Pharmaphobia: Fear and Loathing of Pharmaceutical Industry Research

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In a recent editorial in the British Medical Journal two physicians, Dent and Hawke, call for, ‘another hurdle which a drug must clear before its routine use in the NHS is permitted,’ adding, ‘an independent body should test a drug’s value with two questions: Is the drug sufficiently well researched, especially its relative effectiveness? Is its cost utility acceptable?’ In a previous editorial, also in the British Medical Journal, the distinguished health economist, Professor Alan Maynard and his colleague Karen Bloor, had made a similar call. As a statistician who made his living in drug development providing information for regulators and who now consults to the pharmaceutical industry, I cannot pretend that I regard proposals for more regulation as always unwelcome. For example, in common with many pharmaceutical industry statisticians, I welcomed the appointment of medical statisticians to the UK Medicines Control Agency (MCA) a few years ago, thus reducing a dangerous disparity compared both to industry and to the USA Food and Drug Administration (FDA).

More regulation means more work for statisticians. It also increases the entry price into any market and, it could be argued, increases the profits of those already providing drugs (especially if at the same time standards are increased for generics). Whether such further hurdles are in the interests of patients is a debatable point. Elsewhere, for example, others have claimed that clinical trials may be too large. What certainly is in the interests of patients is the provision of more information. On this point I am in complete agreement with Dent and Hawke and, for that matter, Maynard and Bloor. The solution I have called for is for clinical trial reports to be made available on the World Wide Web once a drug is registered. This is, of course, entirely in the spirit of evidence based medicine. It is then up to the ‘customer’ to decide whether the documentation is adequate to justify prescription. I should prefer these ‘customers’ to be somewhat more ‘local’ than Dent and Hawke and Maynard and Bloor, who seem to envisage these decisions being made at national level by some grand committee, but I do not dispute the value of more information.

However, there is one point on which I disagree completely with Dent and Hawke. They write, ‘The unpublished data seen by the licensing authorities have not been scrutinised by the scientific community and may not have been peer reviewed, which limit their suitability for use in prescribing and funding decisions.’ This is a depressingly widespread misapprehension. The situation is quite the reverse: their suitability would be limited if the results had only been published in the medical press but not provided to the regulator in the usual way. The average standard of clinical research is much higher inside the industry than outside. The scrutiny afforded to regulatory dossiers by the full-time professionals employed by the MCA, the FDA and other regulatory agencies is also much tougher than that which any ‘peer review’ for a journal can provide.

The following are all areas in which pharmaceutical industry research is superior to that outside. 1) There is full interdisciplinary integration. For example, no clinical trials get planned or analysed within the industry without the help of a qualified statistician (chapter 5). 2) Standard operating procedures are available to cover all aspects of the clinical trial. 3) All clinical trials have detailed protocols with pre-specified analyses and proper power calculations. 4) Trial reports present all of the original data for scrutiny. 5) On site monitoring is carried out by trained personnel. 6) Clinical trial and trial report audits are regularly performed. 7) All clinical trials run for a particular product are presented at registration. There

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a This article was originally posted on PharmInfoNet
b This is a position I held from 1995 to 2003
c This was my email at the time of publication. You should now use stephen@senns.demon.co.uk
is no question of reports being suppressed in the way that they are by journals because the results are not significant. (Although, of course, if the product is a failure the final results may not be presented to the regulator.) 8) Care is taken to document the date on which all actions, including for example to decode the database, were taken. 9) Independent and detailed scrutiny of results is carried out by professionals.

Only for the last of these can the scientific publication claim to come anywhere near the standard of the industry clinical trial report but, as one who has reviewed for both statistical and medical journals. I know full well that we reviewers cannot match the FDA and the MCA in this. Of course, there are other ways in which scientific publications might be claimed to score. The first is that results, if not scrutinised in the same depth, are at least more widely disseminated, so that in principle, a challenge of the results is possible at any time. (This, presumably, is the point of Dent and Hawke.) The second is that the profit motive distorts pharmaceutical industry research and that therefore the results are subject to all sorts of biases. The third is that the cutting edge of scientific discovery has traditionally been in the universities, so that whatever disadvantages such research may suffer in terms of finance, attention to detail and more mundane professionalism, is more than made good in terms of flair, originality, imagination, innovative brilliance and scientific excellence.

The first has some truth in it. The solution would be to make clinical reports available on the web as I have argued and, indeed, this is, essentially, point three of the four proposals for reform put forward by Maynard and Bloor. This step can be taken without any requirement for further hurdles. Nevertheless, one should be cautious in supposing that industry research currently suffers from an information disadvantage in comparison to that done elsewhere. Every serious meta-analyst knows that a search must be made for unpublished trials. (Identification of such trials is of course a trivial matter if you are doing a meta-analysis for the expert report for a regulatory dossier. You cannot define the body of public sector research by that which is published. Some research is unpublished and often for the wrong reasons (lack of significance). Then again, of course, the results of many pharmaceutical industry trials are also published and hence are available for public scrutiny. Furthermore, much public-sector research that is published is misleading despite peer review. As a single example to illustrate this, I choose a paper by Smith, Song and Sheldon, not because its results are particularly questionable (although its conclusions are not justified by its methods), but because it is both published in the British Medical Journal and co-authored from the same university as Maynard and Bloor. (To be fair to Maynard and Bloor, however, it was Dent and Hawke, and not they, who made the point about the quality of review of industry reports.) The paper by Smith et al uses a meta-analysis to relate treatment benefit from cholesterol lowering to ‘baseline risk’, where, however, such risk is defined by the control group rate, coming to the conclusion that benefit is greatest where the baseline risk is highest. As I have pointed out elsewhere, however, even in the case where the true treatment effect is identical from trial to trial, by a phenomenon analogous to regression to the mean, a correlation will be induced if the results are stratified in this way. The reason is that if, by chance, the control group rate is poor it will, other things being equal, make the intervention group look comparatively good. Hence, this naïve form of analysis is misleading. Eventually, this serious flaw in this otherwise well-conducted piece of research, did receive attention in the British Medical Journal but I should not be surprised if many readers who were impressed by the original paper did not get the subsequent message.

As regards the second point, I do not claim that we should not be distrustful of the motives of the pharmaceutical industry, although, I think that this is more of a problem for drugs that are already registered. Here, the results of research are not necessarily incorporated in regulatory dossiers and the temptation, for example, to offer unreasonable defence, in the face of bad news, of a drug that is an important money-earner, can be considerable. (For drugs in development there is often no interest in making things look better than they are. A poor drug should be abandoned to make way for another.) However, it would be naïve to suppose that researchers outside the industry are not subject to similar pressures. As an example, consider a personal anecdote from my time in the industry. I failed to gain the signature of a trialist on a

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Note added 2013. In fact Smith et al quite clearly identify this as a potential problem but bizarrely do not adjust their method accordingly.
trial report because he disapproved of the analysis, despite the fact that the detailed analysis plan, which had been followed to the letter, was one to which he had given formal approval. (He had signed the trial protocol.) When questioned it seemed that his difficulty was that a competitor drug produced a significant effect at a time in the trial when it would no longer be expected to be effective. I pointed out that this was probably a type I error and bound to happen from time to time but that we could not suppress this finding, however embarrassing to us it might be. He then replied that no serious journal would publish the results and that he would publish his own report on this trial as he now had the treatment code and no longer needed our help. Despite the fact that the opinion of a further expert, nominated by him, eventually supported me, we did not get him to change his mind and he refused to sign the trial report. Eventually he published his version of the trial report. I would be very surprised if the reviewers for the journal were provided with the original trial protocol!

As regards the third point, it would be foolish of me, writing from my current address, to denigrate university-based research. Of course the universities are centres of scientific excellence. But one must be careful. First, the regulator's concern is, quite rightly, that the quality, efficacy and safety of medicines should have been adequately researched and that claims made regarding these points should be adequately documented. For this purpose dogged professionalism may be more valuable than scientific brilliance. Secondly, it is snobbish arrogance to suppose that the pharmaceutical industry does not have its share of brilliant scientists. There is a two-way traffic with the universities and many prestigious prizes, including the Nobel Prize, have been won by scientists who have worked in the pharmaceutical industry.

If you are not convinced by the arguments that profits are not inimical to trustworthy research, then I invite you to consider that other most regulated of industries: the airline industry. Which would you rather take for your next trip to Paris? A Boeing sold for profit to British Airways who run it for profit, or the plane designed, built and flown by the brilliant professor of aeronautics at your local university with help from his colleagues?

In short, while debate on drug regulation is healthy and should not be stifled, I feel that those who wish to influence policy in drug development but who are neither active as sponsors, nor as regulators should consider the following. They are commenting on an industry in which many brilliant and hardworking scientists have not only been developing drugs but have been developing standards for the development of drugs for years. No doubt, the process can be improved but the same surely applies to dissemination of scientific results. The CONSORT statement on the publications of clinical trials is an important initiative but, compared to the various guidelines which provide the framework for drug development, Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) and so forth, not to mention those which have been proposed from within the industry, for example by statisticians or professional statistical associations, it is a very junior Johnny-come-lately. Of course, I accept that reimbursers have the right to insist on value for money. Elsewhere, Professor Maynard has drawn attention to the importance of economics in deciding on treatment choice for patients and, although I believe he has made an unfair target of evidence based medicine (which is no worse than conventional approaches as regards its treatment of costs and a lot better as regards scientific evaluation), his general thesis that considerations of costs cannot be avoided is important and correct. (Where Maynard and Bloor call for direct state interference in the setting of pharmaceutical industry priorities they go too far, however.)

We have a society in which television and press provide frequent uncritical publicity for alternative medicine. (Whether some of these alternatives are effective or not is not the point: double-standards of proof of efficacy, safety and quality clearly apply.) It would be better, in my view, if academics regarded pharmaceutical industry scientists as fellow-members of the constituency of scientific medicine, rather than as terminally tainted technologists.
References

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