CURRENT OPINION

Drug Safety 2003; 26 (3): 135-143
0114-5916/03/0003-0135/$30.00/0

The Science and Politics of Medicines Control

John Abraham

Centre for Research in Health and Medicine, University of Sussex, Brighton, United Kingdom

Abstract

Drug development and regulation are often presented as purely matters of technical science. In this paper it is argued that, in principle, toxicology, clinical pharmacology and pharmacovigilance in drug testing and regulation are necessarily a combination of science and politics. This has important implications for how one attempts to make progress in drug regulation, such as in interpreting technical evidence and in the setting of regulatory standards with which evidence should be evaluated. In practice, drug testing and regulation are shown to be hybrids of science and politics. Moreover, drawing on existing empirical evidence, it is suggested that this mixture currently, and for some time, has had the wrong ingredients for optimal drug safety and public health outcomes. For example, too often the balance of the scientific doubts about drug safety are weighed to the interests of manufacturers rather than to those of patients and public health, while some scientific standards with which drug safety is to be interpreted are being reshaped in ways that give insufficient priority to the protection of public health. Finally, it is proposed that: drug regulation should include comparative efficacy testing; regulatory agencies should conduct some key tests, charging the costs to industry and without duplication; and the regulatory system should be less secretive and more accountable to public scrutiny. Greater efforts should be made to eliminate experts' conflicts of interest within the regulatory process.

Drug development and regulation are often presented as purely matters of technical science. However, I argue that, in principle, the toxicology, clinical pharmacology and pharmacovigilance involved in drug testing and regulation are necessarily a combination of science and politics. This has important implications for how one attempts to make progress in drug regulation, such as in interpreting technical evidence and in the setting of regulatory standards with which evidence should be evaluated. In practice, drug testing and regulation are hybrids of science and politics, but I suggest that this mixture currently, and for some time, has had the wrong ingredients for optimal drug safety and public health outcomes.

Given that all drugs have risks, when regulators make decisions about approving them, they are making judgements about *acceptable* risks. But acceptable for whom and by what criteria? If the fundamental rationale for drug testing and regulation is the promotion and protection of public health, then the answer must be acceptable for consumers

and patients in relation to some illness and potential therapeutic benefit. Although it may be informed by evidence from medical science, this is necessarily a political judgement, which places the interests of public health over and above potentially competing interests of drugs manufacturers or elite medical scientists who advise governments. Furthermore, toxicology, pharmacology and pharmacovigilance are characterised by a great deal of scientific uncertainty. In this context, how the balance of the many scientific doubts about drug safety is weighed between these competing interests during drug testing and regulation is also a crucial *political* phenomenon that occurs within the closed doors of pharmaceutical companies and regulatory institutions. If drugs are being developed and regulated in the interests of public health, then one would expect to find that the balance of these scientific doubts would be weighed in favour of the interests of patients and consumers.

Consistent with the above argument, one would expect to find a social and scientific system of drug development and regulation that is accountable to the interests of public health, and that shares its evidence with the wider medical research and clinical practice communities in order to maximise the education and vigilance of doctors and citizens about new drugs. Indeed, writing in the 1930s, Merton argued that there needed to be an open and free exchange of scientific ideas and findings in order for science to flourish.[1] An important aspect of this openness is the potential for the scientific community to learn from failures. As Popper argued, one learns a great deal about how to make scientific progress from *failed* conjectures and not merely successes.[2]

Yet a cursory survey of the state of drug testing and regulation demonstrates how far they are from this model of scientific activity. Most drug testing is conducted and/or organised by scientists employed by institutions with direct commercial interests in the outcomes of the tests. These pharmaceutical companies frequently do not publish their scientific studies. The vast majority of drug regulatory systems are highly secretive, often making it impossible to access toxicological and clinical tests.[3,4] This is justified by the argument that pharmaceutical companies do not trust each other to refrain from exploiting each others scientific work for their own selfish gain. This justification in itself implies that pharmaceutical companies' commercial interests do not necessarily coincide with the interests of public health. Yet, illogically, because pharmaceutical companies do not trust each other, governments set laws within which the wider medical community, patients and the general public are expected to trust the industry and government to protect the interests of public health.[5] The expectation of public trust is made even more implausible and illogical by the fact that expert advisers to regulatory agencies are permitted to hold, and frequently do hold, consultancies with, or shares in, pharmaceutical companies.[6] Even in the US, home to one of the most open drug regulatory systems, it is very difficult to gain access to scientific information about drugs which are not given marketing approval (i.e. failed applications). Moreover, in many countries, including the US, regulators give companies advance warning that they intend to deny approval so that the company can 'voluntarily' withdraw their application. Thus, very few people ever know that the company failed with a particular application, not to mention the lessons from why it did so.

Supporters of the current drug regulatory authorities typically argue that it does not matter if the regulatory system is illogical so long as it enables new therapeutic drugs, which are reasonably safe, to be developed and made available to patients.[7] Such complacency reflects bizarre reasoning because the extent to which the current system falls short of optimal results for public health cannot even be determined comprehensively due to the cloak of secrecy surrounding it. Nevertheless, as I shall discuss, there is evidence, albeit much less than comprehensive, that drug safety is suboptimal under current regulatory arrangements.

1. Interpretation of Evidence

Government regulators often argue that pharmaceutical companies should be given poetic licence to present their drug products in the most favourable light.[7] For example, there may be an imbalance of commitment to product defence compared with patient safety; manufacturers may go to enormous lengths to undermine criticisms and critics of their drug products, while showing rather less commitment to ensure adequate flows of high quality information about drug safety.[8-10] Regulators frequently claim that this is not a problem because they take such imbalance into account when they review companies' new drug applications and other data.[11] Yet there are numerous examples of regulators not detecting such imbalances, and of cases in which the inaccessibility of data has undermined toxicological, pharmacological and pharmacovigilant understanding of a drug. Two well-known examples are the British regulatory authorities' early assessments of the adverse psychiatric effects of triazolam and the US FDA's early regulatory judgements regarding the renal toxicity of suprofen.[12,13]

Moreover, the huge amount of trust which regulatory agencies invest in pharmaceutical companies tends to emphasise perceived benefits over risks. This is evident in regulators' increasing tendency to refer to marketing approval as a 'provisional' decision as Abraham and Sheppard explain by quoting a former member of the UK Committee on Safety of Medicines (CSM): ". . . you really cannot judge what a drug is going to be like at the time of licensing. You haven't really got a clue as to what the drug is like. We [the British regulatory authorities] license early in this country [the UK] because we are well aware that you can't really get to know a drug until it is used the way it will be used by doctors in the rough and tumble of clinical practice. Clinical trials are very artificial; patients are carefully selected, the indications are very carefully observed. This is not so in ordinary clinical practice".[14]

Thus, regulators favour companies in weighing the balance of the scientific doubt about clinical and pre-clinical testing at the marketing approval stage on the grounds that they cannot really know a drug's risks until it is tried out in the real conditions of general clinical practice. In the UK, US and some other regulatory agencies, this occurred with the assessments of: the carcinogenic risk of benoxaprofen, naproxen and zomepirac; the phototoxicity of benoxaprofen; the gastrointestinal toxicity of piroxicam; and the clinical efficacy of piroxicam.[12]

This approach to regulation has implications for establishing an adequate margin of safety as Abraham and Sheppard note, quoting another former member of the CSM explained: "By far the most usual thing which happens is that on the basis of the clinical trials, because that is all we have to go on, a drug is licensed at a particular dose and over the next couple of years the yellow cards [spontaneous ADR reports] come in showing that people are grossly overdosed, some individuals are much overdosed and then the CSM calls the company in and then everybody agrees that you should go down to a quarter or even a tenth of the conventional dose."[15]

When recommended dosage should be reduced in order to establish a margin of safety, this can threaten the efficacy of the drug treatment. The tendency to emphasise perceived benefits over risks has resulted in regulators employing inconsistent criteria towards safety and efficacy in order to maintain the viability of the drug. Such a suboptimal outcome for drug safety occurred, for example, with the FDA's risk-benefit assessment of triazolam in 1992, when clinical trial data on safety were used to undermine spontaneous adverse drug reaction (ADR) reports, while anecdotal data on efficacy were accepted to bolster up insufficient clinical trial evidence.[16]

In particular, once a drug is on the market, regulators can be reluctant to remove it because such action might be seen as admission that an initial approval decision was mistaken, in which case very powerful evidence is required to overturn an approval decision. As Abraham and Sheppard illustrate, quoting from an influential British

regulator: "You have to have sufficient evidence to make you feel that the drug should be withdrawn. You don't have an option of saying you don't know – if you don't know then you leave the drug on the market by and large."[13]

Hence, in the preapproval stage, regulators tend to weigh the balance of the many scientific doubts about drug safety in favour of the drug's promotors in order to facilitate early licensing; and in the postmarketing stage, they also take this approach to the interpretation of spontaneous ADR and other safety data by, for example, requiring compelling evidence of lack of safety before withdrawing a drug from the market. The latter occurred in the FDA's continued approval of triazolam in the US and the CSM's belated recommendation to withdraw benoxaprofen from the UK market.[12,13,16]

Insofar as any lessons have been learned from these episodes in the 1980s and 1990s, they have tended to be piecemeal and construed as purely technocratic responses, such as more co-operation between regulatory agencies and increased attention to dosage regulation. Valuable as these responses are, they commit the error of supposing that drug safety problems are devoid of politics. Consequently, social and political deficiencies of drug regulatory systems remain unchanged. The result is that ever more safety problems emerge in new aspects of drug regulation despite previous technocratic responses in other aspects because the deficiencies in the social and political arrangements simply continue to express themselves across technical fields according to the context.

2. The Construction of Scientific Standards

In section1 I discussed the interpretation of drug safety evidence with respect to the regulatory standards existing at the time of interpretation. However, the political penetration of the science of drug testing and regulation is even more complex because it shapes the construction of those standards themselves. The most recent and important manifestation of this is the work of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) during the 1990s. The key participants are the three pharmaceutical industry associations and three government drug regulatory agencies of the European Union (EU), Japan and the US – the three largest pharmaceutical markets in the world. According to the industry, inconsistencies between national regulatory standards produce wasteful duplication in drug testing, driving up drug development costs and delaying patients' access to new medicines.[17] The transnational pharmaceutical industry seeks to decrease the cost and duration of research and development by reducing regulatory requirements imposed by the state, and to reach larger markets more effectively by international harmonisation.[18] Indeed, some in industry regard ICH as the first step towards global harmonisation and the production of a global registration dossier, which would contain all the data needed for marketing approval in any country in the world.[19]

The ICH excluded public health advocacy groups and consumer organisations. While its proceedings were published, many data upon judgements were made are not in the public domain. Using the publicly available sources, in this section, I examine the implications of the work of ICH for five important areas of drug safety standards, namely: ADR reporting; patient exposure and clinical risk assessment; carcinogenicity testing and the risk to patients on clinical trials; number of species for carcinogenicity testing; and duration of toxicity testing in non-rodents. It is beyond the scope of this paper to discuss whether ICH might accelerate the availability of new medicines needed by patients. However, on this point, readers should note that, rather than blanket harmonisation, this could be more effectively and efficiently achieved by comparative efficacy assessments to ensure that new drugs are therapeutic advances on what is already available followed by fast-tracking regulation for those that are really needed (see section 4 on 'policy implications'). ICH ignored these considerations.

2.1 Reporting of Adverse Drug Reactions

Regulators require pharmaceutical companies to report ADRs that come to their attention in a timely manner. This is important because if a drug is associated with many more, or more serious, adverse reactions than others in its therapeutic class, then it may be that its risks outweigh its benefits and it should be withdrawn from the market by regulators. The ICH process, therefore, presented an opportunity to harmonise safety standards upwards in line with best practice.

Unfortunately, this opportunity was not taken. The FDA requires *quarterly* periodic safety update reports (PSURs) during the first 3 years of marketing, while the EU and Japan require PSURs only *every 6 months*. Yet ICH made no attempt to harmonise these requirements upwards to the FDA's standards so as to maximise protection of public health. Regarding which kinds of ADRs require expedited reporting to regulators, the ICH also fell considerably short of the highest level of safety checks available on the international scene. Before ICH, 12 of the 17 countries in the three regions required expedited reporting (i.e. within a matter of days) of serious ADRs even if they were expected reactions with the new drug, while four of the 17 required such reporting of non-serious ADRs if they were unexpected. One of the 17 countries required expedited reporting of non-serious ADRs that could be expected.[20] However, ICH recommended that expedited reporting to regulators 'is not generally appropriate for expected, unrelated, or non-serious cases'.[21] In other words, ICH opted for the *lowest* common denominator on this safety issue.

2.2 Patient Exposure and Clinical Risk Assessment

It is widely appreciated that drugs intended for the chronic treatment of a non-life-threatening disease need to be tested in long-term clinical trials. Before ICH, the long-term exposure standard for assessing the clinical safety of such drugs was at least 100 patients in trials of at least 1 year's duration. However, under the auspices of ICH, the European Commission, the FDA and the Japanese regulatory authorities agreed to allow an initial marketing application to be made with trial data on 300–600 patients treated for just 6 months. Clinical observations of at least 100 of these patients continued on treatment for 1 year would need to be made as a supplement before marketing approval in the US and Japan, but could be made *after marketing* in the EU.[22]

The ICH experts made these recommendations even though research made available to them demonstrated that about a quarter of serious ADRs in 1-year clinical trials, analysed retrospectively, occurred after 6 months, and about one-eighth *first* occurred after 6 months.[23] Furthermore, the ICH did not harmonise the regulatory requirements in the EU *up* to the safety standards in the US and Japan. Rather, the European Commission has chosen to permit marketing before 1-year clinical trial data are analysed or even collected, thus putting EU patients at greater risk that their counterparts in the other two regions.

2.3 Carcinogenicity Testing and the Risk to Patients on Clinical Trials

The purpose of carcinogenicity testing is to determine whether a drug causes cancer in the experimental animals and, therefore, poses a carcinogenic risk to humans. According to the FDA, pharmaceuticals generally used for 3 months or more require carcinogenicity testing, while under the drug regulations of the EU and Japan such studies are required if patients take the drug continuously for at least 6 months or frequently in an intermittent manner so that the total exposure is similar to continual exposure of 6 months or more.[24] The clear implication of this is that exposure to a drug for more than 3 or 6 months presents a potential carcinogenic risk, which needs to be screened for by animal testing.

This is relevant to the exposure of patients in clinical trials because, in order for potential ADRs to be detected during clinical drug evaluation, the trials need to last for up to a year, as recommended

by ICH experts themselves.[25] In other words, when conducting clinical trials with new drugs intended to be used long-term to treat non-life-threatening illnesses, some serious and non-serious ADRs might not be detected properly without trials of up to 1-year's duration.[26] Yet ICH experts recommended that "completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population",[24] even though this means that patients are exposed to new drugs, of unknown carcinogenicity, for more than 3 months or even 6 months during clinical trials. The ICH did not even consider the possibility of the international harmonisation of regulations so that the completion of carcinogenicity testing in rodents is required prior to exposing patients to long-term clinical trials of over 6 months' duration.

2.4 Number of Rodent Species for Carcinogenicity Testing

Before ICH, the established toxicological standard for carcinogenicity testing of new drugs comprised rodent lifespan studies in two species, typically rats and mice.[27,28] Two lifespan studies in two species were required so that it was possible to identify trans-species carcinogens, which are considered more likely to represent carcinogenic risks to humans. Nevertheless, at ICH, the pharmaceutical industry representatives and the European and Japanese regulatory authorities recommended that this battery of toxicological testing should be reduced to just one rodent species – the rat – in order to save time and resources. The FDA scientists at ICH disagreed because this would make it impossible to identify trans-species carcinogens, and because there was evidence that mouse-only carcinogens were sometimes relevant to human risk.[29] However, rather than accept this precautionary approach advocated by FDA scientists, the ICH adopted a compromise consisting of one rodent lifespan study plus a cheap, short-term *in vivo* animal test, even though the new short-term animal tests had not been validated by toxicological science.[30,31] Consequently, ICH is most likely to have lowered drug safety standards with respect to carcinogenicity testing.

2.5 Duration of Toxicity Testing in Non-Rodents

Before ICH, in the EU, 6-month animal toxicity testing in non-rodents was required prior to marketing approval, while in the US, such testing was required for 12 months. The ICH experts set about an investigation of whether there could be international harmonisation of the testing duration down to 6 months if studies of 12 months did not detect any toxicity that had not already been identified after 6 months. However, "in a number of cases there were findings observed by 12 months, but not by 6 months".[32] The ICH experts "concluded that these [toxicity findings] would, or could have been detected in a study of 9 months' duration".[32] In other words, they concluded that new, unforeseen toxicities were being detected *after 6 months* of testing in non-rodents. Yet the ICH finally recommended that the duration toxicity testing in non-rodents should be for a *maximum* (not minimum) of 9 months in the EU, Japan and the US. This downward harmonisation prevented the FDA from maintaining its 12-month requirements, while allowing the EU regulatory authorities to continue to accept studies of only 6 months' duration.[32]

That this was largely a political judgement was confirmed by an official at the European Commission who commented: "Europe was between a rock and a hard place on this one. There was no way politically that we could go to 9 months because we could potentially have undermined all the existing products on the market by saying that they were incorrectly tested."[33]

Hence, international harmonisation *upwards* to the safety standards of the FDA on toxicity testing was never even considered by the ICH.

3. Conclusion

Across five major areas of drug safety addressed by ICH, there are two striking trends: a consistent failure to harmonise regulatory standards upwards; and a concentration of efforts to

lower regulatory standards. This is a consequence of *political* influences, especially of the pharmaceutical industry, on science within the regulatory system. In these five areas the regulatory system has prioritised industrial interests over optimal safety checks. Similarly, I have shown that, by reference to their own contemporary standards, drug regulatory authorities have interpreted evidence about particular drug cases in ways that are suboptimal for public health by awarding the benefit of the scientific doubts about drug safety to the manufacturer, rather than to patient protection.

This evidence implies that the current drug regulatory systems lack adequate public accountability, exhibit extensive conflicts of interests and are dominated by drug testing at the service of commercial interests. This is illogical and contrary to what one would expect from a system wishing to further the interests of public health. They also produce suboptimal outcomes for drug safety and public health *in practice*. I am not suggesting that the current regulatory authorities always do this, but it is found with notable frequency given the secretive nature of existing regulatory decision-making. Nor can I say what proportion of regulatory judgements are suboptimal for drug safety and public health because of the secrecy of regulatory systems. Indeed, one cannot know *precisely* how bad (or how good) the current systems are in protecting public health because of the secrecy involved in drug testing and regulation. This in itself indicates how ridiculous the current systems are, and why they need to be reformed. As I have explained, these reforms are not solely problems of technical science, but also political in nature. Just as social scientists and policy analysts, with an interest in drug regulation, need to learn about, and engage with, the relevant technical sciences (toxicology, clinical pharmacology, epidemiology, pharmacovigilance, etc.) so technical scientists in this field need to learn about, and engage with, the political challenges of developing a regulatory system capable of delivering optimal results for drug safety and public health.

4. Policy Implications

Regulatory agencies should identify a small number of key clinical tests that are needed as part of drug evaluation, inform the manufacturer that it must pay for the tests and then conduct them employing their own government scientists. Thus, the manufacturer's control over the drug testing process would be removed for these few crucial trials. To avoid duplication of testing on the same product, regulatory agencies in different countries could share their governmental testing by direct communication and/or via a special journal devoted solely to the rapid publication of drug testing by regulatory scientists. In the long-term, this has the added advantage of increasing medical expertise in drug testing, independently of industry.

It is well established that rational prescribing, which maximises patients' safety, is undermined by a plethora of drugs designed to treat the same illness, but with no therapeutic advantage over each other. To improve this situation, and to increase the chances of patients receiving the medications they really need, regulatory agencies should introduce comparative efficacy testing so that manufacturers of new drugs are required to demonstrate that they are a therapeutic advance on existing therapies, rather than merely effective. Comparative risk-benefit assessments of drugs already on the market also need to be updated as part of an overall comparative risk-benefit management of drugs across therapeutic classes.

Subject to the usual confidentiality procedures to protect the identity of patients/subjects and narrowly defined manufacturing trade secrets, drug testing data should be open to public scrutiny. The pharmaceutical industries would almost certainly object to public access to its drug testing data on the grounds that it would infringe their intellectual property rights. No doubt they would also argue that it would hamper competitiveness and innovation. I believe that it would be more likely to stimulate innovations in safer and more effective new drugs. In any case, the changes to drug testing that I have proposed above could enable public access to key pre-approval drug testing data without use

of industry data. This is because I have proposed that certain key pre-approval clinical testing ought to be conducted by government scientists under the auspices of the regulatory authorities. Consequently, the wider medical profession and consumer organisations could participate in the regulatory process at an earlier stage, almost certainly giving rise to better and more robust science. Just as important, greater openness in decision-making encourages consumers and patients to share responsibility for drug safety. This in itself contributes to the protection of public health because there is a more informed and vigilant citizenry.

Expert advisers to regulatory agencies should be free from conflicts of interest. If necessary, governments should pay these advisers higher fees for their services, passing the costs on to the manufacturers when payment for the proposed government drug testing is made.

All of the above proposals are likely to improve drug safety and pharmacovigilance because:

- there would be better flows of information between the fields of toxicology, clinical pharmacology and pharmacovigilance;
- data would be subjected to the rigours of public scrutiny, motivating greater robustness in regulatory science;
- regulatory agencies would operate in a much more public way, so would be forced to engage much more directly with public health priorities and those advancing such priorities by, for example, working to integrate pharmacovigilance data about drug use into regulatory thinking;
- there would be a more vigilant citizenry of doctors and patients; and
- pharmaceutical companies would be given a clear signal that the full rigours of public scientific scrutiny, rather than institutional trust, would attend their product development, leading to the withering of defensive research and promotional claims.

Acknowledgements

The author has provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. Merton RK. Science and the social order. In: Storer NW, editor. The sociology of science: theoretical and empirical investigations. Chicago (IL): University of Chicago Press, 1938
2. Popper KR. The logic of scientific discovery. London: Harper, 1965
3. Abraham J, Lewis G. Secrecy and transparency of medicines licensing in the EU. Lancet 1998; II: 480-2
4. Bardelay D. An ISDB survey to assess the degree of transparency of drug regulatory agencies. Int J Risk Saf Med 1996; 9: 151-5
5. Abraham J, Sheppard J, Reed T. Rethinking transparency and accountability in medicines regulation in the UK. BMJ 1999; 318: 46-7
6. Abraham J, Lewis G. Regulating medicines in Europe: competition, expertise and public health. London: Routledge, 2000
7. Abraham J. Regulatory science as culture. Science Culture 2002; 11: 309-36
8. Abraham J. Bias in science and medical knowledge. Sociology 1984; 28: 717-36
9. Abraham J. The production and reception of science papers in the academic-industrial complex. Br J Sociol 1995; 46 (2): 167-90
10. Abraham J. Transnational industrial power, the medical profession and the regulatory state: adverse drug reactions and the crisis over the safety of halcion in The Netherlands and the UK. Soc Sci Med 2002; 55 (9): 1671-90
11. Abraham J. Distributing the benefit of the doubt: scientific, regulatory and drug safety. Sci Technol Human Values 1994; 19: 493-522
12. Abraham J. Science, politics and the pharmaceutical industry: controversy and bias in drug regulation. London: UCL Press/Taylor and Francis, 1995
13. Abraham J, Sheppard J. The therapeutic nightmare: the battle over the world's most controversial sleeping pill. London: Earthscan, 1999
14. Abraham J, Sheppard J. The therapeutic nightmare. The therapeutic nightmare: the battle over the world's most controversial sleeping pill. London: Earthscan, 1999: 139
15. Abraham J, Sheppard J. Democracy, technocracy and the secret state of medicine control: expert and non-expert perspectives. Sci Technol Human Values 1997; 22: 139-67
16. Abraham J. Drug safety and the safety of patients: the challenge to medicine and health from permissive expert risk assessments. Health, Risk Soc 2002; 4: 19-29
17. International Federation of Pharmaceutical Manufacturers Associations (IFPMA). The value and benefits of ICH to industry. IFPMA; 2000
18. McIntyre A. Key issues in the pharmaceutical industry. Chichester: John Wiley & Sons, 1999
19. International Conference on Harmonisation (ICH). Progress on single dossier. Scrip 2000; 2522: 17
20. Garutti RJ. Clinical safety data management: definitions and standards for expedited reporting. In: D'Arcy PF, Harron DWG, editors. Proceedings of the Second International Conference on Harmonisation. Belfast: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1994: 373-74
21. Gordon AJ. Clinical safety data management ICH guideline recommendations and reasoning. In: D'Arcy PF, Harron DWG, editors. Proceedings of the Second International Conference on Harmonisation. Belfast: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1994: 380-88

22. International Conference on Harmonisation 2 (ICH2). Status of tripartite harmonisation initiatives. Scrip 1993; 1872: 19
23. Brown JS, Kaitin KI, McAuslane N, et al. Population exposure required to assess clinical safety: report to the ICH working group. Drug Inf J 1996; 30: 17-27
24. International Conference on Harmonisation (ICH). Guideline on the need for carcinogenicity studies of pharmaceuticals. 1995 Nov 29
25. International Conference on Harmonisation (ICH). Guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. 1994 Oct 27
26. Sjoberg P. Data to support the extension of clinical trials. In: D'Arcy PF, Harron DWG, editors. Proceedings of the Third International Conference on Harmonisation. Belfast: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1996: 343-45
27. Abraham J. Scientific standards and institutional interests: carcinogenic risk assessment in the UK and US. Soc Stud Sci 1993; 23: 387-444
28. Abraham J. Regulating the cancer-inducing potential of non-steroidal anti-inflammatory drugs. Soc Sci Med 1998; 46: 39-51
29. Contrera JF, Jacobs AC, DeGeorge JJ. Carcinogenicity testing and the evaluation of regulatory requirements for pharmaceuticals. Regul Toxicol Pharmacol 1997; 25: 130-45
30. MacDonald JS. Evaluation of mew models II. In: D'Arcy PF, Harron DWG, editors. Proceedings of the Fourth International Conference on Harmonisation. Belfast: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1998: 272-77
31. Mitsumori K. Evaluation of new models I: initiation and promotion models and the Hras 2 mouse model. In: D'Arcy PF, Harron DWG, editors. Proceedings of the Fourth International Conference on Harmonisation. Belfast: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1998: 263-71
32. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. Duration of chronic toxicity testing in animals. 1997 Jul 16
33. Abraham J, Reed T. Trading risks for markets: the international harmonisation of pharmaceutical regulation. Health Risk Society 1998; 3: 113-28

Correspondence and offprints: Dr *John Abraham*, University of Sussex School of Social Sciences, Falmer, Brighton, East Sussex, BN1 9QN, UK.
E-mail: J.W.Abraham@sussex.ac.uk