



Reform without Reason: What's Wrong with the FDA Revitalization Act

By John E. Calfee

Congress is about to pass the Food and Drug Administration Revitalization Act (FDARA), and it will become law before the end of this month. FDARA actually combines at least two laws. One renews the Prescription Drug User Fee Act (PDUFA), which sets deadlines for FDA action on new drug applications and assesses user fees to cover the salaries of extra FDA employees. PDUFA expires on September 30. Hardly anyone wants to see the massive FDA layoffs that would ensue if user fees cease to flow, so FDARA is must-pass legislation. The second part of FDARA—the part that gives this law its name—is Congress's response to the perceived drug safety crisis that burst forth in October 2004 after the arthritis pain reliever Vioxx was pulled from the market because of excess heart attacks (Calfee 2005). With the two parts intertwined, reform of FDA's drug safety oversight will also arrive by October 1. As far as this Health Policy Outlook is concerned, FDARA is an FDA reform law. It commands attention because it promises to bring the most important changes in FDA regulation in at least a decade and probably since the landmark 1962 amendments that created the modern FDA.

FDARA rests upon two foundations. One is the assumption that we are in the middle of a drug safety crisis. The other is that there is something seriously wrong at the FDA in the sense that the agency has become too friendly to the pharmaceutical industry and has downplayed drug safety in favor of approving new drugs.

The Institute of Medicine Report and Other Influences

Before explaining why these assumptions are mistaken, a few words about their origins will be useful. FDARA and FDA reform have been supported by the editorials, a wide array of members of Congress, a highly visible dissident FDA staffer (Kohn and Bor 2004), and, especially, high-profile medical journals, which have mounted an assault on the

FDA's competence and culture while suggesting numerous legislative and regulatory solutions (e.g., Topol 2004b; Furberg et al. 2006; Strom 2006; Avorn 2007; Hennessy and Strom 2007).

By all accounts, however, a central influence has been a September 2006 report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (NAS 2006; all citations are to the "uncorrected proofs" released at that time), published by the Institute of Medicine (IOM), which is part of the National Academy of Sciences. The IOM report was actually commissioned by the FDA itself, but it offered harsh criticism of the agency and recommended sweeping changes. Many FDARA provisions reflect IOM recommendations. Reform proponents, especially in academia, routinely cite the IOM report (e.g., Curfman, Morrissey, and Drazen 2006; *New York Times* 2006; Smith 2007).

Despite its influence and provenance, the IOM report was deeply flawed. One problem is

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that none of the authors were drug development specialists, which virtually guaranteed that the exigencies of new drug development would be slighted in comparison to drug safety. Worse, the report was remarkably unscholarly and provided only cursory scientific support for much of its analysis and recommendations. On direct-to-consumer advertising of prescription drugs, for example, the authors cited a few largely irrelevant older articles while ignoring a flood of recent econometric research (Berndt 2006; Calfee 2007) and a much-cited randomized trial that revealed large health benefits from antidepressant advertising (Kravitz et al. 2005). On another crucial topic—"off-label" prescribing for uses not explicitly approved by the FDA—the only citation (pp. 2–7) was to a *Washington Post* article (Boodman 2006) instead of the *Archives of Internal Medicine* article (Radley et al. 2006) that the *Post* article was about. On yet another central issue—whether FDA drug warnings are effective—the report (pp. 2–16) cited a trade press report (*Medical News Today* 2006) rather than the *Archives of Internal Medicine* study it was about (Lasser et al. 2006). That article actually found that medical harm from prescriptions that violated warnings was extremely rare (an estimated total of sixteen such events among the 324,548 patients in the study).

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Amazingly, the IOM report avoided the most important question: is there a drug safety crisis at all? The report stated at the outset, "The committee did not attempt to document whether or not a drug safety crisis exists, and this report should not be interpreted as commenting on that claim one way or the other" (p. 1-1). The authors argued, however, that various events—notably the withdrawal of Vioxx and a controversy over clinical trial results suggesting a suicide risk from the widely prescribed selective serotonin reuptake inhibitor (SSRI) class of antidepressants—had "contributed to a public perception that the drug safety system is in crisis" (p. 1-1). The rest of the report essentially assumed that this perception is true.

The Drug Safety Crisis That Wasn't There

The widespread perception of a drug safety crisis has been driven by elaborate anecdotes rather than systematic

evidence. Sifting through the rapidly accumulating literature on the episodes that animated the IOM and Congress, one is struck by two things. First, there is no evidence of a drug safety crisis or even a worsening of drug safety. And second, there is little in the most telling drug safety episodes for which the FDA could be held seriously at fault.

Vioxx, SSRIs, and More. The triggering event for FDARA was Merck's withdrawal of Vioxx on September 30, 2004, after an ongoing clinical trial revealed excess heart attacks among Vioxx users (Psaty and Furberg 2005). As the FDA presciently pointed out at the time, it was far from clear that Vioxx or its competing Cox-2 inhibitor, Celebrex, was significantly riskier than the much older non-steroidal anti-inflammatory drugs (NSAIDs) they replaced, given that these older drugs had never been subjected to rigorous clinical trials like the one that brought Vioxx down. Subsequent research has largely vindicated that view, with the entire class of NSAIDs (old and new, Cox-2s or not) now bearing heart attack warnings (Calfee 2005; Kearney et al. 2006).

The second-ranking triggering event was controversy over previously non-public clinical trial results in which children and adolescents taking one of the SSRI class of antidepressants (Prozac or Zoloft, for example) were more likely to exhibit suicidal "ideation" or thoughts (but not to attempt or commit suicide). Faced with relentless criticism from litigators, politicians, popular press editorialists, and elite medical journals, the FDA implemented its strongest warning (a "black box," which appears on the FDA-approved label) for all antidepressants, not just SSRIs (because again, there was little reason to think that older drugs, which can cause fatal overdoses, are safer). Subsequent research taking a variety of approaches has found that SSRI use is strongly associated with lower, not higher, suicide rates, and that the highly publicized warnings probably did more harm than good by reducing antidepressant use. In particular, a series of reports has found that there is a striking, inverse relationship between SSRI prescriptions and youth suicides in a variety of data sets and that the imposition of new FDA warnings (beginning with public health alerts) is strongly associated with reduced antidepressant prescribing for children (and younger adults) and higher suicide rates (Shogren 2004; McKeown, Cuffe, and Schulz 2006; Ludwig, Marcotte, and Norberg 2007; Brent 2007; Gibbons et al. 2007; Lubell et al. 2007; Bridge et al. 2007; Pfeffer 2007).

Other frequently cited examples of FDA failure also do not withstand scrutiny. An example is the pioneer antibiotic Ketek. The FDA was actually slow in approving this drug, mainly because of fraud in one of the pivotal clinical trials, and it finally approved Ketek partly on the basis of five years of experience in Europe (where it remains in use). This unorthodox process provoked much criticism, but any new class of reasonably safe and effective antibiotics is a valuable addition, and despite the controversy, there is little reason to think this particular drug is especially dangerous (Usdin 2006a, 2006b).

Avandia and the *New England Journal's* FDA Reform Agenda. Finally, there is Avandia, a popular diabetes drug first approved in 1999. On May 21, 2007, the *New England Journal of Medicine* published a meta-analysis of adverse cardiovascular events in clinical trials of Avandia (Nissen and Wolski 2007). Coauthored by a prominent critic (Nissen) of the FDA's handling of Vioxx, the meta-analysis revealed excess heart attacks and strokes among Avandia users. Accompanying the meta-analysis was an editorial by two well-known advocates of FDA reform (Psaty and Furberg 2007a), one of whom (Psaty) was among the IOM authors. They declared that the Avandia meta-analysis revealed FDA neglect and was reason enough to implement one of the more radical reforms, the creation of an independent drug safety board (something the IOM report declined to recommend).

Events since publication of the *New England Journal* meta-analysis have been instructive. Very soon, the public learned that the meta-analysis authors and the journal editors were politically motivated (Usdin 2007b, Gottlieb 2007c [May 29]), with Nissen having worked closely with Representative Henry Waxman's (D-Calif.) pro-reform staff. Dissent quickly emerged from the academic medical community regarding both policy and research methods. Endocrinologists (who research and treat diabetes) and the editors of *The Lancet*, a leading British journal often critical of the FDA, declared themselves deeply troubled by the precipitous May 21 *New England Journal* editorial and its reliance upon what was clearly very tentative evidence (*Lancet* 2007). FDA staff, researchers at Glaxo-Smith-Kline (GSK, the manufacturer of Avandia), and others pointed out that significant cardiovascular risk had not been revealed by large randomized trials, including the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which was designed to address cardiovascular safety (Krall 2007; Home et al. 2007). In July

2007, an editorial in the journal *Nature Clinical Practice* vigorously attacked the Avandia meta-analysis on methodological grounds and criticized the *New England Journal* for rushing it into print and causing confusion among patients (Fuster and Farkouh 2007).

Academic controversy over the *New England Journal* meta-analysis and its meaning has continued. Some of this appeared in the *New England Journal* itself, where communications focused on methodological weaknesses that strongly undermined the basic results of that analysis (see the letters by Bracken; Brett; Diamond and Kaul; and Mannucci et al. 2007). Nonetheless, the *New England Journal* published another editorial endorsing stronger FDA reform (Psaty and Furberg 2007b). On September 11, 2007, the *Journal of the American Medical Association* (JAMA) published two more meta-analyses. One found, again, excess heart attacks (but slightly fewer deaths) for Avandia users (Singh et al. 2007). The other revealed slightly reduced cardiovascular risk for Actos, Avandia's chief competitor (Lincoff et al. 2007). A JAMA editorial largely echoed the earlier *New England Journal* editorials (Solomon and Winkelmayr 2007).

Subsequent research taking a variety of approaches has found that SSRI use is strongly associated with lower, not higher, suicide rates, and that the highly publicized warnings probably did more harm than good by reducing antidepressant use.

In the middle of all this came a July 30, 2007, joint meeting of two FDA advisory committees. The members voted 23–1 that Avandia involves an elevated risk of (minor) heart attacks compared to placebos, but they offered no consistent view on cardiovascular risks compared to alternative drugs, including Actos (Hampton 2007; Usdin 2007d). The committee also voted 21–3 in favor of keeping Avandia on the market and in support of new label warnings, but not the FDA's strongest "black box" warning. In the meantime, the liability bar began its inevitable work on Avandia litigation (Usdin 2007c).

These results are very mixed. The imprecision and questionable reliability of meta-analyses have been made clear, as articles have demonstrated how modest changes in data and statistical methods (which involve

considerable judgment even on such basic matters as whether to include trials in which no adverse events occurred) can dramatically alter the results. Many, if not most, endocrinologists clearly want to maintain treatment options for a condition (diabetes) that is notoriously variable among patients and correspondingly difficult to treat. Avandia clinical trials continue, under FDA oversight as always. Obviously, experts can disagree over such matters as the nature and timing of cardiovascular warnings for Avandia, but that is very different from a finding that the FDA tended to downplay risks while approving Avandia and monitoring its risks afterward.

Are New Drugs Riskier than Old Ones? Running through the drug safety debate is a common assumption that new drugs tend to be riskier than old ones. The IOM report, for example, recommends that all newly approved drugs and indications carry a prominent black triangle, and that direct-to-consumer advertising be restricted for the first two years (NAS 2007, p. S-10). This attitude has little basis. Certainly it is true that much of the most important safety information about drug risks is revealed only after FDA approval, but this does not mean that new drugs are riskier. They are often designed (successfully) to avoid the side effects caused by older drugs. The first non-sedating antihistamines, for example, probably began to prevent fatal automobile accidents as soon as they came into use (Weiler et al. 2000). Also relevant is that many new drugs are studied more intensely than older ones both before and soon after approval. The effect is to reveal more risk information faster, which can make newer drugs appear less safe relative to older ones than they really are. In each of the three major drug safety episodes that captured the attention of Congress (Vioxx, SSRI antidepressants, and Avandia, discussed below), the safety crisis was triggered mainly by post-approval clinical trials, and additional research and analysis soon revealed either a lack of a safety problem (in the case of SSRIs) or risks for the entire classes to which these drugs belonged. Thus, slowing down the uptake of newer drugs would not necessarily improve safety, although it would sacrifice those drugs' benefits.

The FDA Problem That Was Not There

The FDA is an immensely powerful bureaucracy with islands of transparency (cf. advisory committee meeting

materials) amidst vast regions of opacity (cf. Calfee 2006). It is surely plagued by dysfunctions of all sorts, but reform advocates have fixed upon the utterly implausible argument that the FDA staff tends to slight drug safety while catering to the industry. Part of their argument is that the FDA's partial reliance on industry user fees undermines safety (Okie 2005). But user-fee deadlines only require faster decisions, not decisions that are favorable to the applicant. The IOM report reviewed the literature on user fees (pp. 3; 5–8) and found no evidence of a diminution in drug safety from faster new drug approvals since 1992 (the report later ignored that evidence, however). The IOM authors also could have cited an estimate that the advent of user fees saved at least several times as many lives through faster drug approvals as might have been lost through safety problems (Philipson et al. 2005).

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What is far more important—but was ignored by the IOM—is the biased incentive structure that causes the FDA staff to put too much weight on drug safety rather than too little. The avalanche of criticism thrown at the agency since 2004 is the latest illustration of the single most powerful and enduring force impinging upon the FDA staff: a profound disparity in how types of errors are penalized. When deciding whether the benefits of a proposed new drug exceed its risks, FDA staff know that if they commit what is often called a Type I error—the approval of a drug that turns out to be insufficiently safe once marketing begins—their error will usually become known (a “public error”). This can and often does lead to impassioned criticism of the agency and correction of the error (although more often than not, critics fix upon something that was probably not an error at all). On the other hand, a Type II error—the failure to permit marketing of a drug that would in fact provide benefits in excess of harms—is typically detected by relatively few people (a “private error”), and its deleterious effects can persist more or less indefinitely.

The net effect of this asymmetry in publicity over Type I and Type II errors is to bias even the best-intentioned FDA regulators toward excessive caution and excessive drug testing. Research on the “drug lag” of

the 1960s and 1970s, when FDA approvals trailed far behind those in European nations, revealed no consumer benefit in terms of safer drugs (Peltzman 1973, 1974; Wardell and Lasagna 1975). Subsequent research revealed that similar patterns persisted long after (Katin and Brown 1995). Yet slow drug approvals here did not bring extra safety. An analysis of the United States, Spain, and the United Kingdom yielded essentially identical drug-withdrawal rates despite the more rapid drug-approval timelines in the European countries (Bakke et al. 1995).

There are many reasons to think that the drug safety provisions of FDARA will work badly from the standpoint of drug development, new drug approvals, and ultimately, the welfare of patients.

There is considerable anecdotal evidence that the FDA quickly became even more cautious in approving new drugs and indications after the Vioxx uproar began in October 2004 (Harris 2005). Earlier this year, for example, the FDA refused to approve the pain reliever Arcoxia and the weight-loss drug Accomplia even though both had been approved by the European Union and many other nations (Gottlieb 2007b [April 17]; Wadman 2007). The FDA has also been unreceptive to some promising new drugs for advanced cancer, including Provenge, Genasense, and others (Usdin 2007a; Miller and Henderson 2007; Miller 2007).

Neither Congress nor the IOM report has paid much attention to another potent force: market-driven manufacturer incentives to maintain drug safety. Such incentives operate with powerful effect in far less regulated high-tech industries such as automobiles, petroleum, and electronics. As in other industries, pharmaceutical manufacturers rely heavily upon maintaining their reputation among customers (especially physicians) for product safety and efficacy. Post-approval clinical trials play a central role in this process. These trials are undertaken to expand markets, but they necessarily open the door to new and possibly alarming (as well as reassuring) safety information. Often, post-approval trials are bigger, longer, and more informative than the trials undergirding drug approvals. Often, they force revisions in

accepted views of such basic matters as, for example, the benefits of lowering serum cholesterol or the safety of all NSAID pain relievers (Topol 2004a; Wadman 2007).

FDARA is best seen as fixing upon a target of opportunity. The relative ease with which post-approval drug safety problems become widely known (“public errors”) guarantees a steady drumbeat of criticism and proposals for reform (for example, Friedman et al. 1999; Wood, Stein, and Woosley 1998; Kleinke and Gottlieb 1998; Moore, Psaty, and Furberg 1998). Although there is little, if any, systematic evidence of real declines in FDA scrutiny or effectiveness in dealing with drug safety, individual episodes can create pressure for change, as occurred after the Vioxx withdrawal and the SSRI antidepressant safety debate. In this context, the prospect of user-fee renewal in 2007 provided a potent vehicle for FDA reform. It is no surprise that in its final paragraph, the IOM report proclaimed: “Now is the time to renew and transform Center for Drug Evaluation and Research’s culture, its authorities, its scientific capacity, and its ability to communicate with health care providers and the public.” Chiming in were the *New England Journal of Medicine* (Hennesy and Strom 2007) and the American Medical Association’s *Archives of Internal Medicine* (Furberg et al. 2006).

The Perils of Passing Unnecessary FDA Reform

Trying to fix something that is not broken provides a reliable path to unintended consequences. There are many reasons to think that the drug safety provisions of FDARA will work badly from the standpoint of drug development, new drug approvals, and ultimately, the welfare of patients.

Unnecessary Additions to FDA Power. FDARA will increase FDA authority in a number of ways. This is unfortunate because the FDA can easily persuade pharmaceutical firms to do virtually anything it asks, up to and including the imposition of severe warnings, controls over prescribing, cessation of advertising campaigns, and the removal of drugs. The FDA will be expected to use the new powers granted by FDARA. The staff will be under considerable pressure to take stronger measures even when those measures would be inappropriate in the complex and obscure circumstances that surround virtually all important regulatory decisions. An example is the power to require manufacturers to complete so-called

phase 4 trials for newly approved drugs. The IOM report (pp. 4-8-4-9) explained very clearly why last-minute negotiations in the drug-approval process often cause the FDA and manufacturers to agree to post-approval trials that turn out to be unnecessary or even harmful. FDARA will worsen the dilemma already faced by FDA when they are criticized for failing to do things that should not have been committed to in the first place.

Inappropriate Responsibilities for Post-Approval Drug Use and Safety. FDARA will be a powerful force in making the FDA responsible for post-approval drug use and safety. Today's question—"Why didn't the FDA catch the problem with that drug?"—will be replaced by a very different one: "Why did the FDA let doctors do that with that drug?" This will trigger a series of unfortunate actions. Faced with the possibility of being blamed when physicians and others fail to use drugs as it had intended, the FDA will have to be far more intrusive in its regulation of medical practice, but the FDA possesses few tools and even less knowledge or other preparation for regulating how doctors go about their work. Forced again to choose among unattractive alternatives, the agency will employ crude measures such as onerous tracking requirements and restrictions on who may treat certain patients.

All this is a logical result of what the IOM report and many other FDA reform advocates have propounded as the necessity of a "life-cycle" approach to drug safety monitoring and regulation. This principle offers virtually no guidance beyond the general principle of a steady expansion of FDA authority and responsibility. We have to assume that if the FDA is to be held responsible for whether especially risky drugs are used properly (as suggested, for example, by the IOM report's recommendation 5.1 and 5.2), it must be able to exercise commensurate power over physicians and other health care providers.

The impetus for regulating medical practice will also arise from a more general aspect of FDARA. It will reinforce and strengthen the bias toward preventing Type I errors (a safety problem with an approved drug) at the cost of Type II errors (such as moving too slowly to facilitate new drug development and approval). For example, a crucial issue in adapting regulation to scientific advances is revising and expanding the use of surrogate markers (such as LDL cholesterol levels rather than heart attacks for cardiovascular drugs, or glycemic levels for diabetes drugs). Many FDA critics see reform as a tool for reining in or nearly eliminating surrogate markers (Psaty and Furlong 2007a), which could drastically retard new

drug development (as pointed out by Brett 2007). Critics who support FDARA or stronger measures also want the FDA to avoid approving drugs that are only on a par with (rather than superior to) existing drugs (Avorn 2005). They applauded when the FDA refused to approve Prexige, a Cox-2 pain reliever for arthritis, on exactly those grounds.

Making Clinical Trial Data Public. FDARA will expand upon a recent trend toward revealing unpublished clinical trial results to which the FDA staff is already privy. This public registry of undigested clinical trial data will probably reinforce the tendency for FDA staff to give disproportionate weight to risks vs. benefits of drugs. It will also tempt medical journals and researchers to cherry-pick the data to support political agendas, at the cost of alarming the public and scaring patients away from ongoing clinical trials. Finally, it can undermine R&D incentives by alerting competitors to R&D and marketing strategies (Lassman 2006). This provision may turn out to be far more important and troublesome than one would infer from its noncontroversial status in the FDARA debate.

FDA Reform is a One-Way Street. Finally, we should give considerable weight to the fact that this FDA reform will probably be a one-way street. FDARA will increase FDA power, extend its reach beyond normal bounds, and expose FDA personnel to yet more scrutiny and criticism for safety problems no matter how unpredictable. There will be no tests or benchmarks for how well this new regime will work. In a world of ever more extensive post-approval clinical trials and database dredging, there is no reason to think drug safety data will become more reassuring or less alarming as time passes. The FDA will find it very difficult to retreat from any sort of regulatory expansion.

Perhaps the only hope is that the FDA, whose resources include some leaders of exceptional ability, will take due account of its inability to regulate usefully medical practice and of the ease with which the agency can slow down the most innovative kind of R&D. If the FDA leadership proceeds with an exceptional measure of wisdom and restraint, they may be able to prevent FDARA from doing great harm. We shall see.

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