Patients and the public deserve big changes in evaluation of drugs

Silvio Garattini and **Iain Chalmers** argue that ending the secrecy surrounding drug trials would benefit all parties

The drug industry has an image problem, and big changes are needed to restore public confidence. The reasons why it has got itself a bad name are well rehearsed. They include research agendas distorted by priorities that are important to industry but not to patients[1]; inappropriately restricted study populations that exclude patients with multiple health problems[2] and children[3]; uninformative trial designs that fail to assess whether new drugs are better than existing treatment options[4]; outcome measures that ignore the effects of treatments on morbidity and mortality or on the quality of life[5]; biased under-reporting and over-reporting, not only of whole studies,[6-8] but also of outcomes within published reports of research[9]; and specious promotion of drugs, including disease mongering.[10]

Industry makes much of the expense of bringing a new drug to market. In fact, directly and indirectly, the public provides most of the support for developing and evaluating new drugs.[11] The public provides most of the academic infrastructure supporting much of the relatively high risk basic research underpinning drug development. It donates to medical research charities that fund much of this basic research and subsidises charities because charities attract tax relief. And through taxes, health insurance premiums, and direct payments for medicines, the public reimburses industry for its costs in a situation in which a true market does not exist. We believe that patients and health services are getting a poor return on this investment. If they are to reap better dividends in terms of better health at lower cost, major changes are needed in the way that drugs are evaluated.

Whose interests?

In countries where drug manufacturers are major contributors to the national economy no government can afford to ignore the industry's commercial wellbeing. In the United Kingdom, for example, pharmaceuticals and armaments are the last two remaining major elements of manufacturing industry, so it is unsurprising that successive governments have been at pains to support both of them.

An inevitable tension confronts all governments that try to balance the interests of patients and health services against the interests of industry and national economies. Within the UK, the drug industry currently interacts mainly with the Department of Health rather than with the Department of Trade and Industry. We believe that this is appropriate because drugs are made for patients.

However, the European Medicines Evaluation Agency (EMEA) is answerable to the Directorate General for Enterprise and Industry. This shows that European governments are currently prepared to encourage a view that drugs should be seen as consumer goods, rather than as agents for promoting and protecting health.[12] The activities of EMEA are paid for by industry and are surrounded by secrecy, so the agency's decisions cannot be scrutinised by outsiders. In addition, when EMEA's Committee on Human Medicinal Products does not unanimously approve a drug, the reasons expressed by the minority are not made public. The European public assessment report and the summary of product characteristics are drafted in collaboration with industry, with no critical scrutiny from stakeholders representing the interests of patients and the public.

The US Food and Drug Administration is more transparent than the EMEA in several aspects. For instance, the FDA makes available the register of ongoing and completed clinical trials, the reports submitted by drug companies for marketing authorisation, the adverse drug reactions database, and the minutes of advisory meetings on pharmacovigilance.[13]

We do not underestimate the balancing act that European governments face, but their continued support of the current situation, with all its conflicted interests and in the knowledge of its adverse consequences for patients and health services, will continue to attract opprobrium from those who believe that patients are getting a raw deal. Below, we suggest four ways in which governments could alter the balance of their support in favour of patients and health services: involving patients in shaping the therapeutic research agenda, making transparency in drug evaluation a legal requirement, requiring and resourcing independent evaluation, and requiring proof of added value for all new drugs.

Involve patients in shaping the therapeutic research agenda

The people who have most to lose from industry's dominance in drug evaluation are patients and those caring for them. The changes that are needed to ensure that patients' views are taken into account are unlikely to occur unless there is much greater public awareness of the problems and active engagement of patients and carers in confronting the powerful institutions and individuals who will wish to maintain the current situation. This presents a considerable challenge because so many patient groups are funded by industry or are in direct collusion with it.[14 15]

One example of a British initiative to highlight unanswered questions about the effects of treatments is the James Lind Alliance (www.lindalliance.org). Drawing on uncertainties harvested for and published in the Database of Uncertainties about the Effects of Treatments (www.library.nhs.uk/duets), the alliance promotes working partnerships and collaborations between patients and clinicians to identify and promote shared priorities for therapeutic research. Asthma was the first health problem it tackled. After considering over 300 uncertainties about the effects of asthma treatments, the alliance selected 10 for referral to research funding organisations. The most important concern relates to uncertainties about the possible adverse effects of long term use of drugs for asthma.

Require transparency in drug evaluation, by law

The public has become increasingly aware that some unfavourable research findings of relevance to the safety and wellbeing of patients have remained inaccessible to them and to prescribers.[16] After nearly two decades

of ineffective lobbying by some academics for prospective registration of clinical trials, industry has voluntarily taken some important steps towards greater transparency, both by prospective registration of clinical trials and by commitment to publishing results.[17] But dependence on voluntary trial registration and publication is not enough. Mandatory, prospective publication of trial protocols should now be required by law because, in addition to biased reporting of whole studies, there is also biased reporting of outcomes within studies.[9] All of the confidentiality that surrounds clinical research and the activity of the regulatory agencies, including EMEA, should be abolished.[18] After all, the data used by EMEA have been contributed by patients, and this information should be made publicly available to protect the interests of patients.

Until recently, governments have not supported such changes. However, the recent US act forcing publication of trial results[19] has created expectations that other governments will take similar steps to protect patients. The UK government seems to be shifting its position after realising that GlaxoSmithKline could not be prosecuted for non-disclosure of trial data that showed it was unsafe for children under 18 to take the antidepressant paroxetine.[20]

Require and resource independent drug evaluation

The monopoly that the drugs industry has in evaluating its own products, and the secrecy surrounding this process, leads to biased evidence that is currently only rarely questioned by independent studies.[21] Independent clinical research to evaluate new drugs is not a new idea. In the 1950s, for example, the British Tuberculosis Association established a Clinical Trials Organisation to act as an interface between companies developing new drugs for chest diseases and clinicians treating these conditions.[22] The Clinical Trials Organisation paid all the necessary expenses from the association's funds, and the companies then refunded the association. No fees of any sort were paid to individuals, and the organisation reserved the right to publish the results of trials that were unfavourable to the drugs tested.[22]

There are similar arrangements today. The Italian Agency for Drugs (AIFA) is responsible for drafting the list of drugs reimbursable through the Italian health service. A recent Italian law requires all drug companies operating in Italy to pay 5% of their promotional expenses to the agency to support independent clinical research on the efficacy of orphan drugs, comparisons of drugs for the same indication, observational outcome studies, and pharmacovigilance.[23]

The Italian precedent has already been emulated by the Spanish drug regulatory agency. Public investment in independent studies has also increased in the UK through the National Institute for Health Research and the US through the National Institutes of Health. For example, the National Eye Institute has launched a trial to assess whether ranibizumab (at $2000 a dose) confers any advantage over bevacizumab (at $40-70 a dose) in age related macular degeneration.[24]

Require demonstration of added value for all new drugs

The evaluations of the European Medicines Evaluation Agency currently do not have to establish whether a new drug represents a real advance: no comparison is required with existing drugs or other (non-drug) forms of treatment. Authorising the marketing of drugs that may be less effective or more toxic, or both, than treatments already available is only in the interests of the market, and certainly not of patients and health services. By making it compulsory to show added value for all new drugs, governments could make clear to the public that they are prepared to deal with current conflicts of interest and ensure that patients and health services receive better value for their investment. European governments could signal this change of emphasis by supporting a transfer of responsibility for drug licensing and evaluation to the EU Directorate General for Health and Consumer Affairs. Furthermore, it would be important for regulatory authorities to require drug companies to have at least one pivotal phase III trial conducted by independent scientific organisations.

How might the proposed changes benefit the drug industry?

Why should policy makers within government and industry take any of these suggestions seriously as long as their current strategies continue to yield acceptable profit margins? Firstly, particularly after forced disclosures of suppressed information about adverse effects of its products, the industry has become concerned about its image.[25 26] Adopting these changes will help restore public confidence.

Secondly, they could help improve returns from investment in research and development, which have been mediocre in terms of real advances in drug treatment. Of 12 sectors examined in terms of the yield of US patents per £10m spent on research and development, only telecommunications did worse than the drug sector.[27] Furthermore, predictions about the economic future of the industry are anything but reassuring.[28] For example, there is a high and increasing failure rate for potential new drugs in phase II studies.[29] The industry is concerned that failure to report disappointing results of phase I studies may be one of the causes of this.[30] Tim Mant, a director of a major contract research organisation, has acknowledged how frustrating it is to be commissioned to organise a clinical trial that he knows is going up a scientific blind ally because he has been there previously with another company but cannot divulge information that is commercially confidential (Academy of Medical Sciences meeting on experimental medicine, 24 April 2006). Science is believed to function most effectively through open exchange of ideas. Perhaps rather more openness might help to transform an industry that is not performing well and begin to deliver better value for the investments made by the public. To compensate industry for the requirement to make

qualitative and quantitative improvements in carrying out clinical trials, governments could extend patent time.

We believe that, if informed and consulted, the public would support the changes we have proposed. It remains to be seen how far governments are prepared to go in promoting changes designed to serve the interests of patients and health services more effectively, and how far the drug industry is prepared to go in acknowledging that its current ways of working are not as effective as they might be, scientifically or financially.

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COMMENTARY

Risks of doing as the Romans do

Garattini and Chalmers make four suggestions for improving the evaluation of drugs—involve patients in establishing research priorities, improve the transparency of drug evaluations and studies, fund independent drug evaluations, and require evidence that new drugs have added clinical value. Although controversial, many of their proposals would benefit patients. However, their suggestion to follow the Italian approach to funding independent clinical trials is unlikely to be a good idea.

In 2003, Italy decided to establish a tax on the drug industry of 5% of their medicines advertising budget. This money is used by the state medicines agency, AIFA, to fund clinical research on the efficacy of orphan drugs, comparisons of drugs for the same indication, observational outcome studies, and pharmacovigilance.[1 2]

We know that there are real problems with clinical trials as currently conducted, such as the use of surrogate end points, weak information on long term efficacy, and biased reporting of findings in industry sponsored clinical trials.[3] But we also know that with the right public policy incentives drug companies will align their research and investment more closely with public priorities.[4] The Italian approach does not take advantage of this knowledge.

Garattini and Chalmers take care to show that their proposed changes will also benefit the drug industry. This shows their understanding that clinical research sits within an interlinked complex system of industry, government, and universities, each with their own interests—a sort of mutually reinforcing "iron triangle" of relationships. The Italian approach dispenses with these relationships by singling out the industry part of this tightly interconnected system rather than by tackling the wider systemic problems. Funding more independent clinical trials does not on its own make the problem of bias, poor design, conflict of interest, and research misconduct go away; greater scrutiny and transparency (as the authors argue separately) might.

Dangerous road

If we follow the money (the 5% tax), we see that the benefits and costs are being distributed through a transfer of money from the "haves" (industry) to the "have nots" (the research community), which will conduct the research. Apparently, the Italian government did not feel compelled to view funding clinical trials as a priority for general taxation. By creating a hypothecated (dedicated) tax, however, the policy is based on weak legs: AIFA's ability to fund independent clinical trials now depends on a compulsory tax on discretionary advertising budgets, which can of course go down.

Furthermore, by creating apparent winners and losers, Italy has missed the opportunity

to seek a wider consensus on how to achieve a better return on the public investment in medicines research—a point made by Garattini and Chalmers. Countries with a weak drug industry base tend to adopt stricter industry price controls and regulation than those with a strong industrial base, and this initiative from Italy is consistent with that view.[5] Spain, another country with a comparatively weak drug industry has followed Italy with a similar tax, but on sales volume.[6]

The worry is that this policy will have unintended consequences. The Italian government's objective to improve research productivity may suffer if investment in drug research is moved to countries with more receptive commercial environments. In addition, the Italian research community may not have the capacity to design and conduct appropriate independent clinical trials if researchers also leave Italy. The industry might also reassess Italy as a congenial jurisdiction in which to do medicines research in the first place, although this may already be the case.

The conclusion is that if you want to build a strong medicines research community that is more likely to act in the wider public interest, copying Italy may not be a good idea.

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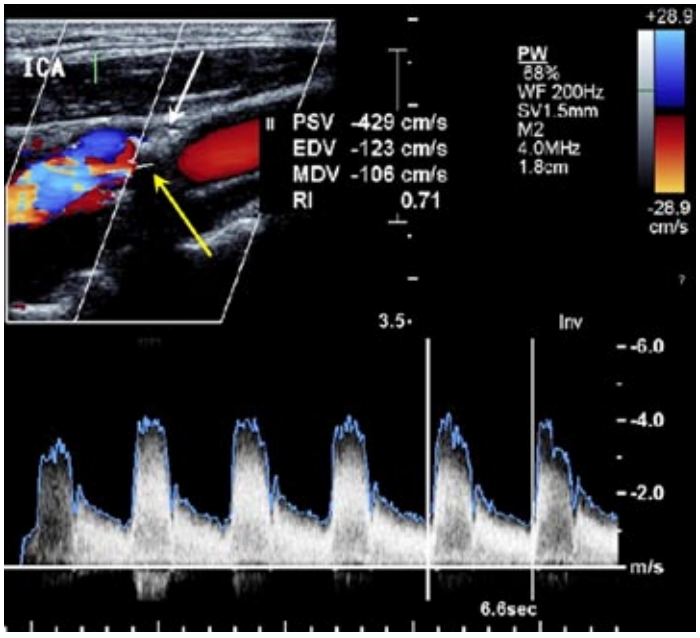
ANSWERS TO ENDGAMES, p 839 For long answers use advanced search at bmj.com and enter question details

PICTURE QUIZ "Brain attack"



CASE STUDY

A breathless man with diffuse chest pain

1 Analysis of the pleural fluid suggests that it is an exudate (pleural fluid protein to total serum protein ratio >0.5). Possible causes include a malignant primary lung tumour with pleural involvement, metastatic malignant pleural effusion, parapneumonic effusion, mesothelioma, tuberculosis, pulmonary embolism, connective tissue disease (such as rheumatoid arthritis), benign asbestos related effusion, pancreatitis, oesophageal rupture, and subphrenic abscess.

2 Computed tomography of the chest and abdomen, and pleural biopsy.

3 Pleural effusion caused by primary lung cancer, mesothelioma, or metastatic disease from another primary source are the most likely causes in this patient. The weight loss, diffuse chest pain, and possible occupational exposure to asbestos (he was a retired joiner) point towards mesothelioma.

1 His ABCD2 score is 3; the cut-off score predicting high risk of very early stroke after "brain attack" is ≥4.

2 The upper part of fig 1 shows a longitudinal greyscale image of the internal carotid artery with superimposed colour flow (colour map); the lower part shows the recordings of flow velocity (spectral Doppler) over six cardiac cycles. In the upper image, calcified plaque causes posterior acoustic shadowing, which obscures the lumen at the site of the stenosis (white arrow) and mimics an occlusion (yellow arrow). There is turbulent flow with aliasing on both the colour map and on the spectral Doppler. In the lower image, the peak systolic velocity at the proximal internal carotid artery is 429 cm/s, and the end diastolic velocity is 123 cm/s. Although velocity critera are specific to the laboratory, many operators use a peak systolic velocity of >230 cm/s to indicate a ≥70% stenosis (by NASCET criteria). An end diastolic velocity of >100 cm/s also suggests a high grade stenosis.

3 The flinging movements of the right arm and leg indicate hemiballismus, which usually indicates a lesion of the subthalamic nucleus. In most cases the likely vascular territory is the posterior circulation, but in a few cases it could be attributed to the middle cerebral artery. Best medical therapy (antiplatelets, a statin, and an angiotensin converting enzyme (ACE) inhibitor if appropriate) is the mainstay of secondary prevention against further cardiovascular or cerebrovascular events. If the symptoms are thought to be attributable to the presumptive "index lesion" in the left internal carotid artery, the degree of stenosis is confirmed to be greater than 70% (using the NACSET method), and alternative sources of embolus are excluded, then carotid intervention in an experienced unit (endarterectomy or stenting) is indicated in a neurologically stable patient and for maximum benefit should be performed within two weeks if the ABCD2 score is ≤4.

4 As duplex ultrasound is operator dependent, it is important to obtain accurate timely imaging to confirm the degree of carotid stenosis, assess the vertebral arteries, and exclude alternative lesions by non-invasive imaging such as contrast enhanced magnetic resonance angiography (CEMRA) or computed tomographic angiography (CTA). Imaging of the brain by magnetic resonance diffusion weighted imaging (DWI) may help confirm the vascular territory if there is any diagnostic uncertainty.

STATISTICAL QUESTION

Comparing length of stay

b, c, d