

Innovative Drug Development
in the Context of FDA Regulation

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1. The Continuing Crisis in the Pharmaceutical Industry

The pharmaceutical industry is widely viewed as being in a state of crisis. Among its problems a long wave of patent expirations for blockbuster drugs (Berndt, et al. 2005), attacks on pricing, increasingly stringent price controls in foreign nations, and vigorous criticism of marketing including direct-to-consumer advertising. But arguably the most serious indictments are, first, that the industry is failing to maintain a steady supply of innovative new drugs, and second, that it pays too little attention to the safety of its products.¹

The Food and Drug Administration, the agency that regulates pharmaceutical firms, is also under attack, probably more so than at any time since the 1962 amendments to the Food, Drug and Cosmetic Act recreated the FDA by mandating it to require proof of efficacy as well as safety when approving new drugs (Peltzman 1973, 1975; Wardell and Lasagna 1975). Some critics charge the FDA with approving too many new drugs of marginal value, diverting resources from more innovative drugs and being too lax in regulating pharmaceutical marketing (Angell 2004, Avorn 2004, Kassirer 2004). The chief criticism by far, however, is that the FDA favors the pharmaceutical industry by placing too little weight on safety both when approving new drugs and in monitoring them afterward. Most of this criticism followed upon Merck's voluntary withdrawal of the pain reliever Vioxx on September 30, 2004 (Lancet 2004; Topol 2004b).

Such controversies are inevitable. Pharmaceuticals are remarkable for the rapidity with which they can bring large and obvious benefits and the persistence with which even old products can continue to provide benefits vastly exceeding their costs. Pricing far above marginal costs is necessary (so that risky investments can yield profits on average) but is also a natural political target. Vigorous marketing is essential (because of massive information deficits surrounding new drugs and new information about older drugs) and inevitable (because low

¹ Book-length critical accounts of the pharmaceutical industry include Angell 2004; Avorn 2004; Gozner 2004; and Kassirer 2005. My reviews of the books by Angell, Gozner, and Kassirer, are Calfee 2004, 2005a, 2005b. On international price controls and their effects, see Danzon and Furukawa 2003; International Trade Administration 2004; and Calfee, DuPre, and Villarreal 2006.

marginal costs can assure payoffs even from very expensive marketing), but marketing also raises the industry's profile and literally advertises its prosperity. In fact, few if any of today's attacks on the pharmaceutical industry are really new. Most issues in today's fevered debates can be found, for example, in the impassioned attacks on the industry in the late 1960s (USDHEW 1968; *Journal of Research in Pharmaceutical Economics* 2001).

The growing importance of pharmaceuticals in health care is also bound to increase scrutiny of the FDA. That is partly because neither costs nor benefits of new drugs are easily measured. When something important is discovered after years of use, there is a natural sense of having learned too late, with a consequent tendency to blame regulators for being too slow and manufacturers for not caring enough.

The industry's problems and the FDA's problems are intimately connected. When the FDA decides that a drug is sufficiently safe and effective for marketing, it explicitly balances risks and benefits. Obviously, the pace with which new drugs are developed depends greatly on the stringency of the FDA's approval standards. But in fact, the connections run much deeper, involving the basic nuts and bolts of the FDA's extensive regulatory apparatus.

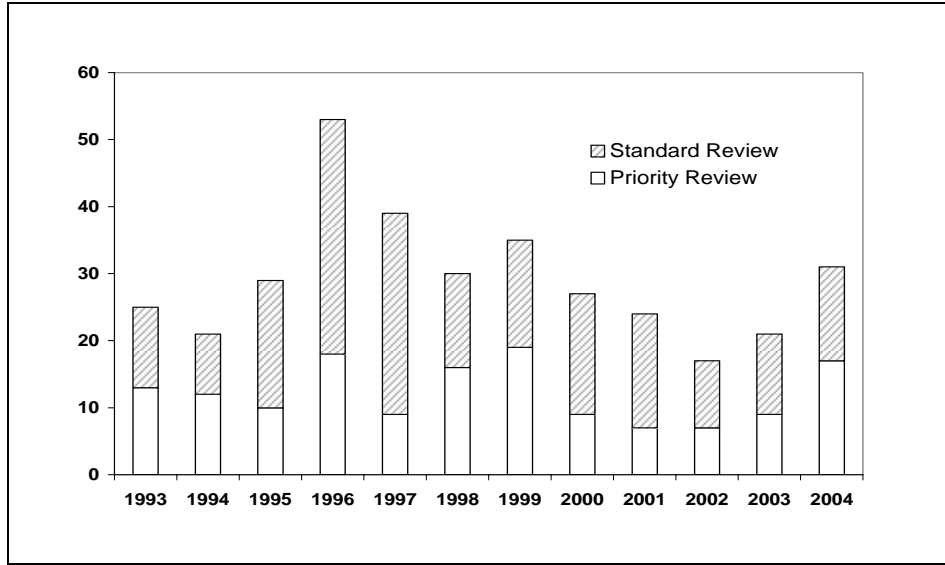
The Pipeline Problem

The usual starting point in measuring the pharma industry's progress is the annual count of FDA approvals of truly new drugs, i.e., new chemical entities (NCEs).² Figure 1 presents annual data since 1993 on new drug approvals (excluding biotech products and biologicals such as vaccines, except for some of the 2004 data). It can be seen that the pace of approvals declined more or less steadily between 1996 and 2003, when levels were a little below those of 1993-1994. The spike in 1996 was probably partly a result of the FDA's gearing up to meet the

² The term "new chemical entity" is increasingly a misnomer because of the increasing importance of biotech drugs, most of which are "biologicals," i.e., substances that are essentially grown or created as the byproduct of a biological process rather being chemicals that can be synthesized in the absence of any biological events. The FDA has traditionally regulated biologicals and traditional "small-molecule" drugs in different centers, each with their own counts of drug approvals and so on. This separation is being rapidly attenuated by organizational changes (www.fda.gov/cder/biologics/default.htm). The numbers cited below are for traditional drugs, but the issues I discuss pertain to all pharmaceuticals including biotech products and vaccines, and to diagnostic tests.

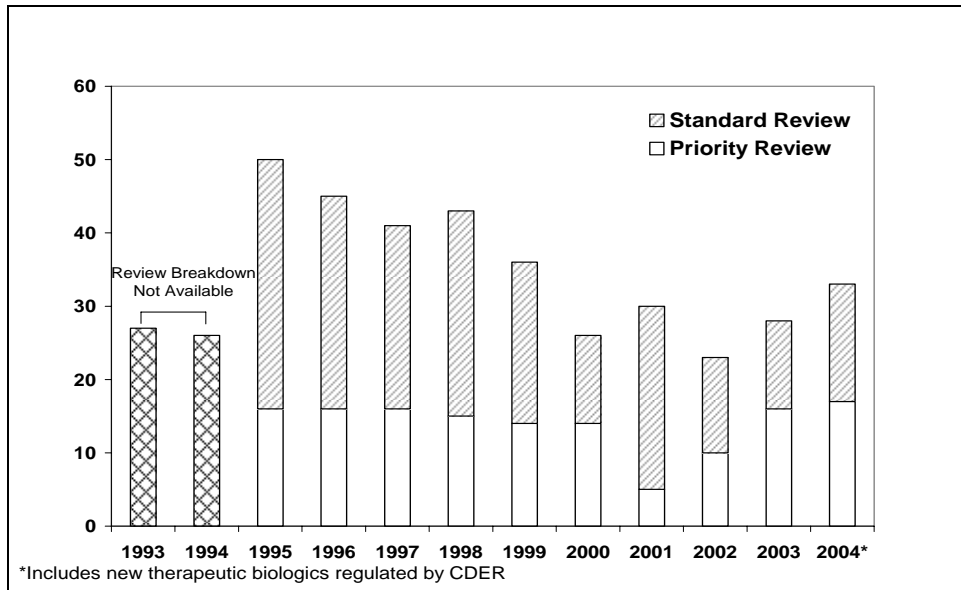
requirements of the Prescription Drug User Fee Act of 1992, which granted the agency large sums from new drug applications while requiring the FDA to meet deadlines for completing its review of those applications. Although the law has not reduced the probability that a new drug application will be approved (Lutter 2005), it has reduced review times and thus modestly accelerated new drug approvals, especially in the mid-1990s (Berndt, et al. 2004). A slightly different picture emerges from data on new drug applications instead of actual approvals, as in Figure 2. Application rates in recent years have been roughly the same as in 1993-1994, again after a substantial peak that began in 1995 instead of 1996.

Figure 1: FDA-approved New Molecular Entities, 1993-2004



Source: www.fda.gov/cder/rdmt/default.htm 2004 data include some biotechnology drugs, pursuant to FDA reorganization (see text).

Figure 2: NME Applications, 1993-2004



Sources: 1993 and 1994 from FDA 2003; other years from FDA 2004a. All data for calendar year.

Too much attention has been paid to the slowdown in new drug applications and approvals in recent years. For one thing, those numbers exclude approvals of supplemental new drug applications (SNDAs, i.e., applications for new uses of old drugs). They also fail to capture the results of new research on old drugs that does not necessarily lead to SNDAs but can generate valuable off-label uses (i.e., uses not approved by the FDA). This is an important omission. The remarkable biotech cancer drugs Gleevec and Avastin, for example, are already being used to treat cancers other than the ones for which they were originally approved. Post-approval research is especially important when a successful pioneer drug entices entry of a series of follow-on drugs with similar biological mechanisms, generating a stream of new research finding on entire drug classes. The now classic example is the statin class cholesterol-reducing drugs. Most of what we know about the effects of cholesterol on heart disease mortality is a result of follow-on drug research on newer statins undertaken for competitive reasons (Langreth 1998; Topol 2004a); and the same is true about statins and stroke prevention. The benefits of this research stream vastly exceed anything one might suspect from the small increment in the number of new drug approvals.

Nonetheless, one must wonder why drug development has not proceeded far more rapidly in the wake of dramatic breakthroughs in applied molecular biology in the past two decades or so. We cannot blame inadequate resources. Moses, et al. (2005) report that between 1994 and 2003, annual biomedical research funding in the United States doubled in real terms, reaching \$94.3 billion. Private industry (pharmaceutical and biotechnology firms) accounted for about 57% of that, and NIH, 28%. Industry funding of clinical trials more than tripled in real terms to \$14.2 billion in 2003. At the same time, however, the costs of bringing new drugs to market have been steadily increasing at rates well above inflation even as technological progress has reduced all manner of peripheral costs (DiMasi, Hansen, and Grabowski 2003).

The central issues today lie not in financial resources but in the difficulty of exploiting DNA-based and other biotechnology-generated applications of new science. The new methods encompass essentially the entire range of activities in drug development, starting with novel biological mechanisms (such as therapeutic vaccines that harness the immune system to treat illnesses such as cancer instead of preventing them), and continuing through toxicity testing (animals and humans), diagnostics, the design and interpretation of clinical trials, dosing,

administration, and safety monitoring before and after FDA approval (Usdin 2005; FDA 2004b). Translating these methods into approvable treatments and diagnostics has proven time-consuming and financially risky even as new technology has begun to generate extraordinary therapeutic advances.

It is only natural that such rapid advances in basic and applied science should pose challenges for the FDA. This is contrast to incremental drug development, which usually does not raise some of the most difficult issues in applied science, such as exploratory clinical trial endpoints, highly novel biological mechanisms, new manufacturing methods, and very different diagnostic tools.

2. How FDA Regulation Works

The FDA is probably unique in the expanse, depth, and obscurity of its regulation, at least among agencies that regulate large industries. These features greatly complicate any attempt to assess how good a job the agency is doing and what needs to be done to improve outcomes in an industry that is crucial to progress in health care.

Like all regulation, the bulk of FDA activities occur behind the scenes with only regulators and regulated firms aware of the essential details. Many of these details are dispersed among many competing firms which have no incentive to share them with the competitors. But in comparison to what happens in other industries, FDA regulation is remarkably opaque. One reason is technical complexity. The point is not just that drug development itself is so complex (which it certainly is), but that FDA regulation reaches into nearly the full range and depth of this complexity. Few if any other industries are subject to regulation of such detail and intrusiveness.

The second reason for the “black box” nature of FDA regulation is that firms do not feel free to publicly criticize FDA policies and especially, FDA decisions (and often avoid criticism even when speaking privately to FDA staff). Pharmaceutical firms’ perceptions of the absolute necessity of maintaining good relations with FDA staff is universally accepted (Hutt 1993). This is compounded by the fact that FDA regulation extends organically through the entire business enterprise all the way through advertising and marketing. The unparalleled comprehensiveness of FDA regulation explains why it can exert without challenge comprehensive controls over

marketing which are unknown in the rest of health care markets, including physicians, hospitals and clinics, and medical devices, all of which are subject to the advertising rules of the Federal Trade Commission rather than the FDA.³

Of course, such circumstances make it difficult for outsiders to appreciate the vastness and especially the complexity of FDA regulation (Hutt 1993). The gulf between what product users see and what goes on behind the regulatory scenes is far greater than with, say, automobile regulation, where the National Highway Traffic Safety Administration (NHTSA) regulates relatively few details of the product, and little if anything in product development, manufacturing, and marketing. In the pharmaceutical market, what we see is mainly the product itself, a very simple thing compared to the rich and diverse streams of densely regulated processes that engendered it. Even the professional and academic medical communities, although constantly aware of the externals of FDA regulation, see mainly the clinical trial results and the FDA staff's assessment of those results when a manufacturer submits an NDA or SNDA. The most important regulatory work remains hidden from view. This is true both of drug development and safety monitoring.

3. Is the FDA Biased, and If So, How?

The opaqueness of FDA regulation raises an obvious question: Is the agency fundamentally biased in its core tasks of approving new drugs and regulating safety? The danger, which medical academics and others have vigorously claimed to be very real indeed, is that by getting too close to industry, partly because of PDUFA fees, the FDA staff has become biased

³ See the discussion in Calfee 2002b. Fisherow (1987, p 231-232), writing as part of the FDA's drug advertising group, pointed to the comprehensive nature of FDA regulation to explain why the FDA, unlike the Federal Trade Commission, had been immune to industry challenges to its advertising rules: "This pervasive involvement in the industry's current and future business means that a corporate decision-maker needs to consider more than just the merits of the company's position in the particular advertising dispute at hand. The executive must also weigh how much disagreement with the FDA staff in a current matter might affect future treatment. No such continuing relationship exists between the FTC and any industry." This situation has not changed.

toward too little safety and too much freedom for firms to introduce new drugs and keep them on the market in the face of safety problems (e.g., Lancet 2004; Topol 2004b).

There are compelling reasons to believe that no such situation has occurred. One reason is that the FDA staff can easily resist industry attempts to accelerate drug development inappropriately or to downplay safety. The staff knows that if and when things come to a standoff, industry will quickly accede to FDA demands to revise or discontinue advertising practices, issue warnings to physicians, alter or delay clinical trials, even remove drugs from the market, and will do so regardless of whether the firm itself believes the measures are necessary. Pfizer's withdrawal of its Cox-2 pain reliever Bextra in April 2005 is an apposite example. Pharmaceutical firms clearly believe they cannot win a public debate with the FDA, so they cave in when the only alternative is a public battle.

The same forces apply to manufacturing, where firms are subject to the FDA's onerous "good manufacturing practices" or GMPs (recently denoted "current GMPs" or cGMPs). Firms routinely accede to requirements that have become obsolete in other high-tech industries such as petroleum, chemicals, and computers, and stick with those requirements for years despite technological progress because of the costs of obtaining FDA approval for changes.⁴ When FDA charges firms with violations of cGMPs, firms clearly feel they have no choice but to comply and they sometimes agree to very large penalties, even including an indefinite moratorium on new product approvals in broad categories. This typically happens despite the fact that the FDA itself believes that patient safety has not been compromised by the measures under scrutiny and thus issues no product recalls or even warnings to physicians to avoid use of the products whose manufacturing methods are under attack (*Wall Street Journal*, January 17, 2002, April 29, and May 16, 2002).

Economists have long argued that this one-sided situation induces a fundamental bias toward excessive drug safety. FDA staff knows that if it errs on the side of approving a drug that

⁴ Many of these points were emphasized in an Oct. 21, 2002 meeting of the Advisory Committee for Pharmaceutical Science. For example, a member of that committee noted: "In the past I think we have seen real reticence to improve products at all and you see some wonderful examples in the industry of products that are being made today the way they were made in 1932 because no one wants to come forward and improve the product for fear of what that means in terms of the marketplace and the regulation of the product." [Arthur Kibbe, speaking at the Oct. 21, 2002 meeting of the Advisory Committee for Pharmaceutical Science, transcript, p. 63.]

turns out badly, the effects will be obvious to all, whereas the effects of the opposite error of retarding new approvals will be seen only by a few insiders at the agency and among a few pharmaceutical firms and their friends (Peltzman 1973, 1975). In fact, drug safety “crises” are a fixture in the modern history of the FDA, an example being events of the late 1990s (cf. Friedman, et al. 1999). Crises over slow drug approvals, on the other hand, are rare.

Recent events have reinforced these pressures. The Vioxx episode makes clear that the incentives for FDA staff to maintain drug safety standards at reasonable or higher-than-reasonable levels remains largely undisturbed. The fusillade of criticism directed at the agency over Vioxx and Cox-2 inhibitors—especially criticism from its most reliable base of support, the academic medical community and the most prestigious medical journals—vastly exceeds any criticism it has received in recent years for being too slow to approve new drugs or too quick to remove them (Calfee 2005c). The Vioxx episode has made it more difficult for the FDA to do its job without tilting toward excessive caution in drug regulation.⁵

4. Toward More Efficient Drug Development

Although the thinking just outlined usually focuses on FDA drug approval standards, it carries over to the FDA's regulation of the entire panoply of drug development and manufacturing. Indeed, the bias against technological advance is probably deeper in drug development than in approval standards. From the staff's perspective, the potential downside from a public error (the release of a drug in which somewhat adventuresome development methods were involved) greatly exceeds the downside from a private error (in the form of largely unseen and unappreciated delays in drug development). It is only when the delays imposed by old technology are publicly scrutinized—as has happened in connection with the chicken-egg manufacturing method for the annual flu vaccines—that the costs of delay in technological progress become obvious to anyone beyond a few insiders. For the most part, errors in the form

⁵ This kind of thing has happened before, albeit less spectacularly. In 2001, the Los Angeles Times won a Pulitzer Prize for a series of stories criticizing the FDA for approving several drugs (most notably the diabetes drug Rezulin) and then failing to pull them from the market in the face of safety problems. See *Los Angeles Times*, April 17, 2001. Rezulin was in fact pulled after safer alternatives became established.

of unnecessary R&D delay are essentially hidden indefinitely. The problems range from toxicity testing to clinical endpoints, the interpretation of trials results, and the role of diagnostics (Usdin 2005). As with manufacturing, firms have acceded to largely obsolete methods in, for example, toxicity testing.

Of course, the same logic applies to manufacturing regulation, the importance of which is largely unappreciated by the general public. Pharmaceutical manufacturing has become increasingly obsolete even as the advent of biotechnology cries out for radical changes (something the FDA has begun to recognize in public; *New York Times*, August 22, 2002).

Thus the crisis in drug development is rooted in FDA regulation as much as in applied science itself. The FDA's Critical Path initiative (FDA 2004b) is to some extent a recognition of this fact, albeit with scant attention to the problems endemic to FDA itself. Whether this initiative and other forces can overcome innate regulatory barriers to technological progress remains to be seen.

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