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Drug Trials and Evidence Bases in International Regulatory Context

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Abstract

The complex ways in which technical challenges of trial design provoke, and are provoked by, ethical, commercial and political factors are considered. It is suggested that the quality of the drug trial evidence base greatly depends on the how ethical, commercial and political priorities are set, and not merely on standardized techniques of data processing. Whether such standardized techniques are raising or lowering the quality of safety information about new drugs, and the protection of patients on clinical trials is explored. It is revealed that these international standards, intended to define valid evidence-based medicine for drug trials, are not themselves robustly evidence-based. It is argued that the internationalized regulatory standards developed to frame the evidence base for drug safety and efficacy are frequently inconsistent with furthering patients' well-being and public health. Rather, those standards reflect a regulatory culture of neoliberal corporate bias, and have been powerfully shaped by the commercial and political interests of the pharmaceutical industry and regulatory institutions. It is questionable that regulatory agencies are thoroughly and robustly scrutinizing the claims that pharmaceutical firms make about their products. New political and regulatory arrangements that could facilitate more ethical drug trials in the interests of patients and public health are proposed.

Keywords drug trials, international regulatory standards, pharmaceutical industry

Pharmaceuticals can be powerful life-saving medicines or they can induce extensive serious, even fatal, adverse reactions in patients. Most prescription drugs, the subset of pharmaceuticals with which this article is concerned, do neither of these. The vast majority of drugs are neither life-savers nor disasters. Nevertheless, it remains important for medical practice and patients to have a methodology with which to distinguish drugs that are safe and effective from those that are not. Since the early 1970s, double-blind controlled clinical trials (RCTs) have emerged in Europe and North America as a key part of that methodology.

In this article, I explore some of the complexities of clinical trials for drug safety and efficacy in the international regulatory context. This is an important matter because the results of clinical trials heavily influence what counts as a valid claim about drug safety or efficacy.

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The ways in which technical challenges of trial design provoke, and are provoked by, ethical, commercial and political factors are considered. It is suggested that the quality of the drug trial evidence base greatly depends on the how ethical, commercial and political priorities are set, and not merely on standardized techniques of data processing divorced from social context.

Following on from this, I investigate the most influential international standardization of clinical trials for drug safety since the 1970s. Such standards define what is, and is not, a valid drug trial across the globe. That is, the standards shape the evidence base by defining how and when the trials are designed and executed, as well as stipulating what types of evidence are collected and disseminated. Given this, it is worth asking whether these standards are raising or lowering the quality of safety information about new drugs, and the protection of patients on clinical trials. Ironically, this leads one to examine whether these international standards for drug trials are themselves robustly evidence-based. I contend that they are not, and that we need to explore new political and regulatory arrangements in order to formulate more ethical drug trials in the interests of patients and public health.

Locating clinical trials in the pharmaceutical knowledge production system

When a pharmaceutical firm begins to develop a drug, it organizes and conducts laboratory and clinical tests using animals, healthy people and patients. Most, if not all, of the animal toxicology testing and early trials involve only scientists fully employed by the company either directly or by contract research organizations (CROs).[1] The scientists' claims to knowledge about the drug from that research will probably never be published and never be subjected to any external scientific peer review, except by regulators. For the later clinical trials during drug development, the manufacturer typically enrols senior clinicians from academia and other non-industry institutions. At this stage, therefore, a select number of medical specialists outside the direct employment of the firm gain substantial information about the experimental drug, but the company generally exerts extensive control over which knowledge-claims from these later clinical trials may be published. Some of these trials, which could involve thousands of patients in total, may never be published and so will receive no review independent of industry scientists, except for the manufacturer's academic consultants and regulators (Abraham, 1995).

When the manufacturer seeks regulatory approval, it is required by law to submit to the regulatory agencies all clinical (and non-clinical) studies pertinent to the safety and efficacy of the drug, but it highlights those studies that are central to its case for approval. During the regulatory decision-making process, neither the public nor the wider medical profession have any rights of access to the clinical data under regulatory review, though some regulatory agencies may choose to make public some aspects of their decision-making, such as the proceedings of an expert advisory committee (Abraham and Lewis, 2002).[2] The role of the regulatory agencies is, therefore, potentially critical because they alone have the legal

1 The role of CROs has substantially increased since the 1980s (Mirowski and Van Horn, 2005).

2 Such pre-approval hearings generally only occur in the US (Abraham and Sheppard, 1997).

powers to demand comprehensive access to the clinical trial database about any drug before it is permitted to enter the market. After a drug is granted marketing approval by regulators, varying amounts of clinical trial information about the drug are made available by regulatory agencies in different countries, but generally there is not comprehensive access to the clinical trial database.[3] The principal published outcomes of clinical trials are: the mandatory knowledge-claims (agreed by the manufacturers and regulators), which must accompany the drug as the official information for prescribing doctors; and the papers in the medical journals/press, which the manufacturer chooses to place in the public domain.

Clinical efficacy trials: scientific, ethical and political dimensions of the evidence base

In general, all drug regulatory agencies require controlled double-blind clinical trials as evidence for drug efficacy. However, the designs and interpretations of clinical trials for drug efficacy regulation remain controversial in other respects that raise scientific, ethical and political issues at global and national levels (Corrigan, 2003; Foster, 2003; Petryna, 2006). Fundamental to these controversies are two interconnected problems: how large should trials be, and should the experimental drug be compared with a placebo or with an approved drug in the same therapeutic class (assuming there is one already available)?

Biostatistics implies that the smaller the difference in efficacy between the experimental drug and its comparator (placebo or established therapy), the larger the number of patients needed on the trial to detect that difference, while a larger difference could be detected with a smaller trial. The difference in efficacy between the experimental drug and valid comparisons is typically not known in advance of the (early major) trials, but the history of therapeutics implies that for many classes of drugs, such as anti-arthritics, antidepressants and benzodiazepines, the differences between newcomers and established therapies are usually small. Thus, the size of trials comparing the experimental drug with placebo (known as placebo trials) can be smaller than those comparing it with an effective alternative drug (known as head-to-head trials). Indeed, regulators have been aware of this since the 1970s. For example, in the field of antidepressants, expert regulators have argued that, when the experimental drug is compared with another antidepressant, if one gave a 60 percent response[4] and the other 70 percent, then 800 patients would be required just to have 50 percent confidence of demonstrating a statistically significant difference; but when it is compared with a placebo, if the experimental drug gave 70 percent response and placebo 30 percent, then only 50 patients would be needed to have 80 percent confidence of demonstrating that difference statistically (Jenner, 1977: 202S). If no statistically significant difference

3 Until 2005, pharmaceutical firms generally claimed that the results of clinical trials involving their drugs were their private property and commercially confidential. This convention was upheld by regulatory agencies. However, in August 2004, the New York State Attorney General brought a lawsuit against GlaxoSmithKline (GSK), alleging that the company had concealed negative clinical trial results. As part of the settlement, GSK agreed to set up a public register of all clinical trials on all its drugs. Other companies soon followed suit, and the industry (through trade associations) made proposals in January 2005 to establish a clinical trials register by 2006 (House of Commons, 2005).

4 That is, 60 percent of the trial patients taking the drug found it effective.

between the drugs is found in a head-to-head trial, then it will not be clear whether this is because both drugs have performed equally effectively *or* ineffectively in that trial.

The intermingling of these technical realities with various commercial and regulatory considerations have motivated many medical scientists in the pharmaceutical industry and drug regulatory agencies to prefer placebo trials over head-to-head trials. With the exception of Norway (until 1994) and the former Soviet bloc (until the early 1990s), the history of drug regulation shows that no countries have required pharmaceutical firms to demonstrate that their new drugs are more efficacious than established therapies already on the market (Mrazek *et al.*, 2004).[5] Legislation and regulations have stipulated merely that manufacturers must provide substantial evidence of clinical efficacy, which regulatory agencies have interpreted as greater efficacy than a placebo in double-blind controlled trials, though evidence from head-to-head trials is not precluded. Indeed, regulatory agencies, especially the US Food and Drug Administration (FDA), tend to prefer placebo trials because they are more likely to give a clear-cut result (Temple, 2002; Vastag, 2004). This regulatory context suits the pharmaceutical industry. For the pharmaceutical companies, placebo trials are more attractive because it is easier to demonstrate that their new drugs are superior to a placebo than to show efficacy against an established therapy. In particular, it is easier to recruit the required number of patients onto trials because placebo trials can be smaller than head-to-head trials.

Of course, pharmaceutical companies have commercial interests in developing effective drugs because the more effective a drug is, the more likely it is to be defined as efficacious by regulators and the medical profession. In turn, drugs that are regarded as efficacious by regulators and the medical profession are more likely to gain marketing approval and attract a substantial market share once launched. The theoretical existence of this market incentive for manufacturers to produce effective drugs is indisputable, but it is highly imperfect and crude in practice. This is because the companies' fundamental objective is to market their products and, while this will usually be more easily achieved if the drug really is highly efficacious, an advance in therapeutic efficacy is neither necessary nor sufficient for a new drug to hit a blockbuster market under existing testing and regulatory conditions. New drugs that are less effective than existing therapies can be promoted to reach huge markets provided that key regulators and elements of the medical profession can be persuaded to define the drugs as efficacious. It is much more important to the pharmaceutical manufacturers that their products are *regarded as effective* by regulators, the medical profession and (increasingly) by patients, *than whether they really are effective*. By contrast, it is whether the drug really is effective that is of paramount importance to patients and public health. This explains why the nature of drug testing and regulatory standards that define what counts as efficacy is so important for all interested parties.

This emphasis on placebo trials, however, is accompanied by ethical and regulatory limitations with significant consequences for patients on clinical trials and public health.

5 Norway's legislation regarding drug safety and efficacy dates back to 1928. The Norwegian regulatory framework incorporated a 'needs clause', which meant that new drugs that were more effective than placebo could only be approved for entry into the market if their efficacy fulfilled some therapeutic need. However, in 1994, in anticipation of a 'yes' vote to join the EU (which did not occur), the Norwegian government abolished its therapeutic 'needs clause' in order to come into line with EU directives on 'fair competition' and trade (Anon., 1993a). In the post-war period, until the collapse of the Stalinist regimes, Hungary and some other Eastern bloc countries regulated new drugs with a similar type of 'needs clause' (Reed, 2002).

Table 1. Ethics of trial type and size for equipoise experimental drug

Placebo trial scenarios (P) number of patients		Head-to-head trial scenarios (H) number of patients		Ethics balance
Placebo	Exp. drug	Established drug	Exp. drug	
N	N	N	N	(H) better[a]
N	N	2N	2N	Equal
N	N	3N	3N	(P) better[b]

Notes a. Here the number of patients exposed to a substance that might have a zero risk-benefit ratio is 2N in the placebo trial, but only N in the head-to-head trial, so the head-to-head trial is ethically superior.
b. Here the number of patients exposed to a substance that might have a zero risk-benefit ratio is 2N in the placebo trial, but 3N in the head-to-head trial, so the placebo trial is ethically superior.

A long-standing ethical objection to placebo trials is that they involve maintaining about half the patients on the trial in a clinical situation in which they receive no treatment, whereas in head-to-head trials all patients are receiving either an established or experimental treatment (World Medical Association, 2000). At first sight, this ethical objection seems very powerful, especially as it first gained prominence in connection with what turned out to be life-saving AIDS drugs, but when considered more broadly the objection boomerangs back to undermine head-to-head trials as well (Epstein, 1996; Walker, 1993). This is because if a head-to-head trial requires more than twice as many patients as a placebo trial in order to demonstrate efficacy (and it could be ten times as many), then the number of patients exposed to the experimental drug in the head-to-head trial will be more than the total number of patients exposed to placebo plus experimental drug in the placebo trial (see Table 1). If the risk–benefit ratio of the experimental drug is equipoise, that is, it is just as likely to be worse than placebo as it is to be better, then having more patients exposed to the experimental drug in the head-to-head trial than are exposed to either a placebo or the experimental drug on the placebo trial may be ethically undesirable.

Of course, in some cases, pre-trial knowledge about the experimental drug might lead one to conclude that it is better than equipoise. In those circumstances the ethical balance cannot be easily struck because one has to weigh the ratio of patient exposures against the extent of the positivity of the benefit to risk ratio. That quandary admits no technical solution because it is like weighing apples and oranges. This raises the question of whether these matters of clinical trial design should be left to technical experts. Given that some of these ethical challenges do not have any technical solutions, it is necessary to acknowledge that subjective and social judgements are involved, and to integrate patients, who are potential trial subjects, into debates and decision-making about trial designs.

In addition to ethical discussions about the implications of trial design for patients there are also regulatory issues regarding clinical trials that are pertinent to public health and medical practice. For example, the execution of a small number of large head-to-head trials may be preferable to a large number of smaller placebo trials as a greater protection of the integrity of the clinical evidence base. If a manufacturer runs a large number of relatively small placebo trials, there is an increased possibility that, just by chance, a few of the trials

will show the experimental drug to be more effective than placebo. This has drawbacks for evidence-based medicine (EBM) and public health because commercially driven pharmaceutical firms may not be able to resist the temptation to highlight the small number of trials showing drug efficacy, while downplaying or even ignoring the majority of trials that do not, by dismissing them as failed experiments. Consequently, doctors, patients and regulators may receive a misleading picture of the efficacy of the new drug.

Moreover, relatively small placebo trials can be problematic because each trial does not provide a sufficiently representative sample of the intended patient population, perhaps in terms of age and/or gender.[6] This makes it difficult to be confident about the implications of the trial, even if it demonstrates that the experimental drug is more efficacious than placebo. To overcome this problem, pharmaceutical firms typically combine (or 'pool') their clinical data from different placebo trials in an attempt to create greater representativeness. However, this is a very malleable technique, within which it can be very difficult to know whether commercial interests have produced valid results or claims that reflect narrow sectional goals contrary to those of the potential users of the drug. For example, it may be inappropriate to pool data from different trials if the sizes of the effect produced by the different ways clinical investigators conduct the trials are larger than the effects of the experimental drug compared with placebo. This is because, under those circumstances, the clinical investigators have made the trials so different that it might be very misleading to aggregate them into a single large trial. However, if the commercial success of a new drug product depends on establishing the representativeness of its clinical trial evidence base, and this can only be done by pooling data, then the manufacturer may not be able to resist inappropriate pooling of data.

These detailed technical aspects of the clinical trial evidence base, which are interpolated with the interests of pharmaceutical firms and their professional consultants, pose substantial challenges for regulatory agencies and their medical expert advisers. Hence, in order to check the validity of pharmaceutical companies' claims about the clinical trial evidence base regarding their drugs, regulators need to ask very searching questions and to conduct in-depth analyses of the datasets submitted by firms. Unfortunately, history tells us that this frequently has not occurred across a wide range of drugs, such as non-steroidal anti-inflammatory drugs, antidepressants, benzodiazepines and heart drugs (Abraham, 1995; Abraham and Sheppard, 1999; Healy, 2004; Medawar, 1992; Moore, 1995).

Furthermore, several trends of 'neo-liberal corporate bias' in the contemporary regulatory context militate against the type of thorough, adversarial regulatory scrutiny of the pharmaceutical industry's construction of the clinical trial evidence base that is needed (Abraham and Lewis, 2000). In the last 15 years, regulatory authorities, especially the FDA, the supranational European Union (EU) and national agencies across Europe, have become increasingly dependent on fees from pharmaceutical companies (Abraham, 2002a; Angell, 2004). Increasingly, this has caused regulators to see pharmaceutical companies as their 'customers' at a time when the industry has pressed relentlessly for regulatory agencies to accelerate drug regulatory review times in order to hasten product entry into the market (Abraham, 2002b). An immediate consequence of such acceleration is that regulators tend

6 The problem of a trial's representativeness of the intended patient population may also result from deliberate exclusion criteria designed by the pharmaceutical manufacturer.

to have less time, inclination and incentive to conduct in-depth re-working of industry clinical trial data, and are more likely to merely review summary data uncritically (Abraham and Lewis, 2000; House of Commons, 2005). Many of the medical experts, who serve on advisory committees to the drug regulatory agencies also have personal and non-personal interests[7] in pharmaceutical companies, and frequently give drug manufacturers the benefit of the doubt over problematic aspects of their clinical efficacy, such as those identified above (Abraham, 1995; Abraham and Sheppard, 1999; House of Commons, 2005; Medawar and Hardon, 2004; US Congress, 1987). The proximity of these experts to the drug development process (and the clinical trials phase, in particular) seems to nurture in them a strong identification with the expectations and hopes of pharmaceutical firms about their new drugs in health care, with little regard to the robustness of the evidence base required by the declared regulatory standards.

A fundamental limitation of placebo trials to further the interests of public health is, of course, that they do not provide knowledge about whether or not the experimental drug is better than existing therapies already available. Yet, as Gale (2001: 1873) argues, what clinicians want—and presumably also patients and national healthcare systems—is: 'rational, cost-effective, evidence-based use of existing drug therapies'. Regarding the introduction of new drugs, the interests of these groups remain the same: where alternative therapies exist, the predominant interest of patients, clinicians and health-care systems lies in knowing how the new drug compares with existing therapies in terms of effect on clinically relevant outcomes. If the clinical trial evidence base does not contain information about the comparative efficacy of a new drug, then it is very difficult for doctors to know how or whether to prescribe it once it comes on to the market, and even more difficult for patients to decide about the various therapeutic options.

While placebo trials can have advantages in some contexts, those advantages do not preclude the need for comparative efficacy testing of new drugs in order to develop an adequate evidence base about the therapeutic advance of new drugs. The lack of such an evidence base has less to do with the performance of individual regulators and companies and more to do with drug legislation and regulatory policies. After over 30 years of modern drug regulation in Europe and North America, by law, pharmaceutical firms are not required to demonstrate that their new drugs provide therapeutic advance over existing therapies, even though such a regulatory policy is surely in the interests of public health. At times, some regulators have claimed that such a regulatory policy would impose formidable technical challenges of clinical trial design on pharmaceutical firms, but the principal opposition is rooted in commercial and trade ideologies of 'fair competition' (Abraham and Lewis, 2000). To put it crudely, it is argued that, if company A has gained marketing approval for drug X, then why should company B not be permitted to market its new drug Y, which is as effective (and safe), but definitely no more effective (or safe) than established drug X? Evidently, debates about the nature of the clinical efficacy evidence base are not merely confined to the realms of techno-science and ethics, but extend to the politics of capitalist ideology.

7 Personal interests are defined as consultancies, fee-paid work and shareholding; non-personal interests as payments that benefit the department/institution for which the committee member is responsible but not received by the member personally.

Internationalizing clinical safety standards: a non-evidence-based evidence base

In the mid to late 1980s, bilateral initiatives between the governments of the US and Japan were taken, including a determined objective on the part of the US to open up Japanese markets. Japan represented about 22 percent of the world pharmaceutical market (Reed-Maurer, 1994: 38). Specifically, a conference in 1985 between the American and Japanese governments on an 'Action Plan for Improved Market Access' committed the Japanese drug regulatory authorities to some international harmonization with the US for the first time (Ferris, 1992: 197–198). In response, the European Commission strengthened its resolve that there should be a single EU market which could compete with Japan and the US in R&D and international trade negotiations (Wyatt-Walter, 1995). In 1988, the first 'mission' of government regulators and industry representatives from the pharmaceutical sector in Europe was sent to Japan to discuss bilateral harmonization of regulation between Japan and the EU, so that Japanese markets might become more accessible to the European industry. However, given the importance of the US market, the European pharmaceutical industry was unenthusiastic about solely bilateral harmonization with Japan. Consequently, the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) took responsibility for organizing trilateral meetings between the industry and government regulators in the pharmaceutical sectors of the EU, Japan and the US during the 1990s.[8]

These trilateral meetings came to be known as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Under the auspices of ICH, the EU, Japanese and US regulatory agencies agreed on regulatory standards that each agency formally adopted and integrated into its own regulatory review system.[9] The drive to harmonize safety standards internationally, and the nature of such harmonization, need to be seen in a broader political and commercial context. By the early 1990s, drug regulatory agencies had come under intense pressure to accelerate their regulatory review processes, but typically without commensurate additional resources from their governments. As a result, the regulatory agencies encouraged international harmonization as a way of reducing their workload through the elimination of duplicative testing requirements.

For the industry it was a way of counteracting its rising costs. According to McIntyre (1999: 17, 49) between 1972 and 1997, the R&D expenditure of the British pharmaceutical industry grew from £42 million (7 percent of gross output) to £2,251 million (21 percent of gross output). Yet the growing complexity of the diseases and illnesses that remained after the antibiotic era of the 1940s and 1950s increased the duration of R&D as well as its expense. The cost to bring a new chemical entity to market could be as high as US$350 million, and it was estimated that the time from first synthesis of a new drug to its marketing quadrupled from 1960 to 1989 (Halliday *et al*., 1997: 63; Tansey *et al*., 1994: 85).

8 During the 1990s, the EU, Japan and the US were the three largest pharmaceutical markets in the world. Of the US$ 22.7 billion spent world-wide on pharmaceutical research and development (R&D), they spent about 90 percent (Nakajima, 1996: 32).

9 The ICH guidelines represented minimal regulatory standards that industry testing was required to meet. Pharmaceutical firms could, of course, supersede those standards.

As patents are awarded when compounds are first synthesized, the consequence of longer R&D times was that companies' new drugs had shorter periods of patent-protected market exclusivity during which to maximize returns on investment and make profits.

Moreover, the industry experienced a decline in productivity in terms of the number of new chemical entities launched on the market between 1975 and 1990 because of the increased rate of failure in increasingly complex experiments (Poggiolini, 1992: 13–14). In response, the industry strove to decrease the cost and duration of R&D by reducing regulatory requirements imposed by the state, and to reach larger markets more effectively. Transnational pharmaceutical firms could get better returns on R&D investments if they could access international markets simultaneously, but faced increased costs if they had to cope with separate, and sometimes divergent, national regulatory regimes (McIntyre, 1999: 96). Indeed, some in industry regarded ICH as the first step towards *global* harmonization and the production of a global registration dossier, which could contain all the data needed for marketing approval in any country in the world (Anon., 2000). Many ICH standards have already been adopted by Australia, Canada and European Free Trade Area (EFTA) countries, while the World Health Organization (WHO) is promoting ICH standards to developing countries (Anon., 1992; Idanpaan-Heikkila, 1998; Ten Ham, 1998). It has even been suggested that new drugs approved by the US, EU and Japan could simply receive 'rubber-stamp' approval in developing countries without additional review of the data by their governments (Poggiolini, 1992: 18).

One can certainly point to the fact that regulators and industry had their own institutional and commercial motivations for establishing ICH. On the other hand, the regulatory agencies and the industry associations always declared that one principle of international harmonization was that it should *not compromise patient safety*. Moreover, the new clinical safety standards developed by ICH were to form the global benchmarks of EBM for drug safety. Yet the standards adopted by ICH relaxed the extent to which trials might detect safety problems, and were not themselves consistent with the evidence base, assuming a commitment not to compromise patient safety.

By the 1990s, it was widely appreciated that drugs intended for the chronic treatment of a non-life-threatening disease needed to be tested in long-term clinical trials. Prior to ICH, the long-term exposure standard for assessing the clinical safety of such drugs was at least 100 patients in trials of at least one-year 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 six months*. Clinical observations, but not controlled clinical trial data, on at least 100 of these patients continued on treatment for one year, would need to be made as a supplement before marketing approval in the US and Japan, but could be made *after* marketing approval in the EU (Anon., 1993b).

The ICH experts made these recommendations even though research made available to them demonstrated that about a quarter of serious adverse drug reactions (ADRs) in one-year clinical trials, analysed retrospectively, occurred *after* six months, and about one-eighth *first* occurred after six months (Brown *et al*., 1996). Furthermore, the ICH failed to harmonize the regulatory requirements in the EU *up* to the safety standards in the US and Japan. Rather, the European Commission chose to permit marketing approval before

one-year clinical trial data were analysed or even collected, thus putting EU patients at greater risk than their counterparts in the other two regions.

Thus, the new ICH standard meant that as many as one-eighth of ADRs from new drugs (for the chronic treatment of non-life-threatening illnesses) might no longer be detected before marketing. Regulators and other medical experts endlessly bemoan the supposed inability of clinical trials to detect many ADRs, resigned to the conviction that drug safety must be largely left to improvements in post-marketing surveillance. For example, when a major drug safety disaster strikes, such as Practolol, Opren or Vioxx, regulators typically claim that it could not have been predicted from clinical trials because they lack the sensitivity to detect many ADRs (Abraham and Davis, 2006). Yet here is a glimpse of how that conviction is constructed. Regulators themselves at ICH acted to undermine the sensitivity of clinical trials to detect safety problems, thus increasing the likelihood that some serious ADRs might only be detected after exposing a very large patient population to the drug post-marketing.

Pharmaceutical companies, for their part, have an interest in avoiding association with drug disasters and concomitant legal liabilities and declining stock market valuations. However, that does not prevent them from lowering safety standards because evidently manufacturers can persuade themselves that the diminished testing practices are sufficient to prevent a large-scale disaster, albeit at the expense of less dramatic safety problems. Thus, the industry's commercial interests in avoiding drug disasters tend to be relatively remote and over-ridden by its more immediate interests in market access, rationalization of development costs and profitability.

Ignoring past evidence and weakening the future evidence base: ICH and ADR reporting requirements

In the previous section, I discussed standards relating to how ADRs could be detected and hence how an evidence base regarding ADRs could be formed. In this section, I consider regulatory standards concerning what happens to information about ADRs when they *are* detected by pharmaceutical companies. While a drug is being tested in clinical trials, and after a new drug has been marketed, its risks to patients are monitored by reports from doctors about adverse reactions to the drug. In the case of clinical trials, the clinical investigator is responsible for recording all ADRs under the supervision of the manufacturer. The regulatory standard, which I consider here, is concerned with requirements on pharmaceutical companies to report to regulatory agencies in a timely manner ADRs that come to their attention. 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 (by regulators) from further development.

As regulatory agencies cannot make timely decisions to withdraw or suspend drugs from further development without adequate information about ADRs, there is clearly a great deal of regulatory trust in industry. However, in the past this regulatory trust has been breached as occurred with Halcion, Merital and Opren/Oraflex (Abraham, 1995; Abraham and Sheppard, 1999; US Congress, 1987). In such cases, transnational pharmaceutical companies often attempt to justify failures to provide regulatory agencies with timely ADR

reports because of poor communication between different parts of the company in various parts of the world. The ICH process, therefore, presented an opportunity to harmonize safety standards *upwards* in this respect, so that such justification could no longer be countenanced. Yet the new ICH standard did not make clear that companies bear full responsibility for the conduct of any foreign subsidiaries.

Furthermore, there have been cases of large increases in the occurrence of known ADRs, but they have not been reported in a timely manner by the pharmaceutical companies on the grounds that the increases did not reflect a 'meaningful change in ADR occurrence or safety profile'. However, that judgement by scientists in industry was not shared by regulators when the regulators were finally furnished with the information. Leaving the matter of what counted as a significant change in risk to the subjective judgement of industry scientists was, in effect, allowing the company to regulate itself in this respect. Such abdication of regulatory intervention in favour of industry self-regulation may not be sufficiently protective of public health and has certainly not been so in some cases in the past (Abraham, 1994). A clear internationally harmonized quantitative standard defined by regulators to counter this problem could have been developed at ICH. Yet, regarding 'expected', serious ADRs, ICH recommended that 'an increase in the rate of occurrence, which is judged to be clinically important' should be reported to regulators, 'as opposed to a more quantitative approach' (ICH, 1994a: 2–3; Gordon, 1994: 384). Similarly, for other ADRs, ICH concluded:

> Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the periodic safety update report (PSUR) to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile. (ICH, 1996: 3)

Regarding which kinds of ADRs require expedited reporting to regulators, the ICH fell considerably short of the highest level of safety checks available on the international scene. Prior to ICH, 12 of the 17 countries involved (Japan, the US and 15 member states in the EU) required expedited reporting (i.e. within a matter of days) of serious ADRs, even if they were expected reactions with the new drug, while 4 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 (Garutti, 1994: 376). However, ICH recommended that expedited reporting to regulators 'is not generally appropriate for expected, unrelated, or non-serious cases' (Gordon, 1994: 384). In other words, ICH opted for the *lowest* common denominator on this safety issue.

The consequence of these approaches by ICH is that regulators' evidence base regarding ADRs has been diminished. At a time when the medical and other health professionals are being asked to take evidence-based medical practice more seriously, drug regulatory agencies have loosened their grip on the evidence base that informs clinical safety assessment of new drugs. In so doing, they are also less able to provide to doctors timely evidence-based advice about drug safety that is independent of the drug's manufacturer. Thus ICH's regulatory framing of the evidence base elevates the importance of the pharmaceutical firms as sources of the latest clinical safety information for the medical profession.

A forgotten evidence base: unethical carcinogenic risk in clinical trials?

Much of the commentary on the ethics of clinical trials over the last decade has focused on what actually happens to patients during the trial itself, especially around issues of informed consent (Corrigan, 2003). However, some ethical aspects of clinical trials are better understood by locating trials in the overall drug development process because the nature of the risks faced by trial subjects can only be appreciated in that context.

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. Animal carcinogenicity testing is important because cancers in humans and other mammals are often induced over long periods of the life-span and may manifest themselves some time after the carcinogenic exposure. Testing on rodents permits life-span exposure (usually for 18 to 30 months), which is *not duplicated* in the clinical sphere because it is impractical and self-defeating to test a drug in patients over their life-span of about 70 years.

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. Furthermore, it is expected that most pharmaceuticals indicated for 3 months' treatment would also be likely to be used for 6 months (ICH, 1995). 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/clinical observation because, in order for potential ADRs to be detected during clinical drug evaluation, the trials/observations need to last for up to a year, as recommended by ICH experts themselves:

> There is concern that, although they are likely to be uncommon, some adverse drug events (ADEs) may increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. (ICH, 1994b: 4)

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, or at all, without trials/observations of up to one year's duration—and some trials/observations last for more than one year (Sjoberg, 1996: 345). As I have noted above, for such drugs, clinical trial/observation data on patients treated for 12 months must be submitted to the regulatory agencies prior to marketing approval in the US and Japan (ICH, 1994b).

Yet ICH experts also 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' (ICH, 1995: 2). Thus, even though it is acknowledged that in Japan and the US, there must be some clinical trial/observation data of 12 months' duration prior to marketing approval, and that the FDA requires carcinogenicity testing for drugs to be used for more than 3 months, the ICH recommends that no carcinogenicity

testing needs to be completed prior to exposing patients to new drugs for more than 3 months (indeed up to a year) during clinical trials/observations. The ICH process did not even consider the possibility of the international harmonization of regulations so that the completion of carcinogenicity testing in rodents is required *before* exposing patients to long-term clinical trials/observations of over 3 or 6 months.

Yet again, it is evident that the major drug regulatory agencies of the world have agreed to standards that will define what counts as clinical evidence in the future, but those very standards have not themselves been robustly derived from the available evidence base about drug safety. A robust application of the evidence base would have implied a delay in the commencement of long-term clinical trials of drugs to treat non-life-threatening illnesses until carcinogenic risk assessment was within 3 months of completion—a consequence of which would be the elongation of drug development time for pharmaceutical firms. Such a scenario conflicted directly with the commercial goals that motivated the pharmaceutical industry's involvement in the ICH process.

It might be argued that the streamlining of clinical trials and the acceleration of their regulatory review are responses to the demands of patients' organizations, such as AIDS activists, for faster access to new needed drugs. Certainly, it is true that AIDS patients' groups in the late 1980s in the US influenced changes to the FDA's regulation of AIDS drugs (Edgar and Rothman, 1990). However, the extrapolation of that phenomenon to argue that patients' organizations have been behind an expedited approval process that permits riskier clinical trials for new drugs more generally can be overstated. The vast majority of new drugs offer little or no therapeutic advance, and are developed to treat non- life-threatening illnesses. The initiatives to generalize the regulatory changes regarding AIDS drugs to other types of new drugs in the US came not from patients' organizations, but from the pharmaceutical industry and the Reagan and Bush (senior) administrations in the late 1980s and early 1990s (Anon., 1988; Willman, 2000).

Moreover, even with respect to AIDS drugs, the demands of patients' groups for expedited regulatory review and riskier clinical trials can be exaggerated. When AIDS patients' organizations demanded these accelerated measures in the late 1980s, a very particular historical situation obtained. A terrifying new life-threatening infectious disease emerged on the scene and there were no drugs at all to treat it. However, by the mid to late 1990s, a different situation existed. For patients who could get comprehensive access to the new anti-retroviral drugs, together with appropriate health-care support, HIV/AIDS was no longer a life-threatening condition/disease.[10] Since the mid 1990s, AIDS patients' organizations have realized that robust clinical trial data, combined with rigorous regulatory review demonstrating that new AIDS drug-combinations are safe and effective, is more important than speed of approval per se. That realization explains why over 100 patients' organizations in the US, including AIDS advocacy groups, formed the Patients' Coalition in order to oppose the Republican Congress's deregulatory reforms of the 1997 FDA Modernization Act, which aimed to force the FDA to reduce its regulatory requirements of clinical trial testing and further accelerate its regulatory review times (AIDS Action Council, 1996; Patients' Coalition, 1997).

10 Of course, it remains a very serious condition for all those infected and it is still life-threatening for the millions of people infected in the world who cannot access adequate drug therapy and supportive health care.

Conclusions

In public, at least, the pharmaceutical industry, the medical profession, regulators, expert science advisers, patient organizations and health advocacy groups all seem to agree that it is desirable to have EBM which benefits patients and good medical practice. The double-blind controlled clinical trial (RCT) has become the flagship or 'gold standard' for such EBM. Yet this characterization masks a plethora of interrelated ethical, technical and political factors that determine the sort of evidence that is actually provided by RCTs of drugs, to whom that evidence is provided and the timeliness of such provision.

Furthermore, an examination of the internationalized regulatory standards developed to frame the evidence base for the clinical safety and efficacy of new drugs suggests that they are frequently inconsistent with furthering patients' well-being and public health. Rather, those standards have been powerfully shaped by the commercial and political interests of the pharmaceutical industry and regulatory institutions. Even within those adopted standards, there are crucial matters of how penetrating, thorough and robust regulatory agencies are in scrutinizing the claims that pharmaceutical firms make about their drug products based on RCTs. The extent to which regulatory agencies reflect a neo-liberal corporate bias in their approach to the pharmaceutical industry implies that regulators invest growing trust in, and deploy diminishing scrutiny of, industry claims.

These findings do not imply that the project of EBM and RCTs for drugs is a hopeless one. Rather they show that different kinds of social and political priorities need to shape regulatory standards and technical analyses. Over a decade ago, it was suggested that the safety and efficacy testing of drugs should be conducted independently of the pharmaceutical industry (Abraham, 1995: 251). Instead, such testing could be done by publicly accountable regulatory agencies that could make public rights of access to information about the regulatory decision-making process one of their top priorities. Regulatory agencies could be given incentives to see patients and the interests of public health as their 'customers', rather than pharmaceutical companies. Such measures could create a different political culture within which the ethics of trial design, standards of technical interpretation and goals of EBM and RCTs could be reformulated to be consistent with patients' well-being and public health.

In the current policy environment, these proposals may seem to be long-term aspirations or even utopian. In the shorter term, there is a need to reverse the dependence of regulatory agencies on fees from pharmaceutical companies to fund their regulatory reviews of industry data—reviews which should enter the public domain upon their completion in order to facilitate broader scientific scrutiny and user vigilance. Expert advisers to regulatory agencies should also be prohibited from having interests in pharmaceutical companies during their period in office. Such reduction in identification of the regulators with the industry's interests could facilitate more demanding regulatory standards regarding clinical trials of drug safety and efficacy, such as the introduction of tests for therapeutic advance and the timely collection and analysis of all ADRs.

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