

Institutionalizing Dissent: A Proposal for an Adversarial System of Pharmaceutical Research¹

ABSTRACT. There are serious problems with the way in which pharmaceutical research is currently practiced, many of which can be traced to the influence of commercial interests on research. One of the most significant is inadequate dissent, or organized skepticism. In order to ameliorate this problem, I develop a proposal that I call the “Adversarial Proceedings for the Evaluation of Pharmaceuticals,” to be instituted within a regulatory agency such as the Food and Drug Administration for the evaluation of controversial new drugs and controversial drugs already in the market. This proposal is an organizational one based upon the “science court” proposal by Arthur Kantrowitz in the 1960s and 1970s. The primary benefit of this system is its ability to institutionalize dissent, thereby ensuring that one set of interests does not dominate all others.

Many observers now acknowledge that there are serious problems with the way in which pharmaceutical research is currently practiced. These problems include the suppression of undesirable results, bias in the design of studies and in the interpretation of results, and neglect of diseases that afflict the poor in developing countries. These problems can be traced at least in part to the influence of commercial interests on research. In what follows, I will discuss some of the main deficiencies of current pharmaceutical research, and I will argue that an important one is inadequate dissent. As many have argued, rigorous scientific research requires dissent, or what Robert Merton called “organized skepticism” (1942). Yet it is increasingly the case that some forms of dissent in pharmaceutical research are either absent or unheard, due to the predominance of one set of interests (i.e., commercial) over others. In order to ameliorate this problem, I develop a proposal that I call the “Adversarial Proceedings for the Evaluation of Pharmaceuticals” (APEP), to be instituted within a regulatory agency such as the Food

and Drug Administration (FDA) for the evaluation of controversial new drugs and controversial drugs already in the market. This proposal is an organizational one based upon the “science court” proposal by Arthur Kantrowitz in the 1960s and 1970s. The primary benefit of this system is its ability to institutionalize dissent, thereby ensuring that one set of interests does not dominate all others.

The perspective of this paper is that of a policy-oriented philosopher. I will attempt to establish an epistemic claim (i.e., that there are serious epistemic failures associated with current pharmaceutical research, including a lack of dissent) with important ethical implications (i.e., the health and well-being of humans) that requires an institutional, or organizational, remedy. I hope to make the APEP proposal plausible in two senses. Firstly, I will argue that it is theoretically plausible, in that it does not presuppose an inadequate theory of science. In particular, it does not presuppose that policy-relevant research such as clinical trials can be done in a completely value-free manner—a presupposition that, as many have argued, is misguided (e.g., Biddle 2013; Douglas 2000; Longino 1990, 2002; Okruhlik 1994; Wilholt 2009). Secondly, I will argue that it is plausible in practice by attempting to describe the proposal in sufficient detail to show that it is implementable. This being said, my aim is not to solve all of the practical problems with implementation; doing this, in my view, would require a “real-world experiment” in which a version of the proposal would be actually instituted. I hope, however, to describe the proposal in enough detail to show that such an experiment would be worthwhile.

The institution of an adversarial system would not be a panacea. While it could represent an important step toward addressing the problems that the privatization of pharmaceutical research is causing, it is only one step. (It does not, for example, address the problem of the neglect of diseases that primarily afflict developing countries.) In this regard, the discussion of an adversarial system is meant to provide a helpful starting point for further inquiry. Near the end of the paper, I highlight some of the difficulties that the implementation of such a system must overcome, and I discuss some of the other steps that must be taken, if we are to organize pharmaceutical research in a more ethically and epistemically responsible manner.

PROBLEMS WITH PHARMACEUTICAL RESEARCH

The deficiencies with current pharmaceutical research can be divided into three categories: epistemic, moral, and socioeconomic (Reiss 2010). These divisions are not analytic, in that principled distinctions between

them cannot always be drawn. The ethical and the epistemic, for example, are often intertwined (e.g., Biddle 2007). Despite this, it is useful to provide at least some rough distinctions between the sorts of problems that we currently face. To illustrate some of these problems, I will provide examples from the Vioxx debacle.²

Epistemic Failures

A serious problem with current pharmaceutical research is bias, including bias in the choice of which hypotheses to investigate (and which to ignore), bias in the design of experiments, and bias in the interpretation of results. The Vioxx debacle offers examples of each of these. In November 2000, the results of a large study comparing Vioxx to naproxen, entitled Vioxx Gastrointestinal Outcomes Research (VIGOR), was published in the *New England Journal of Medicine* (Bombardier et al. 2000). The goal of the study was to compare the number of gastrointestinal events in patients with rheumatoid arthritis. The study concluded that Vioxx and naproxen were similarly efficacious in alleviating pain and that there were significantly fewer gastrointestinal events in the Vioxx group than in the naproxen group. In addition, the study found that there were four times as many heart attacks in the Vioxx group (p. 1520). The most straightforward way to interpret the latter result is that Vioxx is associated with heart attacks; moreover, this has been the accepted interpretation since 2004, when Merck pulled Vioxx off the market. Yet this was not the interpretation originally adopted by the study authors. They hypothesized, on the basis of little evidence, that naproxen possesses cardioprotective effects that Vioxx does not. Vioxx, on this account, does not cause heart attacks; it simply does not protect against them. This is a clear example of bias in the interpretation of results.

Merck's response to the VIGOR results is an example of bias in the choice of which hypotheses to investigate. As noted, there was very little evidence that naproxen possessed cardioprotective effects sufficient to account for the difference in cardiovascular events between the two groups. Neither was there much evidence that Vioxx does cause heart attacks; its cardiovascular effects were simply not known. A prudent—and epistemically responsible—response to this uncertainty would have been to investigate the issue. In May 2000, executives at Merck met to discuss exactly this question (Berenson et al. 2004). But after input from both scientists and marketing officials, the company decided against further investigation. While Merck asserts that its decision was based upon sound

science rather than marketing, marketing officials at the meeting were decidedly against investigating this question. A slide at the meeting read: “At present, there is no compelling marketing need for such a study. . . . The implied message is not favorable.” The “implied message” of such a study, of course, is that Vioxx might be associated with heart attacks, and this was not a message that marketers at Merck were eager to convey (Biddle 2007, p. 25).

Bias in experimental design is also a common form of bias in clinical research. There are at least four ways in which sponsors design trials in order to make preferred drugs look better than they really are. The first is to compare the drug to a placebo (Garattini, Bertele, and Bassi 2003). The most important piece of information regarding the efficacy of a drug is whether it is better than the best available treatment, not whether it is better than nothing. Unfortunately, sponsors often compare their drugs to placebo as a means of lowering the standard against which their drugs are measured. The second way involves testing a preferred drug against relatively smaller doses of another drug. This is another way of lowering the standard against which a drug is measured. The third way concerns the choice of endpoints. It is now common to test drugs against surrogate endpoints rather than clinical outcomes (2003). Yet association with a particular surrogate endpoint does not always involve association with the relevant clinical outcome. This is another way of making a drug look better than it actually is (Psaty et al. 1999). The fourth way involves choosing clinical trial subjects that are different from the population for which the preferred drug is targeted (Angell 2004). This is another way raising the probability of obtaining a desired result—and it is another form of bias that was on display in the Vioxx affair (Abramson 2004). In this case, more than half of the people in the study were taking steroids (glucocorticoid therapy)—hardly representative of the general population likely to take Vioxx (Bombardier et al. 2000, p. 1523). This is significant because the conjunction of glucocorticoid and NSAID therapy is known to raise the risk of gastrointestinal events; comparing Vioxx to this group could thus have the effect of exaggerating the gastrointestinal benefits of Vioxx.

These types of bias are not examples of commercial interests *determining* the outcomes of research. Rather, they are examples of “preference bias,” which occurs when the preferences of researchers unduly influence a study in such a way as to increase the likelihood of obtaining a desired result (Wilholt 2009, p. 92). Preference bias, moreover, is not limited to the examples that I have discussed; it is now widespread in medical

research (DeAngelis and Fontanarosa 2008). Its prevalence explains the well-established finding that the source of funding in biomedical research has a significant impact upon research results (e.g., Als-Nielsen et al. 2003; Friedberg et al. 1999; Stelfox et al. 1998). The existence of a “funding effect” has been confirmed by a large review article that analyzed the literature on the effects of conflicts of interest in biomedical research (Bekelman, Li, and Gross 2003). According to the article’s authors:

Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions. By combining data from [37] articles examining 1140 studies, we found that industry-sponsored studies were significantly more likely to reach conclusions that were favorable to the sponsor than were nonindustry studies. (p. 463)

The now-extensive literature on the effects of conflicts of interest in biomedical research indicates that many of the epistemic failures that occurred in the Vioxx debacle are in fact widespread problems.

Moral Failures

One of the most important moral failures of current pharmaceutical research is the tendency to suppress or underreport unwanted results. (This failing also has a clear epistemic dimension, as the suppression or underreporting of results inhibits the growth of knowledge.) One prominent example of the suppression of results concerns the Pharmacia-sponsored study on Celebrex, which was published in the *Journal of the American Medical Association*. The study concluded that Celebrex is associated with significantly fewer stomach problems, especially ulcers, than are traditional anti-inflammatory drugs such as ibuprofen (Silverstein et al. 2000). This conclusion was based on six months’ worth of data. The authors neglected to mention that twelve months’ worth of data had been taken and that, when these twelve months were analyzed, Celebrex appeared to be no safer on the stomach than traditional anti-inflammatory drugs (Jüni, Rutjes, and Dieppe 2002). A second example concerns the SSRI Paxil and its association with suicidal thoughts and behavior. In June 2004, Eliot Spitzer, then Attorney General of New York, sued GlaxoSmithKline, charging that it had withheld data on Paxil since at least 1998. Following this, the company posted the results of the studies on its website—some of which show significantly higher rates of suicide, suicidal actions, and “hostility”—where “hostility” can include homicidal behavior (Boseley 2004).³ In August 2004, Spitzer and GlaxoSmithKline

agreed to a settlement, in which the company agreed to pay \$2.5 million to the state of New York. Examples such as these, moreover, are far from isolated incidents. For example, one early study found that roughly half of the clinical trials reported initially in summary form lacked sufficient detail to make an informed judgment regarding the validity of the results (Chalmers et al. 1990).

Another significant moral failure—which also has an epistemic dimension—is the prevalence of ghost writing. A high percentage of articles in prestigious medical journals are written by pharmaceutical companies or medical publishing companies and then attributed to academic investigators (Kukla 2012; Moffatt and Elliott 2007; Sismondo 2007). In many cases, the studies are not merely ghost written but also “ghost managed,” in the sense that the companies manage the entire research process, including the choice of research question, study design, statistical packages, and publication strategies (Sismondo 2007). This obscures the origins of the published results and lends them unwarranted prestige—and it dramatically increases the likelihood of obtaining a desired result. In their study of articles on Sertraline (Zoloft), for example, Healy and Cattell find that 100% of identifiable ghost-written articles report positive results, while 56% of non-ghost-written articles reported either neutral or unfavorable results (2003). Many of the studies on Vioxx were also ghost written (Ross et al. 2008), including some in which the medical professionals who put their name on papers were not given access to key pieces of information (Biddle 2007).

A different set of ethical concerns stems from the tendency of the pharmaceutical industry to neglect the problems of the very poor, such as those in the developing world. This neglect comes in two different forms. The first is known as the “problem of access,” or the problem of ensuring that the poor can obtain medicines that already exist. Nearly 2 billion people—almost 30% of the global population—lack access to potentially life-saving medicines; because of this, approximately 10 million people die unnecessarily every year (Grover 2009, p. 7). The second is the problem of availability, or the problem of incentivizing new medicines for diseases that afflict primarily or exclusively the developing world (or Type II and Type III diseases, respectively). For example, of the 1,223 drugs approved for sale between 1975 and 1997, only 13 (approximately 1%) specifically treated tropical diseases (Trouiller and Olliaro 1999). These problems, and some potential candidate solutions to them, have been described in more detail elsewhere (e.g., Biddle, *forthcoming*; Hollis 2008; Pogge 2005; Rav-

vin 2008; Reiss and Kitcher 2009; Schroeder and Singer 2011). As noted, the proposal that I develop in this paper does not address these problems.

Socioeconomic Failures

Some of the moral failures discussed above—for example, the problems of access and availability—could also be classified as socioeconomic failures. The distinction between these categories, again, is not analytic. I will restrict my discussion of the socioeconomic failures of recent pharmaceutical research to one—namely, the lack of genuine innovation. Much of what the pharmaceutical industry produces are duplicative drugs—or “me too” drugs—which are drugs that are sufficiently different from already-existing medicines to obtain a separate patent, but which have therapeutic effects that are the same as, or very similar to, drugs already on the market. For example, between 1990 and 2004, 77% of drugs approved by the FDA were duplicative in this sense (Angell 2004, p. 75). Given the high costs of pharmaceuticals to the public and the corresponding high profits of the industry, it is reasonable to expect more innovation than we are currently receiving.

DISSENT AND THE ORGANIZATION OF RESEARCH

It might be tempting to explain these failures by appealing to the greed of individuals. A better explanation, however, appeals to the broader institutional environment in which individual scientists operate (Biddle 2007; Reiss 2010). While there are many features of this environment that are important, two in particular are worth highlighting. The first concerns changes in the landscape of pharmaceutical research. Prior to the early 1980s, it was common for pharmaceutical companies to provide grants to universities or academic medical centers to conduct research. During this time, faculty investigators—who typically had no financial ties to the pharmaceutical industry—designed and conducted the trials, interpreted the results, and decided where and how to publish the results. This system allowed investigators to conduct research in a relatively impartial manner. Since the early 1980s, however, pharmaceutical companies have increasingly contracted their research out to private, for-profit companies known as “contract research organizations” (CROs) (Angell 2004; Mirowski and van Horn 2005). This organizational shift raises serious epistemic worries. As private, for-profit corporations, CROs have as their primary duty the maximization of profits within the bounds of the law. Moreover, their only source of revenue is the pharmaceutical industry. Because of this, CROs

have an incentive to structure the research process in ways that are either stipulated by, or in the interests of, their clients; in other words, they have an incentive to maximize the likelihood of obtaining clients' desired results in a minimum amount of time. They have little incentive to question the preferred methodologies of its client, or to insist that the research be impartial. Doing so could endanger a CRO's prospect of obtaining future contracts, and even threaten its future viability.

The second important institutional feature concerns the changing regulatory environment of pharmaceuticals. Over the past quarter century or more, the FDA has become increasingly dependent on the pharmaceutical industry. This dependence comes in a variety of forms. One of them is the increasing number of FDA officials or advisory committee members who have financial ties to pharmaceutical companies. For example, in September 2000, *USA Today* published a study of 18 FDA advisory committees, consisting of approximately 300 individuals (Cauchon 2000). These committees performed a variety of advisory functions, including recommending how a study should be designed, whether a drug should be approved for sale, whether a drug should receive a stronger warning label, and whether a drug should be taken off the market. Of the 159 committee meetings analyzed between January 1998 and September 2000, 55% consisted of groups in which at least half of the FDA advisors had financial conflicts of interests. These conflicts included the evaluation of a drug that they had helped a pharmaceutical company to develop and consulting for or owning stock in the company that owned the drug they were evaluating. Furthermore, at the 102 meetings that dealt with the fate of a specific drug, 33% of the committee members had a financial conflict of interest.

The effect of these conflicts of interests is to predispose advisory committee members toward conclusions that are in the interests of pharmaceutical companies (Bekelman, Li, and Gross 2003). One example of this was the recommendation in February 2005 by an FDA advisory committee to put Vioxx back on the market, after Merck had withdrawn it from the market due to its potential cardiovascular side effects (Center for Science in the Public Interest 2005). The committee that made this recommendation consisted of 32 voting members. The vote in favor of putting Vioxx back on the market was 17–15. Ten of these committee members had financial conflicts of interest with at least one of the pharmaceutical companies that had drugs under examination—namely Merck, Pfizer, and Novartis. Of these 10, 9 voted in favor of putting Vioxx back on the market. Had these ten individuals abstained from voting, the committee vote would have favored keeping Vioxx off the market.

There are other ways in which the FDA is dependent upon the pharmaceutical industry. Since 1992, pharmaceutical companies have been required to pay “user fees” to the FDA in order to help to cover the costs of drug approval (Hilts 2003). This financial dependence of the FDA on the pharmaceutical industry has increased the influence of industry over FDA regulatory practices. Since 1992, the percentage of FDA money provided by the federal government has been declining, while that provided by industry has risen steadily (Harris 2004). The increasing dependence upon industry money has led the FDA to shift its priorities increasingly away from the postmarket safety testing of drugs and toward the approval of new drugs. For example, while the total amount of funding to the FDA has remained approximately the same, the percentage of funding devoted to the approval of new drugs has risen from 53 percent in 1992 to 79 percent in 2003 (Harris 2004).

The increasing inability of the FDA to handle the surveillance of drugs that are already on the market has made the agency increasingly reliant upon drug companies to report adverse events. In some cases, pharmaceutical companies—as a condition of approval of their drug—agree to conduct certain postmarket tests of their drug. Yet, a significant percentage of these studies are never completed, and many are never even initiated (Fontanarosa, Rennie, and DeAngelis 2004; GAO 2006).

All of this suggests that the privatization of biomedical research is consolidating the pharmaceutical industry’s power over the entirety of the research and development process, which it can then use to marginalize perspectives that are different from its own. Pharmaceutical companies are increasingly organized so as to allow financial considerations to influence scientific decision-making, and the agencies that are supposed to be regulating the pharmaceutical industry are, in a variety of ways, so dependent upon that industry that they cannot effectively regulate it. The result of this, again, is a growing number of instances of biased research and withholding of information from the public. The appropriate response to this, in my view, is to design systems that institutionalize certain types of criticism and that, more generally, counteract the power of entities that have large financial stakes in the outcomes of research. As is apparent, not all institutional arrangements are conducive to the kinds of critical exchange that epistemically rigorous research requires. In the remainder of this essay, I will discuss a potential organizational change that could help to facilitate such critical exchange, namely an adversarial system of research within the FDA. I will begin this discussion by examining Kantrowitz’s proposal in the 1960s and 1970s for an adversarial system of research.

KANTROWITZ'S SCIENCE COURT PROPOSAL

In 1967, Arthur Kantrowitz published an article in the journal *Science* entitled “Proposal for an Institution of Scientific Judgment,” in which he argued for the establishment of a “science court” where scientific questions that are relevant to public policy debates would be adjudicated (Kantrowitz 1967; see also his 1975, 1976, 1993).⁴ Kantrowitz, the founder and former director of the Avco Everett Research Laboratory in Everett, Massachusetts, was one of many scientists in the 1960s and 1970s who were concerned about our ability to make wise decisions regarding science-based public policy questions. Emphasizing the growing entanglement of science and politics, Kantrowitz argued that we are increasingly forced to make consequential “mixed decisions,” or decisions that have both a scientific and a moral/political component (1967). Whether it is the decision to build an atomic bomb or to enact policies to curb ozone depletion, we are increasingly confronted with science-based public policy decisions that have wide-ranging effects on the social and political landscape (1967, 1976).

In a number of essays beginning in 1967, Kantrowitz argued that we do not have the appropriate organizational structures for making mixed decisions effectively. The primary reason for this, he argued, is that individual scientists engaged in cutting-edge research are almost always affected by various biases. For example, scientists who become involved in the policy-making process almost inevitably allow their moral and political beliefs to influence their appraisal of scientific hypotheses (1967, p. 763). Similarly, scientists who are immersed in researching a particular question for an extended period of time almost always develop cognitive prejudices, including preconceptions about the results of future experiments (p. 763). In addition, the fact that mixed decisions must be made quickly, typically before a consensus is formed within the scientific community, makes it even more likely that such biases will affect individual scientists.

Kantrowitz argued that while biases or prejudices—including moral and political ones—inevitably affect the mixed decisions of *individuals*, it is reasonable to expect *communities* to separate the scientific, or purely factual, components of mixed decisions from the moral and political components (1995). While individuals *qua* individuals cannot make such a separation (at least within policy-relevant research), communities can attain this via, and only via, certain sorts of social arrangements. Given that the exclusion of moral and political values from the evaluation of policy-relevant research is, in his view, a necessary condition for the objectivity of

research, he conceives of objectivity as an inherently social phenomenon.

What kinds of communities can ensure the objectivity of science? Kantrowitz answered this question by suggesting a sort of epistemic experiment. He proposed that scientific issues that are relevant to public policy disputes be debated within an adversarial setting that he termed a “science court,” and he suggested that the effectiveness of such adversarial proceedings be tested experimentally (1967, 1976). He envisioned the science court as an institution created by Congress in order to aid its ability to make good public policy decisions. Unfortunately, the grand experiments that he planned to test his court were never undertaken—more on this later.

Kantrowitz proposed a system that consists of two groups of advocates and a panel of scientist-judges; the two groups of advocates argue for opposing sides of a given issue, and the panel of judges adjudicates between the two sides. This system, he argued, would eliminate prejudices from scientific decision-making by separating those who argue for a particular position (the advocates) from those who decide on the merits of that position (the judges). It would have the further benefit of forcing scientists to engage in public policy disputes in an ethically and epistemically appropriate way. Kantrowitz held that a serious problem with science-based public policy debates is that many scientists make public policy pronouncements without being willing to answer the scientific challenges of critics. Through its institutionalized adversarial proceedings, the science court would ensure that scientists who engage in such disputes take responsibility for their claims (Masters and Kantrowitz 1988).

While Kantrowitz left many of the details of the science court to be worked out in the future—especially on the basis of the planned experimental tests of the proposal—he did address a number of them in his essay, “The Science Court Experiment: An Interim Report” (1976). These include the determination of questions to be addressed by the court, how the court is to be funded, the selection of advocates and judges, and the establishment of adversary procedures. Regarding the determination of issues to be addressed by the court, he provided three rough criteria to help to identify such issues. Firstly, the issues should be relevant to policies that are currently being debated within a governmental agency, and they “must have technical components that are both important and apparently disputed” (p. 654). Secondly, those issues that allow for an easy separation of facts from values should be preferred. Kantrowitz insisted that the science court debate solely the scientific or technical components of mixed questions; the value-components of such questions were to be decided

by elected officials. Finally, issues “for which informed and credible case managers [or advocates] can be obtained” should be preferred (p. 193).

How are advocates, or “case managers,” to be chosen? Kantrowitz mentioned two possibilities, and he left the choice between them for the future. According to the first, the selection of an issue would be followed by a request for proposals from potential case managers. In their proposals, case managers must exhibit an expertise in the relevant issue as well as demonstrating that they speak for one side of that issue. “For example, a group such as the Union of Concerned Scientists, the Sierra Club, or Friends of the Earth might be a reasonable bidder to represent the antinuclear power side of that issue” (p. 654). Case managers could form alliances with nonprofit groups, scientific institutions, or individual scientists. Thus, for example, the Union of Concerned Scientists, the Sierra Club, and a group of individual scientists could form an alliance and work as an advocate for a specific side of an issue. Once the court settles upon a set of case managers, they will be funded by the court, “perhaps on a time-and-materials basis or by some other suitable contractual mechanism.” In his discussion of this possibility, Kantrowitz continually refers to “the Science Court” as the entity that will select case managers; he is not explicit about which specific group within the court will make the decision.

The second possibility is discussed by Kantrowitz only very briefly. His remarks on it are confined to the following sentence: “When an issue is clearly polarized, the case managers might be found by polling the interest groups involved on each side” (p. 654). Precisely how such polling is to be conducted, he does not say.

Who is to provide the court’s funding? Given that the issues to be decided by the court are relevant to public policy and, hence, to a given governmental agency, thought was given to the idea of that agency providing the requisite funding. The problem could arise, however, that an agency’s willingness to provide such funding in the future might depend upon whether earlier court decisions were consistent with the views of that agency. As a result, Kantrowitz suggested that funding come not only from governmental agencies but a variety of sources, including the National Science Foundation, private foundations, and businesses. “In every case,” he argued, “assurances must be had that no strings are attached” (p. 654). Unfortunately, he says nothing about how such assurances are to be had.

Arguments within the science court would be overseen by a panel of judges and a referee. The panel of judges would be responsible for ad-

judicating between the arguments of the advocates and for publishing a final opinion. Regarding the selection of these judges, Kantrowitz wrote:

It is currently envisioned that the Science Court with consultation from appropriate scientific societies and organizations will produce a list of prospective judges certified as unusually capable scientists having no obvious connections to the disputed issue. These will then be examined by the case managers for prejudice. After acceptance, a panel of judges . . . will be formed. (p. 654)

However, he did not rule out alternative means of selecting judges, such as allowing institutions such as the National Academy of Sciences to make the selections and, in some instances, to mandate the random selection of judges from a pool of acceptable candidates. While he did not state this explicitly, I assume that he intended for the judges to perform this service freely.

In addition to the panel of judges, a referee would oversee the proceedings to ensure that the agreed-upon procedures are respected. Kantrowitz proposed that the referee be a scientist who is advised by legal counsel. What are the procedures that must be respected? Many of these, he acknowledged, are not yet worked out, including the powers that the science court would have in compelling the disclosure of scientific information. He was clear, however, that the adversarial procedures of the science court would be different from those of a court of law. Most importantly, the panel of judges would not act as a gatekeeper and determine who counts as a legitimate expert. “There will be no necessity to prove the expertise of a witness, since his statements will be open to detailed challenge” (p. 655). The US Supreme Court has recently expanded the powers of judges to determine what counts as reliable expert testimony, in part because of concerns regarding the ability of a jury to make such determinations adequately (Edmond 2002). In the science court, however, such concerns are alleviated by the fact that those adjudicating the case are trained scientists.

Kantrowitz’s proposal was, for a time, very popular. He convinced the Ford administration to set up the “Task Force of the Presidential Advisory Group on Anticipated Advances in Science and Technology” for the purpose of investigating the viability of the proposal. In Kantrowitz 1976 he argued the case for the court, and he proposed that an experiment be performed to further test his proposal. He announced a colloquium in Leesburg, Virginia to discuss the science court and the ways in which it could be tested. Soon after this event, however, President Carter replaced

Ford, and while Carter's administration was not opposed to the experiment, it did not make it a priority.⁵

Despite the fact that there was never a serious attempt to implement or test Kantrowitz's science court, it is nevertheless a proposal that deserves continued attention. This is especially true given the problems arising from the privatization of biomedical research. As argued, privatization is impeding the ability of communities to instantiate the norm of organized skepticism. Yet, as should be clear from the discussion of Kantrowitz's proposal, one of the primary epistemic benefits of an adversarial system is the way in which it institutionalizes dissent. Given this, it is plausible to think that an adversarial system could help to alleviate some of the problems that privatization is causing. In particular, an adversarial system could help to expose the kinds of bias that are so often found in current pharmaceutical research, such as bias in the choice of hypotheses, bias in the interpretation of results, and bias in experimental design. Additionally, as I will discuss later, it could help to expose situations in which pharmaceutical companies fail to report data to journals and to the public.

Consider, for example, the possibility of instituting an adversarial system of research into the processes of drug approval and postmarket safety evaluation in the FDA. The currently existing processes treat pharmaceutical companies, FDA scientists, and expert advisory committees as disinterested evaluators of research. Pharmaceutical companies present data to the agency, and agency officials and advisory committees evaluate this data in a purportedly unbiased fashion. Pharmaceutical companies are not viewed, at least explicitly, as interested parties, and there is no group within the process that takes an explicitly adversarial position toward these companies. Indeed, industry representatives and many politicians—both Democrats and Republicans—are encouraging the FDA to view pharmaceutical companies as cooperative partners. In an adversarial system, on the other hand, a pharmaceutical company would be viewed explicitly as *advocating* the safety and efficaciousness of its drug; another group would develop a case against this position, and a third group would adjudicate between the previous two. Within such a system, the critical scrutiny given to controversial drugs would very likely be heightened.

Would implementing some version of Kantrowitz's science court into these processes be feasible? Would it alleviate some of the problems resulting from the recent privatization of pharmaceutical research? The remainder of the essay will address these questions.

A SKETCH OF AN ADVERSARIAL SYSTEM OF PHARMACEUTICAL RESEARCH

The adversarial system of pharmaceutical research that I will outline—Adversarial Proceedings for the Evaluation of Pharmaceuticals (APEP)—retains several of the features of Kantrowitz’s original science court proposal. Two groups of advocates would present arguments for a specific position, and a panel of judges would adjudicate between these two groups. The issues to be discussed should be issues that are controversial; in certain circumstances, there will be previously-existing evidence that is sufficient to close the controversy, but in general, the central questions will be underdetermined. The conclusions arrived at by the panel of judges should not be considered definitively true, but should rather be viewed as provisional and subject to change with the acquisition of further information. There are, however, many divergences from the original Kantrowitz proposal. Some of these result from APEP being a system for evaluating pharmaceutical research in particular, whereas Kantrowitz proposed that his science court address issues in any area of policy-relevant science. Other differences result from deficiencies in Kantrowitz’s original proposal, including his insistence that technical questions be sharply separated from policy. In order to clarify the differences between APEP and the original science court proposal and, more generally, to articulate how APEP would be structured, I will pose and respond to a series of questions that the reader has no doubt been asking.

How would issues be selected? The most common questions to be addressed by APEP would be: (1) whether a new drug should be placed on the market, (2) whether a drug that is already on the market should remain on the market, and (3) the conditions under which a drug should be placed, or remain, on the market. Because of the length of time that each set of proceedings would require (I envision approximately 1–2 months), not every drug that comes on the market can (or should) be subject to such intense scrutiny. Controversy, however, surrounds many new drug applications (NDAs) and already-marketed drugs, and these cases should be subject to more intense review than they currently receive; the institution of APEP is meant to ensure that this takes place. In the process of reviewing an NDA or an already-marketed drug, officials from governmental agencies (including the FDA and public health agencies such as the Centers for Disease Control and Prevention) and outside scientists would have the ability to call for proceedings to debate whether, or the conditions under which, the drug should be allowed on the market.

APEP should convene only in cases of controversy.⁶ In order to ensure that this condition is satisfied, and that a set of proceedings is not called for needlessly or unjustifiably, anyone who calls for proceedings must present his or her case before an advisory panel consisting of independent scientists. The function of this panel would not be to determine whether the drug in question really is unsafe or ineffective; rather, it would merely seek to ensure that there are sufficient reasons for believing the issue in question to be legitimately controversial. For example, the panel would seek to ensure that the individual or group calling for the proceedings has recourse to legitimate studies that call into question the safety or efficacy of a given drug, even if those studies do not show definitively that the drug is unsafe or ineffective.⁷

The panel should consist of scientists from a variety of different fields that are relevant to the issue at hand. Because the panel would not seek to determine what the outcome of a set of proceedings should be, but only whether a set of proceedings should be initiated in the first place, the scientists who make up the board would not need to be specialists on the drug in question. One could even argue that the process would be best served by *excluding* panelists who are specialists on the drug in question, as such specialists would likely already have a stake in the issue under consideration. The conclusion of the panel would be binding; it would not be a mere recommendation that the FDA conduct adversarial proceedings, but would rather initiate them automatically.

Which agency would house APEP? The simplest and most obvious answer to this question is the FDA. The FDA, after all, is the agency charged with protecting the public health by, among other things, ensuring that pharmaceuticals are both safe and effective. Because APEP's primary function would be to evaluate controversial new drug applications and controversial drugs that are already on the market, and because the FDA is the agency that currently handles both of these tasks, the FDA is the simplest choice for housing APEP.

It must be acknowledged, however, that instituting APEP within the FDA would be no easy feat. One of the primary reasons for this pertains to the previously-discussed inability, in many areas of science, to draw a strict distinction between science and policy. Because technical and policy issues are often inextricably intertwined, APEP would not shy away from making policy proposals. For example, one possible outcome of a set of proceedings would be the provisional determination that a drug is safe but that, in most cases, it is no more effective than already-existing, lower

priced medications. This is a scientific judgment, but one with obvious practical implications. While recommendations of this sort would be provided by APEP, the FDA has consistently resisted offering any such policy proposals, and it has remained firm in its commitment to do little more than attempting to ensure that a drug is safe and effective—i.e., safe and slightly better than placebo.

The fact that the FDA's criteria for drug approval are limited to safety and effectiveness is one of the most criticized aspects of the FDA approval process. Comparisons with placebo, of course, are important, but an adequate health care system requires that we understand which drugs are most effective in treating an illness. In other words, it requires that we have reliable studies that compare the effectiveness of different drugs, studies that pharmaceutical companies are sometimes unwilling to perform. Furthermore, given that all health care systems operate under funding constraints, we should also have a thorough understanding of which drugs can treat an illness in the most effective and most cost-efficient manner. The FDA's current regulatory procedures do nothing to address these fundamental questions; getting it to expand the kinds of evaluations that it makes will not be easy.

How would APEP be funded? On the face of it, this is one of the most difficult questions that a proposal for an adversarial system of pharmaceutical research faces. Presently, there is an abundance of funding for groups advocating on behalf of pharmaceutical companies and precious little for groups that criticize the research of these companies. Given this state of affairs, how could the funding requisite for an adversarial process—including funding for those who criticize the research of a particular company—be obtained? In answer to this, it is important to recognize that while everyday citizens and public interest groups clearly have a stake in ensuring the quality of pharmaceutical research, there are other, more well-funded groups—such as insurance companies and HMOs—that also have such a stake. The consequences of epistemically inadequate pharmaceutical research for these groups are clear.

When a doctor who works for an HMO prescribes an expensive drug over a cheaper, equally effective, one, the HMO pays more money than is necessary. When a doctor who works for an HMO prescribes a drug that is unsafe and that worsens the condition of a patient, the HMO often ends up paying to treat the worsened condition of the patient; in such a situation, the HMO, again, pays more money than it would have if an appropriate treatment had been prescribed in the first place. Furthermore,

just as the prescribing of drugs that are either unsafe or more expensive than is necessary runs counter to the financial interests of HMOs, it also runs counter to the financial interests of insurance companies, and it does little to help the already horrendous financial conditions of government programs such as Medicare and Medicaid.

I suggest, then, that the bulk of the funds for APEP be collected from a conglomeration of for-profit companies, especially pharmaceutical companies, HMOs, and insurance companies. Given the large profits of these companies—for example, Merck, despite all of its troubles stemming from Vioxx, made over \$4.6 billion in profits in 2005—adequate funding for the process could be obtained through a very small tax on profits.⁸ The funds collected from this tax would be pooled together and used to fund the entire adversarial process. In other words, it would *not* be the case that funds collected from pharmaceutical companies would fund only their advocates, and that funds from HMOs and insurance companies would fund only their advocates.

How would the advocates and panels of judges be chosen? The scientists that argue on behalf of a pharmaceutical company would be chosen by that company. These scientists could either be company employees or university scientists. The question of how the other set of advocates should be chosen is a more difficult one. One possibility would be to institute a mechanism whereby the HMOs, insurance companies, or government health care agencies could choose a set of advocates. It is not clear, however, how such a mechanism could work. Perhaps a more plausible alternative would be to have FDA officials select advocates who are known for their criticisms of a particular drug, and to require that the selection of advocates be approved by a board of representatives of HMOs, insurance companies, and government health care agencies. Public interest groups such as Public Citizen and the Center for Science in the Public Interest would also be encouraged to participate in the selection of advocates, perhaps by recommending particular groups or individuals to the FDA for consideration.

There are a variety of ways that the panels of judges could be chosen; two plausible possibilities proposed by Kantrowitz have already been discussed. For example, the FDA could petition the National Academy of Sciences to draw up a list of capable scientists from a variety of relevant disciplines who have no direct connections to the issue under consideration. Both sets of advocates could then have the ability to exclude a given number of scientists from participation. The final panel would consist

of those scientists remaining on the list. What is most important is that the panel of judges be independent of industry. These panels, in other words, should resemble traditional scientific advisory committees, with the exception that scientists who are either employees of or consultants for pharmaceutical companies (or, for that matter, HMOs and insurance companies) would be excluded from participation.

Would the APEP conclusions be binding on the FDA, or would they be considered to be recommendations? At least preliminarily, I suggest that the conclusions be recommendations that the FDA could either accept or reject. One of the primary reasons for this suggestion is the practical one that FDA would probably never agree to institute APEP if its conclusions were anything but recommendations. There is, of course, the worry that the FDA would all too often ignore the recommendations of APEP. However, given that APEP would address only controversial issues, there would no doubt be much attention paid to the conclusions reached through these proceedings. The publication of the results of the proceedings—which, as I will suggest shortly, should be required—would only increase the amount of attention that they receive. Given the high-profile character of the proceedings, the FDA would be subject to an extreme level of negative publicity were it to disregard the conclusion of the APEP panel. As a result, there is reason to hope that the number of cases in which APEP recommendations are not taken up would be very small.

How could public participation be facilitated? Because APEP would be charged with evaluating scientific issues that are relevant to policy, it is important that there be mechanisms for public participation. One possibility would be to follow a format similar to the Consensus Development Program of the National Institutes of Health (NIH), according to which the adversarial proceedings would take place in a public forum (Institute of Medicine 1990; Solomon 2007).⁹ The panel's preliminary conclusions could be presented publicly and then revised on the basis of the discussions that arise. Following such public discussions, a summary of the arguments put forward by both sets of advocates, together with the conclusions of the panel of judges, would be published, preferably in a high-profile medical journal such as the *Journal of the American Medical Association* or the *New England Journal of Medicine*. Another possibility for incorporating public participation would be to include citizen representatives on the panel of judges (Shrader-Frechette 1985). Working out this process would require further empirical study; if it could be accomplished successfully, however, it would represent an important step toward including the necessary amount of public participation.

How would APEP proceedings be conducted so as not to reveal proprietary information? Representatives of pharmaceutical companies might object to the institution of APEP on the grounds that it would reveal proprietary secrets, especially if mechanisms of public participation were included. This, however, is an ill-founded criticism. By the time that an NDA is submitted, the drug in question has been developed, and a company has already received a patent on it. Thus, by the time that APEP proceedings would be undertaken, companies would have legal recourse against anyone who attempted to profit from proprietary information.

This sketch of APEP represents a starting point for further discussions regarding the feasibility of an adversarial system of pharmaceutical research. In my view, the APEP proposal is sufficiently plausible as to merit further research and discussion. More specifically, it represents a plausible way of facilitating heightened levels of organized skepticism within pharmaceutical research. There are, however, a number of questions that remain to be answered. In particular, there are some characteristics of the current institutional arrangement of pharmaceutical research that call into question the feasibility of such an adversarial system.

ON THE FEASIBILITY OF AN ADVERSARIAL SYSTEM OF RESEARCH

Given that APEP requires that its panels of scientific advisors be financially independent of the pharmaceutical industry, perhaps the most important question regarding the feasibility of APEP is the following. *Are there enough independent pharmaceutical researchers to allow APEP to function properly?* As the private sector funding for pharmaceutical research grows, the number of qualified scientists without financial ties to pharmaceutical companies and biotechnology firms is diminishing rapidly. This is one of the most serious issues facing an adversarial system of pharmaceutical research, and it suggests that instituting an adversarial system, by itself, would not be sufficient to ensure epistemic reliability.

What kinds of institutional changes must be made in order to ensure that an adequate number of pharmaceutical researchers do not enter into financial arrangements with for-profit companies? This is a complicated question that will not receive adequate treatment in this essay. One helpful starting point, however, would be to ensure that NIH scientists are prohibited from having conflicts of interests with pharmaceutical companies or biotechnology firms. The funding for the NIH is still very large, and prohibiting NIH researchers from having conflicts of interest would ensure that significant, if still relatively small, numbers of scientists were

independent of industry funding. In this respect, the recent changes in NIH conflict of interest guidelines are encouraging. In response to a Senate investigation that was spurred by David Willman's blistering expose in the *Los Angeles Times* of the prevalence of conflicts of interests among leading NIH researchers (2003), the NIH has adopted new guidelines that ban NIH researchers from consulting for pharmaceutical companies and biotechnology firms.¹⁰ In addition, these guidelines prohibit senior researchers from holding shares of stock in companies that are directly related to their research. While these guidelines alone will not ensure that there is a sufficient supply of independently-funded pharmaceutical researchers, it is a step in the right direction.

Another possibility for attempting to ensure a sufficient supply of independently-funded pharmaceutical researchers would be to make the position of APEP panel member a long-term, highly-paid position. In this case, the APEP panel would look less like a scientific advisory committee and more like a panel of judges. Because of the long-term nature of the position, the selection of panel members would become even more complicated than the previous discussion has allowed. Furthermore, depending upon how highly-paid the position would be, it might be difficult to attract well-qualified scientists to sit on the committee. If these issues could be worked out, however, it would help to solve the problem of finding independently-funded scientists to serve on the committee.

How would APEP ensure that all relevant information regarding a drug is communicated by a pharmaceutical company? As discussed earlier, a significant problem with much recent pharmaceutical research is the tendency of companies to withhold any information that might call the safety or efficacy of their drugs into question. How can we ensure that companies disclose all relevant information regarding their drugs so that intelligent regulatory decisions can be made?

Concerns regarding the withholding of data are alleviated, at least to some extent, when one clarifies the issue at hand; while the failure to publish or to disseminate negative results publicly is a very significant problem, the withholding of information from the FDA is not nearly so common. Consider, for example, the aforementioned cases of GlaxoSmithKline and Pharmacia. GlaxoSmithKline conducted nine clinical trials on its SSRI, Paxil, and as of early 2004, only one of these studies had been published; all of these data, however, were disclosed to the FDA (Harris 2003). Similarly, Pharmacia caused a scandal when investigators discovered that it had failed to disclose six months' worth of data to the *Journal of the*

American Medical Association; all of this data, however, was disclosed to the FDA. This provides some reason for optimism that APEP, if instituted, would receive the information that it needed.

Furthermore, there are steps that could be taken that would help to ensure that negative results would be disclosed not only to the FDA, but also to the public. An example of this would be a publicly-accessible database in which pharmaceutical companies would be required, by law, to register all of their clinical trials. Marcia Angell, for example, has called for the creation of an NIH-administered registry, in which companies would be required to register *all* of the clinical trials that they conduct; these trials, moreover, would be registered upon their inception, as a condition of enrolling subjects (2004). The lengths, endpoints, and other features of the trials should be specified in advance, so as to reduce the amount of “fudging” that can occur once the data are collected. This would have prevented Pharmacia, for example, from surreptitiously reporting only the first six months of the collected data on Celebrex. Many steps have been taken to mandate registration of clinical trials, though there is still much more to be done (e.g., Prayle, Hurley, and Smyth 2012).

In addition to the problem of ensuring that the FDA has access to the data that it needs during the process of drug approval, there is the further problem of ensuring that it has access to the data required to perform adequate postmarket safety evaluations. To ensure this, the FDA should be given the authority to require drug companies to conduct postmarket safety studies (GAO 2006). At present, the FDA can request that pharmaceutical companies conduct postmarket safety studies as a condition of drug approval. However, it does not have the ability to compel companies to conduct these studies; it, for example, has no legal or financial recourse if companies choose not to conduct them. Given this, it comes as no surprise that many of the postmarket safety studies that companies agree to conduct are never brought to completion. Most, in fact, are never even initiated. In March 2006, for example, the FDA admitted that nearly two thirds of the postmarket studies that companies agree to perform are never initiated (Harris 2006). Providing the FDA with the ability to compel companies to undertake such studies would help to ensure that adequate postmarket safety evaluations can be obtained. Furthermore, it would help to ensure that APEP would have access to the data that it would need to function appropriately.

CONCLUSION

I have argued that there are serious problems with the way in which pharmaceutical research is currently done—epistemic, moral, and socio-economic problems—and that an important cause of these problems is inadequate dissent. As a means of improving this situation, I have proposed consideration (and perhaps testing) of an adversarial system of pharmaceutical research, APEP, which would be instituted within a regulatory agency such as the FDA. The adversarial nature of APEP represents an acknowledgment that pharmaceutical companies, and the scientists that they sponsor, should not be viewed as disinterested arbiters of research but, rather, as advocates for particular hypotheses. APEP, in other words, is an institution that acknowledges that interests play an inevitable role in the evaluation of pharmaceutical research, and it ensures that the interests of pharmaceutical companies are not allowed free rein, but rather are checked by interests that are diametrically opposed to them. In this way, it enforces organized skepticism.

As I have acknowledged, however, APEP would not be a panacea. Significant obstacles must be overcome in order to implement APEP and to ensure that it functions appropriately. One of the most important of these concerns the current paucity of independently-funded pharmaceutical researchers; another concerns the question of how pharmaceutical companies can be compelled to disclose all of the relevant data on their drugs—including data that calls into question their safety or efficacy. These obstacles suggest that the institution of APEP alone would not be sufficient for ensuring the epistemic reliability of research. The proposal for an adversarial system is sufficiently promising, however, as to represent an important step in the direction of improving the quality of pharmaceutical research.

NOTES

1. Thanks to Nancy Cartwright, Kevin Elliott, Michael Feuer, Dan Fouke, Chris Hamlin, Nils Roll Hansen, Don Howard, Matthias Kaiser, Rebecca Kukla, Miriam Solomon, Eric Winsberg, and two anonymous reviewers for their comments on earlier versions of this paper. Thanks also to the participants of the workshop, “Institutionalising Epistemic Standards for Science,” at the London School of Economics, where an early version of this paper was presented.
2. The discussion in this section is indebted to work on the commercialization of biomedical research by Avorn (2004), Angell (2004), Kassirer (2005),

- Krimsky (2004), McHenry and Jureidini (2009), and others. The discussion of the Vioxx case draws on Biddle (2007).
3. For links to the studies, see <http://www.gsk.com/media/paroxetine.htm> (accessed 21 June 2012).
 4. Thanks to Chris Hamlin for referring me to Kantrowitz's work. Hamlin 2005 contains a brief discussion of James B. Conant's earlier proposal for an adversarial system of research, which Conant lays out in Conant 1951. For a discussion of Conant's proposal, see Biddle 2011.
 5. While the plans for a "grand experiment" were never realized, Kantrowitz did test a revised and scaled-down version of his proposal—which he called the "Scientific Adversary Procedures"—in the 1980s (Masters and Kantrowitz 1988). In 1983, he and Frank Hurlbut organized adversarial proceedings at the University of California, Berkeley on the topic of the health hazards at Love Canal, and in 1985, he organized similar proceedings at Dartmouth on Reagan's Strategic Defense Initiative. While the proceedings were in many respects successful, they were dramatically different—and dramatically more modest in aims—than the original science court proposal. As a result, they provide little basis for judging whether something more closely resembling the original science court proposal could be successful.
 6. Thanks to Don Howard for discussion on this matter.
 7. One might wonder how cases of genuine controversy will arise when pharmaceutical companies are responsible for doing safety-tests on their own drugs. (Thanks to Miriam Solomon for raising this question.) In response, it is often the case that controversies arise as a result of gaps in the data and/or reasoning provided by pharmaceutical companies. For discussion of an example of this in the research on Vioxx, see Biddle 2007.
 8. This figure comes from Merck's 2005 annual report, which can be accessed on Merck's website: http://www.merck.com/finance/annualreport/ar2005/pdf/merck_2005_financial_section.pdf.
 9. An anonymous reviewer points out that NIH Consensus Development Conferences are inspired by Kantrowitz's science court proposal and suggests that the problems with the NIH model should give rise to skepticism regarding proposals for an adversarial system. However, while there is a genetic relationship between the NIH model and Kantrowitz's proposal, NIH Consensus Development Conferences are so different from Kantrowitz's proposal that they cannot legitimately be called adversarial proceedings. See Biddle 2006 and Jacoby 1993 for details.
 10. The Senate investigation was conducted by the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education. For testi-

mony, see <http://olpa.od.nih.gov/hearings/108/session2/summaries/conflict.asp>. Regarding the reformed NIH conflict of interest guidelines, the most recent guidelines can be accessed at http://www.nih.gov/about/ethics_coi.htm (accessed 6 January 2013).

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