market.

The medical knowledge developed and made available during pre-market testing and post-marketing surveillance of a drug can be in the thick of such conflict because it commands so much authority in defining a drug's therapeutic value. In particular, when prescribing doctors seek to inform themselves about the medical characteristics of drugs they turn to two crucial sources of scientific knowledge: the *government-approved product data sheet*,

which may be thought of as the medicine's official labelling; and the *published medical literature*. The general practitioner draws on these sources as the 'medical facts' about a drug.

In order to identify technical inconsistencies and to relate them to the influence of social interests it is necessary to take an in-depth case study approach. The scientific controversy over the safety/toxicity of *Opren* in the elderly has been chosen as a case study not only because of its sociological significance as one of the largest single drug disasters in modern Britain, but also because it is a subject upon which sociology can make an important contribution to policy debate.

The data cited in this article are derived from the publicly available transcripts of the testimonies of scientists, including many employed by the manufacturers of *Opren*, Parliamentary debates, questions and answers in *Hansard*, and leaflets, letters, consultation papers and other documentation disposed by the British regulatory authority in respect of its duties under the 1968 British Medicines Act. Computer searches and Science Citation Indices are used to survey systematically the relevant scientific literature. I requested access to the minutes and files of the CSM on *Opren*, but was refused permission and further informed that representatives of the Committee were not allowed to discuss its business regarding individual drug products under the confidentiality rules of the 1968 Medicines Act (Personal Communication 1988a, 1988b). For this reason the internal workings of the CSM are least well documented in this article.

Background to the Controversy

Opren is one of a class of medicines known as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which are used to treat osteo- and rheumatoid arthritis, and is the British trade name for the compound known as benoxaprofen. It was manufactured by Eli Lilly as a prescription NSAID during the 1970s. Lilly is a multinational company, but its main headquarters are in Indianapolis in the US. Lilly's British subsidiary, Dista Products Ltd (Dista), was responsible for organising safety testing, marketing and adverse reaction monitoring of *Opren* in the UK. The market for NSAIDs is extensive because arthritic diseases are chronic and incurable and because of the increasing number and proportion of elderly people, who are most commonly afflicted by arthritis (Woods and Britton 1985:2-6). For example, in 1980 in England and Wales alone arthritis and rheumatism accounted for 15.8 million prescriptions (Bland *et al.* 1985:156). Hence, during the 1980s pharmaceutical companies had very substantial commercial interests in the successful market- ing of NSAIDs.

In April 1980 the British regulatory authorities, then the Department of Health and Social Security (DHSS), approved the marketing of *Opren* in the

UK with a product data sheet *recommending a daily dose of 600mg*, following the advice of the CSM. *Opren* was not significantly more effective than other NSAIDs so its toxicity in the elderly was a very significant factor in judging its therapeutic value. The medicine was withdrawn from the market world-wide in August 1982 following reports of many serious adverse reactions associated with its use.

Technically, the controversy centred on *pharmacokinetics*, the study of how drugs are absorbed, distributed and eliminated (i.e. excreted) from the body, which can have important implications for the safety of medicines. Some particularly relevant parameters are: (i) elimination half-life, i.e. the time taken for concentration of a drug in the blood to drop to half its initial value; (ii) steady state, i.e. the amount of a drug in the blood reached when additional doses cause no further accumulation; and (iii) renal functioning, i.e. the kidneys' ability to eliminate a drug from the body. If the latter is impaired then a possible consequence is toxic accumulation of the drug in the body (Barber and Petrie 1981).

When initially marketed, one of *Opren*'s perceived therapeutic advantages was its long elimination half-life, enabling it to be taken only once a day. This was especially advantageous for elderly patients, whose compliance with taking tablets is known to decrease with the frequency with which they have to take them (WHO 1981). *Opren*'s long elimination half-life was known to Lilly and the regulatory authorities before marketing the drug in the UK, but until 1981, neither had investigated its pharmacokinetics specifically in the elderly (Gennery 1983a:37; Hamdy 1983:17; Mikulaschek 1983:236–43).

The Hamdy and Kamal Studies

It was in this context that Ronald Hamdy, a specialist in geriatric medicine at St. John's Hospital, London, approached Dista's medical department to arrange a pharmacokinetic study of *Opren* in the elderly, which was undertaken in March 1981 (Gennery 1983a:39; Hamdy 1983:21). Initially Hamdy had two groups of elderly patients. One group of six patients with average age 81.8 and youngest 76 received a single dose of 600mg of *Opren*, while the other group of five patients with average age 86.2 and youngest 72 received a single dose of 300mg. For both groups blood levels of *Opren* were measured for five days (120 hours). They found elimination half-lives of 111 hours and 86.4 hours in these two groups respectively (Hamdy, Murnane, Perera, Woodcock and Koch 1982). This compared with an elimination half-life of 30–35 hours in 'normal' subjects (i.e. sampled from a population including very few elderly patients).

These results were presented at a Paris symposium in June 1981. The possible relevance of Hamdy's findings to *Opren* therapy is illustrated by the following comment in the published version of his symposium paper:

The metabolism and excretion of compounds with a prolonged half-life, however, may be slower in old age as a result of impaired renal function commonly seen in this age group. The continuous administration of compounds [with long elimination half-lives] at the normally recommended doses to elderly patients, therefore, may result in unnecessarily elevated and potentially harmful [blood] plasma levels (Hamdy *et al.* 1982:69–70).

Also presented at the Paris symposium was a paper by Kamal from St. George's Hospital in Lincoln. He studied the blood profiles of *Opren* over a 17 day period in 10 elderly patients given a daily 600mg dose of the drug for the first 10 days. The mean age of these patients was 77; the youngest being seventy. Kamal found an elimination half-life of 101 hours and drew the following conclusions:

The markedly extended [blood] plasma half-life could be attributed to an age-related reduction in benoxaprofen elimination. Since steady-state levels were not achieved within 11 days in these patients, a reduction in dosage may be necessary in elderly patients. . . . The higher benoxaprofen concentrations and the long elimination half-life show evidence of accumulation in the elderly, probably due to several causes, including . . . decreased renal clearance common with increasing age. The recommended dose may require modification in geriatric patients (Kamal and Koch 1982:76, 81).

Thus Kamal's multiple dose study provided particularly strong evidence of accumulation in the elderly since a steady-state was not reached even after 10 days.

After the Paris symposium Lilly's pharmacokinetic group in Indianapolis, including Walter Mikulaschek, Lilly's Medical Monitor for clinical trials with benoxaprofen, Ian Shedden, Lilly's Medical Director, and Karl Desante, a Senior Pharmacokineticist in the company, reviewed Hamdy's data. They argued that blood samples should have been taken for as long as up to five times the half-life, and that the renal functioning of the elderly patients should have been determined before the study began (Gennery 1983a:43; Hamdy 1983:23). Samples for up to five times the half-life had not been taken because neither Hamdy nor any scientists at Lilly had anticipated that the half-life in the elderly would be so long (Chatfield, Tarrant, Smith and Spiers 1977:579).

Lilly's own pharmacokinetic research on *Opren* in Indianapolis, however, did not meet the standards demanded of Hamdy. In early Spring 1982 Desante and Ridolfo, a Senior Clinical Pharmacologist at Lilly in Indianapolis, co-authored a paper, which reported a single dose study of 20 patients, whose blood levels were measured for up to 7 days (168 hours). Yet the mean half-life for eight of those patients was just over 62 hours, and for another eight it was over fifty-one (Aronoff, Ozawa, Ridolfo, Nash and Desante 1982). For the former eight, five half-lives amounted to no less than 310 hours (12.9 days), and for the latter no less than 255 hours (10.6 days) (Aronoff *et al.* 1982).

Nevertheless, Hamdy agreed to conduct a further single dose study with four other patients, measuring levels of *Opren* in the blood for as long as 21 days (504 hours) (Hamdy *et al.* 1982:69; Hamdy 1983:23). These patients had a mean age of 79.5 years with youngest being 71 years old. In this study, which was completed by the end of July 1981, Hamdy found a half-life of 147.9 hours. Based on Kamal's results and his own, Hamdy reached the conclusion that in elderly patients *Opren* tended to accumulate to a much greater extent than in younger patients, and that 600mg of the drug should be given to the elderly only once or twice per week, rather than on a daily basis because of the risk of adverse effects that could arise from its accumulation (BBC 1983; Hamdy 1983:27).

Hamdy communicated this conclusion to Lilly in June 1981, whence he was referred to the company's headquarters in Indianapolis. He wanted Lilly 'to look at the use of benoxaprofen using it once a week or twice a week in elderly patients with osteoarthritis' in order to establish whether it remained effective (and, therefore, market competitive) at such infrequent doses (Hamdy 1983:29). Instead, Lilly headquarters told Hamdy that they wanted more proof of his findings.

The parent company in Indianapolis was extremely reluctant to publish Hamdy's findings, or those of Kamal. According to Charles Vaughan, one of Lilly's medical writers, who was responsible for preparing drafts for the publication of the Paris symposium papers, it was initially decided at Indianapolis not to do so. Any publication of either Hamdy's or Kamal's findings was to wait until after Ridolfo and Desante had carried out a further pharmacokinetic study of *Opren* in five elderly patients because senior scientists at Lilly's headquarters demanded 'further clarification' and found it 'difficult to believe that benoxaprofen pharmacokinetics in the elderly are significantly different from those in young people in the absence of renal impairment' (Gennery 1983a:78; Vaughan 1983:56).

Yet a very significant body of medical literature was available which directly opposed the view taken by senior Lilly scientists on this matter. Davies and Shock (1950) concluded that there was a decline in effective renal blood plasma flow amounting to fifty-three per cent between the ages of twenty and ninety. Even the authors of the Lilly-sponsored research into the effects on geriatrics of the Lilly NSAID, fenoprofen, in 1976 commented that such patients would be 'expected to be highly susceptible to any drug toxicity' (McMahon, Jain and Onel 1976:76, 82).

By the late 1970s concern about the accumulation of drugs in the elderly because of reduced drug elimination, even without clinical evidence of renal failure was 'well established' (Castleden 1978:90-91). Perhaps most significantly, in early 1981 the WHO's committee on the 'Use of Medicaments by the Elderly' concluded:

The elderly differ from the young in the quantity of the drug delivered to the target organ, and possibly in the sensitivity of that organ to the drug. Although

such knowledge has been present for a number of years, there are very few drugs for which a specific geriatric dosage is recommended, and dosage regimens for new drugs are still established on data obtained in younger individuals. . . . the elderly are at risk from relative overdosage of drugs due to inefficient pathways for drug elimination and metabolism (WHO 1981:280).

Thus, Lilly applied *inconsistent* criteria in judging the validity of the studies by Hamdy and Kamal, compared with those of the company's own scientists. While the latter studies were published, senior scientists at Lilly's headquarters in the US argued against the publication of the former. Moreover, Lilly scientists' technical objections to the Hamdy and Kamal studies were in *contradiction* with a massive body of scientific knowledge at that time, including some scientists who had conducted clinical work on one of Lilly's other NSAIDs.

The Ridolfo Study

Ridolfo's study, which was *single* dose, also featured prolonged half-lives (40–50 hours) in the five elderly patients involved, but less dramatically than the research of Hamdy or Kamal. Senior scientists at Lilly took the view that Ridolfo's study was more scientifically rigorous than Hamdy's or Kamal's because it contained 'good tests of renal function, and a good correlation between half-life and renal function' (Gennery 1983a:50).

According to Brian Gennery, Dista's Medical Director, the scientific justification for carrying out the Ridolfo study was not only to test the validity of the Hamdy and Kamal findings, but also to evaluate *Opren*'s pharmacokinetics in the elderly aged 65–75, rather than the very elderly aged over 75, who were the primary focus of Hamdy and Kamal (Gennery 1983a:50–55). Such justification is, however, highly questionable. For if Ridolfo's study were designed to test the *validity* of the Hamdy and Kamal studies it should have attempted to compare patients of the same size and age group. Despite this, Gennery admitted that Ridolfo's patients were 'substantially heavier and significantly younger' (Gennery 1983a:52). If, on the other hand, Ridolfo's study were intended to explore the *reliability* of extrapolating the Hamdy and Kamal findings in the over 75 age group to the 65 to 75 age group, then there was an implicit assumption on the part of Lilly that age did indeed play an important role in defining *Opren* pharmacokinetics, as Hamdy and Kamal had claimed. Yet, on this assumption, there was no justification for Shedden's argument not to publish the Hamdy and Kamal findings on the grounds that they needed 'further clarification'.

Lilly scientists seem to have been aware that there were safety implications of these pharmacokinetic studies in the elderly because, on the basis of his findings, Ridolfo recommended, in an internal Lilly report on 25 September 1981, that the daily dose of *Opren* in elderly patients, with small body weight

and reduced renal function, should be decreased by fifty to seventy-five per cent (Desante 1983:81). He suggested that this could be achieved by a dosage of 300 mg every twenty-four to forty-eight hours (Desante 1983:81). Desante, Ridolfo's co-researcher, concurred with these recommendations and believed them to have been made because of the study's 'important implications for safety in those patients' (1983:73, 81).

Similarly, Christensen, Vice President of Lilly's Research Laboratories in Indianapolis, has testified that the Hamdy, Kamal and Ridolfo studies were 'a red flag in that you may want to use a reduced dosage in patients where it might accumulate' because 'you're not sure what might come out of that sort of thing' (Christensen 1983:59). And for Mikulaschek these studies implied that 'you have to be careful because you have an accumulation of drug, and whenever you have accumulation of any drug there is increased risk' (1983:245). Nevertheless, the Ridolfo study was never published (Desante 1983:70–73). This can be contrasted with the company's keen efforts to publicise the fact that *Opren*'s elimination half-life made possible the therapeutically convenient once-a-day dosage.

It is clear from this analysis that the arguments used by senior Lilly scientists to justify a delay in the publication of the Hamdy and Kamal studies until such time as they were confirmed by Ridolfo's research were *internally contradictory*. Furthermore, by electing not to publish Ridolfo's pharmacokinetic study, senior scientists at Lilly reduced the weight of scientific evidence in the public domain in favour of reducing the dosage of *Opren* in the elderly.

The Publication of the Hamdy and Kamal Studies

Despite his disagreements with the findings of Hamdy and Kamal, Gennery did not welcome the proposal from Lilly's headquarters not to *publish* their research. Fundamentally, he was concerned that the credibility and interests of the company might be damaged if Hamdy felt the need to submit his paper to a major journal such as the *British Medical Journal*:

Kellogg: And did you tell the people in Indianapolis that it would create a lot of attention to the subject if Dr. Hamdy's paper were for some reason omitted from the European Journal and then he published it somewhere else?

Gennery: Well, yes. My approach to the publication was not based so much on the scientific finesse and nicety of the situation, but just the very pragmatic approach that we have had eighty-five rheumatologists at the meeting who have heard these papers presented, and we would find it difficult to explain to them why they weren't published.

Kellogg: Those eighty-five rheumatologists would in fact find it strange that these papers weren't in that journal?

Gennery: Absolutely (Gennery 1983a:65).

Gennery believed that the Hamdy and Kamal studies were technically satisfactory, but the dispute between Gennery and Lilly's senior scientists in Indianapolis was as much about where the best interests of the company lay on this matter as it was about the internal validity of the scientific arguments. By agreeing to publish the Hamdy and Kamal studies, Lilly maintained greater editorial control over their fate because the company was sponsoring the journal edition in which the Paris symposium proceedings were to appear. Ultimately Gennery's view prevailed within the company and the Hamdy and Kamal papers were published in early Spring 1982.

The Regulatory Inaction of the CSM

Throughout Lilly's deliberations about the pharmacokinetics of *Opren* in the elderly the company engaged in intermittent discussions about it with the CSM (Gennery 1983b). The Committee decided that no regulatory action should be taken, but that Lilly should complete the Ridolfo study by 1 October 1981, when the situation would be reconsidered. The CSM made this recommendation even though, according to Sir Abraham Goldberg, the Committee's chairman, they thought that Hamdy had conducted a 'good study', and that the Hamdy and Kamal studies 'warned there might be a problem with benoxaprofen in the elderly' (BBC 1983).

Lilly complied with the CSM's suggestion, and on 7 October 1981 proposed to the Committee that the *Opren* data sheet should be changed to include a statement that elderly debilitated patients with evidence of renal impairment should be given only 300 mg *Opren* per day, and that debilitated elderly patients aged seventy-five or older should also receive the reduced daily dose of 300 mg. It is notable that of all the pharmacokinetic data being considered Lilly decided to adopt the Ridolfo study, which had the most conservative implications for dosage reduction, and to propose to the CSM the *smallest* dose reduction recommended by Ridolfo (Gennery 1983a:130). This approach may be contrasted sharply with advice in the *British Medical Journal* on 10 January 1981 to 'always err on the side of *low doses* in the elderly' (Ramsay and Tucker 1981:126).

In any case, on 17 November 1981 the CSM did not accept Lilly's proposal for dosage reduction, and according to Gennery, had seen a conflict between the results of the Ridolfo study and those of Hamdy and Kamal. This seems to be confirmed by Goldberg's explanation of the Committee's inertia in February 1982 when fatal hepato-renal reactions associated with *Opren* therapy began to be reported by doctors:

Mangold: Professor, you had two studies [Hamdy and Kamal studies] that warned you that benoxaprofen might be toxic to the elderly. You already had, two unexplained liver deaths, – what more information did you need before acting?

Goldberg: There were other pharmacokinetic studies, drug-handling studies, in relationship to benoxaprofen which didn't fully confirm these initial studies (BBC 1983).

In particular, Gennery has testified that the CSM wanted Lilly 'to repeat the Kamal protocol in patients aged 65 to 75', when the situation would be considered again (Gennery 1983a:78).

An additional explanation for the regulatory inaction of the CSM in February 1982 put forward by Goldberg is that the total adverse reactions of *Opren* at that time were no greater than for other NSAIDs. As he put it:

... there was no difference from a group of about three or four other drugs. If we had to sound warnings on benoxaprofen, we would have had to do the same for these other drugs as well (BBC 1983).

The *Opren* data sheet remained as approved in August 1980 until May 1982, making no reference to the elderly (Dista 1980). That decision was certainly controversial, especially since Michael Rawlins, a member of the CSM between 1979 and 1985, (CSM 1979–85) stated under 'Pharmacokinetics' in an article published in the *British Medical Journal* on 21 March 1981:

Patients with impaired renal function (including the elderly) are particularly liable to develop ... [adverse pharmacological] reactions when given doses designed for healthy young adults (Rawlins 1981:974–75).

Moreover, in January 1983 Laurence Prescott, a toxicologist, who had sat on the CSM's Toxicology Sub-Committee, argued that the Hamdy and Kamal studies implied that the dosage for the elderly needed to be reduced to a quarter of the dose given to a younger person (BBC 1983). In fact, on reviewing all the citations to the Hamdy and Kamal studies listed in the *Science Citation Index* from 1982 to 1990, I found many which treated the studies as authoritative and none that challenged their findings.

Thus the CSM required extensive confirmation of accumulation of *Opren* in the elderly and attendant potential risks before they could feel justified in recommending a reduced dosage for elderly patients. Initially the CSM's approach coincided with Lilly's, but after the Ridolfo study, even Dista were prepared to recommend a modest dosage reduction for the elderly. The CSM, however, interpreted uncertainty in this instance as grounds for inaction.

The Approved Safety Warnings Regarding the Elderly

Lilly did carry out the further study requested by the CSM, but preliminary results were not available until the end of July 1982. Nevertheless,

at the end of April 1982, following the deaths of several elderly patients from a hepato-renal syndrome whilst taking *Opren*, the CSM told Lilly that they were not prepared to wait for the additional study, and that they wanted the *Opren* data sheet changed urgently to stipulate that patients over sixty-five should receive no more than 300 mg per day because adverse effects were more common in the elderly (Gennery 1983a:86).

In fact, the new May 1982 *Opren* data sheet produced by Dista and approved by the CSM stated merely:

A daily dosage of 300 mg may be advisable in patients with impaired renal function. This applies particularly to aged, frail patients (Dista 1982a).

This was not an instruction to doctors not to prescribe more than a daily dose of 300 mg benoxaprofen for elderly patients, though it was advice not to do so for the elderly *and frail*. The findings of Hamdy and Kamal did not imply potential risks solely to frail elderly patients, but over seventy-five year olds in general. Whilst some very elderly patients may have extraordinarily healthy kidneys and livers, the view taken by Hamdy and Kamal was that such patients would, *in general*, have reduced renal and/or hepatic function, and so to err on the side of safety, doctors should have been warned about the drug's accumulation in this population group. However, the approach taken by Lilly and the CSM was to give a warning which minimised the elderly patient group supposed to be at risk, disregarding the WHO's exhortations that ageing could alter drug metabolism in ways not reducible to renal function.

For Hamdy, the minimalist measures taken by Lilly and the CSM in May 1982 may have had severe consequences. He believed that his research, together with that of Kamal's, had anticipated the fatalities reported among elderly patients taking *Opren* (BBC 1983; Hamdy 1983:115–6). Mikulaschek, however, denied that the Hamdy or Kamal studies predicted deaths in the elderly, but he did consider that they implied the need for precautions, such as unusually frequent monitoring of kidney and liver functioning (Mikulaschek 1983:244). Yet Dista's *Opren* data sheets stated no such precautions (Dista 1980; 1982a; 1982b).

It was not until June 1982, following the publication of the aforementioned deaths by McA Taggart in the *British Medical Journal* that the CSM and Lilly issued a clear warning that the elderly should receive no more than a daily dose of 300 mg of *Opren* (Lilly 1982d). Moreover, the scientific reason for the reduced dosage given in the June 1982 *Opren* data sheet confirmed the concerns expressed by Hamdy and Kamal in Paris one year previously:

The elderly: In patients over the age of 65, a daily dose of 300 mg should not normally be exceeded, because the elimination rate of *Opren* is commonly reduced in such patients (Dista 1982b).

Thus, when the CSM and Lilly did decide to recommend some dosage reduction in the prescribing of *Opren* in the elderly the wording initially

chosen would cause minimal damage to the commercial success of the drug. Furthermore, it was not consistent with the standards advocated by Mikulaschek, one of Lilly's key scientists in the assessment of benoxaprofen's safety. Ultimately Dista and the CSM recommended a clear consumer-protective warning. However, the reason asserted in support of that advice, though belatedly in agreement with Hamdy's views, flatly *contradicted* the earlier approach by the Committee and the technical arguments advanced by senior scientists at Lilly.

Discussion and Conclusion

The foregoing analysis provides further evidence that the Mertonian perspective on the norms of science, which still holds considerable sway (Bunge 1991; Hammersley 1992), is of limited relevance to the *industrial* and *government* contexts. Senior Lilly scientists sought to obstruct the open exchange of Hamdy's findings and did not treat his research on its merits. Insofar as there were disagreements between company scientists about whether Hamdy's research should be published this resulted from concerns about how to secure the best interests of the company, rather than any tension between supposed norms of scientists and the commercial discipline of industry. This paper supports the surveys of scientists' opinions by Ellis (1969), Barnes (1971) and Sklair (1973), who found that industrial scientists take an *instrumentalist* view of scientific research; but it goes beyond them to demonstrate the consequences of such instrumentalism for the production of scientific knowledge.

Lilly scientists applied criteria which were internally contradictory and/or logically inconsistent with established knowledge about medication at that time. Moreover, those inconsistencies repeatedly coincided with the commercial interests of the company in representing *Opren* as minimally toxic. This suggests that commercial interests *biased* the production of medical knowledge. However, different kinds of 'interested action' are embedded in such bias. Evidently interests may be closely attached to certain technical commitments, such as whether or not old age is a significant factor in relating the pharmacokinetics of a drug to its toxicity. Interests may also frame technical requirements of adequate proof so that the burden of proof is greater for critical work threatening those interests than for sympathetic innocuous work. Such inconsistencies in requirements of adequate proof can be related to research priorities as indicated by a willingness to publish findings in line with those priorities and by a reluctance to publish results disrupting them.

The subtle nature of that bias is of sociological and policy significance. Gieryn's (1983) concept of boundary-work has usually been invoked to describe how professional scientists exclude non-scientists from policy debates (Jasanoff 1988; 1990) and how professional interests police the

established methodologies of orthodox medicine (Richards 1988, 1991). The controversy over the safety of *Opren* in the elderly highlights boundary-work to protect Lilly's *institutional* rather than professional interests. Key Lilly scientists sought to monopolise scientific authority by attempting to undermine the legitimacy of the clinical methodologies of Hamdy and Kamal, even though those methodologies had substantial credibility within the medical profession. Hence, Bartley's (1990) 'bandwagon', which aims to focus (medical) sociological attention on professional interests at the expense of social and political interest may have considerable analytical drawbacks.

In saying this, it is important to appreciate that commercial and institutional interests are dynamic (Wynne 1992). Gennery constructed Lilly's interests differently from his company colleagues in Indianapolis. In effect, Gennery argued that the company had vital interests in maintaining professional credibility amongst its medical public by being willing to publish the Hamdy and Kamal studies. Clearly Gennery's intervention affected the bias of the medical literature about *Opren* by influencing the course of publication. An important conclusion from this episode is that agents' constructions of interests, including expectations about 'social viability' and 'public legitimacy' need to be incorporated into an understanding of the interplay between institutional interests and bias in science (Schwarz and Thompson 1990). Lilly's biasing of medical knowledge about *Opren* safety was filtered by Gennery's construction of the company's institutional interests.

As regards the regulatory authorities, Mertonian norms of 'communism' and 'disinterestedness' are little in evidence in the work of the CSM, whose members function behind a cloak of secrecy impenetrable to virtually the entire medical community, and in many cases frequently have direct or indirect commercial links with the pharmaceutical industry – links which were published for the first time in 1989 (see Appendix) and have remained substantial (Scrip 1991). Such financial links are sought entirely voluntarily by these government-affiliated academic scientists so it may be deduced that they experience little or no 'role strain' in the government context due to violating supposed Mertonian norms of science. Furthermore, it is clear that scientists themselves, and not merely technically incompetent politicians as Merton suggested, are very much involved in the economic and political penetration of science.²

It is possible to interpret the CSM's regulatory caution regarding changes to the *Opren* data sheet as a reflection of 'organised scepticism'. Insofar as that is the case such scepticism seems to be dysfunctional for medicine regulation as *consumer protection* because it is contrary to the interests of patients to have to wait until after people have died from anti-arthritis medication before being warned about the serious risks involved. This suggests a CSM bias against consumers' interests derived from the practice of 'scientific politics' whereby social and political judgements are reduced to technical calculations (Keat 1981:12–37).

Whilst 'scientific politics' seems to be a significant factor in explaining the CSM's handling of the *Opren* data sheet, it is not sufficient to account for the complexities of the Committee's regulatory decisions. The CSM was reluctant to take regulatory action against a number of NSAIDs, which would potentially damage commercial interests *across* the pharmaceutical industry. It is likely that such action would have been met with opposition from the industry demanding rigorous justification by the CSM. The CSM avoided such a conflict with industry by defining the 'scientific' basis for its regulatory action in terms of compelling evidence that *Opren* was more toxic than other NSAIDs. In effect the CSM opted to give Lilly rather than patients the benefit of the many scientific doubts about *Opren*'s safety in the elderly. The CSM's bias in awarding the benefit of the doubt to Lilly is indicated by the technical inconsistencies inherent in the Committee's decisions on *Opren*.

Any attempt to explain why the CSM distributed the benefit of the scientific doubt in favour of Lilly and the pharmaceutical industry rather than patients must necessarily be tentative because of the intense secrecy that surrounds the internal workings of the Committee. Nevertheless, it is notable that Goldberg, who had been appointed as chairman of the CSM in July 1980 gave advice on a Lilly-funded *Opren* clinical study conducted by his university department between 1978 and 1980 (House of Commons 1985: 1142). Moreover, Goldberg's department was funded by Lilly to conduct a further *Opren* study – though Goldberg himself took no part in this later study – throughout the period when he chaired the CSM's deliberations about the toxicity of *Opren* during 1981 and 1982 (House of Commons 1985:1142). This close contact with industry may be contrasted with the CSM's virtual insulation from consumer and other non-scientist representation, and even from the wider medical community. There is no direct evidence available that these factors influenced the CSM's decisions, but then, because the Committee's minutes and internal proceedings are protected by secrecy laws, such evidence as there *might* be cannot be collected.

Of course, the fact that Goldberg or any other scientist had 'personal' or 'non-personal' financial links with the pharmaceutical industry does not necessarily imply that their judgement was biased (consciously or unconsciously) in favour of commercial interests, and it is not being suggested that Goldberg behaved improperly. Nevertheless, the gross imbalance in industrial and consumer access to the CSM does increase the risk that the regulatory authorities might be predisposed to such bias, especially when industrial and consumer interests conflict. In the case of *Opren* that risk would seem to be significant.

Many relativist and constructionist sociologists of science either eschew the suggestion that their work implies bias in science (Collins 1983a:99; Collins 1985:159–60; Woolgar 1982:484) or believe that the removal of bias in science is a misguided goal because all science is necessarily biased by values and interests (Martin 1979; Richards 1991; Schwarz and Thompson 1990). This

paper's examination of the relationships between institutional interests and the production of medical knowledge does not imply that knowledge is reducible to interests. The internal contradictions contained within some of the positions taken by Lilly and the CSM make their technical claims less robust, less valid and less reliable than the more consistent stances of Hamdy and Kamal. It follows that some knowledge claims can be less biased than others, but not necessarily from a standpoint of value- or interest-freedom. Hamdy maintained a consistent technical stance based on a professional/ethical commitment to safe prescribing in the elderly. Relatively unaffected by the interests of industry or government, his commitment was convergent with the interests of patients in broad terms.

The above sociological analysis of *Opren* safety evaluation in the elderly has demonstrated *specific* institutional biases in the work of industrial and government scientists through the identification of technical inconsistencies and their convergence with certain interests. Whilst the removal of all bias in science may be an unrealistic goal, it does not follow that policy changes cannot be implemented to deter the persistence of *particular* biases, and to encourage the development of alternative values and interests, which are better equipped to generate more valid and reliable knowledge which is much needed by prescribing doctors and patients.

Over the last decade the government has encouraged de-regulation of the pharmaceutical industry. Consequently, state responsibilities and costs have been transferred to the private sector on the assumption that the industry can be trusted to regulate its own affairs without compromising consumer safety. This case study directly challenges that assumption. The debacle between Gennery and senior Lilly scientists at Indianapolis about the publication of the Hamdy and Kamal studies suggests that exposure of pharmaceutical companies' clinical testing to the wider medical profession militates against company scientists defining their institutional interests in narrow commercial terms. In particular, commercial bias could be reduced by developing regulatory policies which require a significant proportion of the clinical testing of a new drug to be conducted by medics who have little or no commercial or institutional interests in its therapeutic success. To help achieve this clinical investigators could be *selected* by the regulatory authorities or, perhaps, consumer organisations rather than the drug's manufacturer. Regulatory bias could be undermined by requiring the regulatory authorities' decision-making processes to be fully open to public scrutiny; to accommodate extensive consumer representation; and to prohibit expert advisors from retaining financial links with pharmaceutical companies.

APPENDIX

Financial Links with the Pharmaceutical Industry in 1989

	Personal Interests*	Non-personal Interests**	Neither
Medicine Commission (n = 24)	17	7	5
CSM (n = 21)	14	15	4
CSM Subcommittee on Safety, Efficacy & Adverse Reactions (n = 18)	12	13	2
Comte on Review of Medicines (n = 17)	7	10	6

*Defined as consultancies, fee paid work and shareholding.

**Defined as payments that benefit department for which member is responsible but are not received by member personally.

Source: DELAMOTHE, T. 1989 .

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Notes

1. Exceptions to this include the sociological studies of tranquillisers by Gabe and Bury (1988) and Gabe (1992). Braithwaite (1984) provides a valuable survey of corporate crime in the pharmaceutical industry, but that is primarily concerned with bribery, extortion and fraud, and neglects the study of government scientists who regulate the industry. While Medawar (1992) provides an extensive review of the control of benzodiazepine safety, he makes no attempt to link it with sociological developments.
2. One response open to Mertonians is to propose that scientists with commercial interests are not 'proper scientists'. However, the sociological cost of this strategy is that the vast majority of people institutionally defined as scientists could no longer be regarded as scientists.

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