



Playing Catch-up: The FDA, Science, and Drug Regulation

John E. Calfee

The Food and Drug Administration (FDA) is under attack for paying too little attention to drug safety, while the pharmaceutical industry is being criticized both for unsafe drugs and too little innovation. Fortunately, incentives for maintaining safety are very strong. But obsolete regulation stands in the way of efficient utilization of recent advances in technology and basic science. With the fates of the FDA and the industry more intertwined than ever, our health depends on regulatory innovation as much as on scientific progress.

The pharmaceutical industry is widely viewed as being in a state of crisis. Among its problems are a long wave of patent expirations for blockbuster drugs (Berndt et al. 2004), 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 (e.g., Angell 2004; Avorn 2004; Goozner 2004; and Kassirer 2004).

The Food and Drug Administration (FDA), 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 agency by mandating it to require proof of efficacy as well as safety for new drugs. 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). By far the chief criticism,

however, is that the FDA favors the pharmaceutical industry by placing too little emphasis on safety both in approving new drugs and in monitoring them afterward. A torrent of such criticism followed upon Merck's voluntary withdrawal of the pain reliever Vioxx on September 30, 2004 (Calfee 2005).

Such controversies are inevitable. Pharmaceuticals are remarkable for the rapidity with which they provide significant and obvious benefits to patients. Prices must be far above marginal costs so that risky research and development investments—which fail more often than they succeed—can yield profits on average. But the gap between prices and marginal costs 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 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 were present, for example, in the impassioned attacks on the industry in the late 1960s (USDHEW 1968; Rucker 2001).

John E. Calfee (jcalfee@aei.org) is a resident scholar at AEI.

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

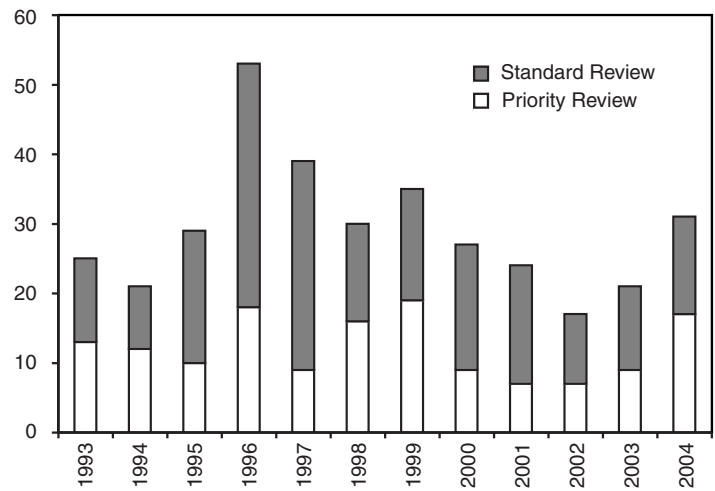
The industry's problems and the FDA's problems are intimately connected. When the FDA decides that a drug is sufficiently safe and effective for marketing, it explicitly balances risks and benefits. Obviously, the pace at which new drugs are developed depends greatly on the stringency of the FDA's approval 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 pharmaceutical industry's progress is the annual count of FDA approvals of truly new drugs (i.e., new chemical or new molecular entities [NCEs or NMEs]).¹ Figure 1 presents annual data since 1993 on new drug approvals (excluding biotech products and biologicals such as vaccines). The pace of approvals declined rather 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 requirements of the Prescription Drug User Fee Act of 1992, which granted the agency large sums from new drug applications while also requiring it to meet deadlines for completing its review of those applications. Although the law has not increased 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).

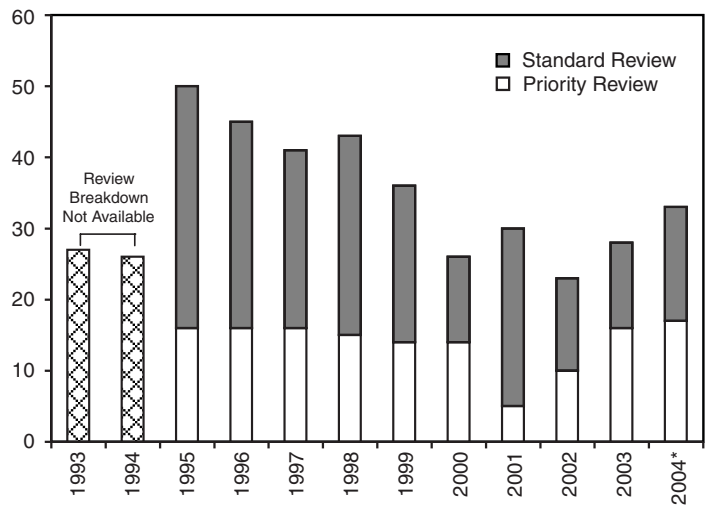
A slightly different picture emerges from data on new drug applications instead of actual approvals, as shown in figure 2. Application rates in recent years have been

FIGURE 1
NUMBER OF FDA-APPROVED NEW MOLECULAR ENTITIES, 1993–2004



SOURCE: Food and Drug Administration (2005).
NOTE: Biologicals excluded from all data.

FIGURE 2
NUMBER OF NEW MOLECULAR ENTITY APPLICATIONS, 1993–2004



*Includes new therapeutic biologics regulated by the Center for Drug Evaluation and Research (CDER).
SOURCES: For 1993 and 1994, FDA 2003; other years, FDA 2004a.

roughly the same as in 1993–1994, again after a substantial peak that began in 1995 instead of 1996.

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 do 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 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. Rituxan was originally approved for non-Hodgkin's lymphoma but was recently approved for rheumatoid arthritis. Enbrel, approved for rheumatoid arthritis, is also used to treat psoriasis. Remicade, first used to treat Crohn's disease, now treats arthritis and colitis, while the HIV drug Viread may be effective against hepatitis B (Calfee, DuPré, and Villarreal 2006).

Post-approval research is especially important when a successful pioneer drug leads to the development of follow-on drugs (sometimes called "me-too" drugs) with similar biological mechanisms, generating a stream of new research findings on entire drug classes. The now-classic example is the statin class of 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 undertaken for competitive reasons on newer statins (Calfee, DuPré, and Villarreal 2006), 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. Similar class-level research has also greatly expanded the science and applications of the selective serotonin reuptake inhibitor class of antidepressants, which proved to be more than just antidepressants (Holden 2003), angiotensin-converting enzyme inhibitors (first approved for hypertension but also useful for congestive heart failure), and other drug classes including the anti-ulcer H₂-blockers and proton pump inhibitors (Usdin 2006, A4). The advent of biotechnology drugs, with their precision targeting of very specific biological processes, is accelerating the phenomenon of follow-on research. Now that Avastin has established proof of principle for antiangiogenesis (i.e., it demonstrated that cutting off the blood supply to dangerous cells can impede cancer progression), the pipeline is full of new angiogenesis inhibitors, each of which will contribute to scientific understanding of this important topic (Flanagan 2006).

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. Hamilton 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 percent of that and the National Institutes of Health 28 percent, with the remainder coming from foundations, other government entities, and nonprofit sources. 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 diseases like 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. Thus Scott Gottlieb, deputy FDA commissioner for medical and scientific affairs and a former senior fellow at AEI, recently observed, "The plain truth is that a lot of the new technologies we've developed over the last five years—proteomics, genomics, and microarrays—have only added to the cost of discovery and development without making the process any faster or more certain" (Gottlieb 2006a).

It is only natural that such rapid advances in basic and applied science should pose challenges for the FDA. This is in contrast to incremental technological progress in 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.

How FDA Regulation Works

The FDA is 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 competing firms that have no incentive to share them with each other. But in comparison to what happens in other industries, FDA regulation is remarkably opaque. One reason why is technical complexity. The point is not just that drug development itself is so complex, 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. The absolute necessity of maintaining good relations with FDA staff is universally accepted by pharmaceutical firms. This is compounded by the fact that FDA regulation extends organically through the entire business enterprise, starting with animal toxicology testing of potential new drugs all the way through advertising and marketing of approved drugs. The unparalleled comprehensiveness of FDA regulation explains why it can exert without challenge extensive controls over marketing which are unknown elsewhere in the health-care sector. Physicians, hospitals and clinics, and medical devices are subject to the far less onerous advertising rules of the Federal Trade Commission (Calfee 2002).

Of course, such circumstances make it difficult for outsiders to appreciate the vastness and especially the complexity of FDA regulation. The gulf between what product users see and what goes on behind the regulatory scenes is far greater than with, say, automobile regulation, in which the National Highway Traffic Safety Administration 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 external aspects of FDA regulation—see mainly the clinical trial results and the FDA staff’s assessment of those results when a manufacturer asks the FDA to approve a new drug or a new use for an old drug. The most important regulatory work remains hidden from view. This is true both of drug development and safety monitoring.

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? One danger which medical academics and others have

warned about with great vigor is that the FDA has gotten too close to industry. User fees account for approximately half of the drug review portion of the FDA budget, suggesting to some that the FDA staff has become biased 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 2004; Henderson and Rowland 2005).

There are compelling reasons to believe that the pro-industry, anti-safety biases that some critics fear simply do not exist. 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, and 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, in which 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. They stick with those requirements for years despite

Like all regulation,
the bulk of FDA
activities occur
behind the scenes
with only regulators
and regulated firms
aware of the
essential details.

technological progress because of the costs of obtaining FDA approval for changes.² When the 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 (Burton 2002; Burton, Anand, and Harris 2002).

Economists have long argued that this one-sided situation creates a fundamental bias toward excessive drug safety. FDA staff knows that if it errs on the side of approving a drug that 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, 1974). In fact, highly public 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 remain largely undisturbed. Events have made clear that the FDA did not slight safety when it approved Vioxx, the second entrant in what promised to be an extremely valuable subclass of the ubiquitous non-steroidal anti-inflammatory drug (NSAID) class of anti-inflammatory pain relievers. Indeed, FDA staff avoided joining high-profile academic critics who urged physicians to switch patients to older NSAIDs, which FDA staff and an advisory panel have since concluded probably pose comparable risk of the same cardiovascular side effects that prompted Merck to withdraw Vioxx from the market. Nonetheless, the fusillade of criticism directed at the agency over Vioxx and Cox-2 inhibitors—especially criticism from its most reliable bases 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 2005). The Vioxx episode has made it even more difficult for the FDA to do its job without tilting toward excessive caution in drug regulation.³

Removing Barriers to Efficient Drug Development

Institutional rigidity and conservatism carries over to the FDA’s regulation of the entire panoply of drug development and manufacturing. Indeed, the regulatory bias against technological advance is probably deeper in the development stage than when a drug comes up for approval. 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 of unnecessary research and development delay are essentially hidden indefinitely. The problems include toxicity testing, clinical endpoints, the interpretation of clinical trial results, and the role of diagnostics. At every stage, firms have acceded to arguably obsolete methods, with toxicity testing as an obvious example (Usdin 2005).

FDA-induced technological obsolescence in manufacturing is especially important for so-called biologicals, which are essentially grown rather than synthesized the way traditional drugs are. This includes most biotech drugs. Because the FDA requires drug developers to construct and validate large-scale manufacturing facilities before starting lengthy clinical trials for drug approval, biotech manufacturing facilities tend to be technologically frozen for long periods of time. The FDA has recognized that the advent of biotechnology cries out for radical changes in its regulations (Associated Press 2002). As it is, manufacturing regulation is another factor impeding more efficient drug development.

Thus the crisis in drug development is rooted in FDA regulation as much as in applied science itself. Indeed, we cannot even answer the question of whether lighter and more enlightened regulation in recent years would have forestalled the apparent slowdown in new drug approvals.

The FDA’s Critical Path Initiative, announced in March 2004, is to some extent a recognition of these circumstances, albeit with scant attention to the problems endemic to the FDA itself.⁴ At any rate, Critical Path merits close attention. There is not sufficient space here

to describe this plan in any detail, but some features are striking. At the center is an invitation for extensive industry-FDA collaboration. In particular, the FDA invites the private sector to play a strong role in matters that have traditionally been the bread and butter of the agency itself. These include such crucial topics as the creation and validation of new toxicity tests (both animal and human), modeling methods to predict safety levels in clinical trials, new markers for human trials (e.g., PET scan changes for cancer), new safety indicators during and after clinical trials, and perhaps most remarkable, a revamping of the traditional phase 1-2-3 sequence for clinical trials (Usdin 2005, 2006).

Here, by chance or intent, the FDA has hit upon a problem in manufacturer incentives: if a firm conceives of a better diagnostic or clinical marker, it must convince the FDA staff to take on the risk that the new approach may later prove inferior or even dangerous. That is not easy to do, as recently emphasized by Deputy Commissioner Gottlieb (Gottlieb 2006a): “It will be the bravest of companies that are willing to innovate the way they actually test a drug and bring a new approach to the agency: ‘We know you’ve done it this way 50 times before but we have a better idea.’”⁵ The incentive problem lies in the fact that if one firm succeeds in persuading the FDA to adopt an efficiency-gaining tool, the benefits will be shared by competitors who avail themselves of the same tool. This creates a potent disincentive to undertake the task of creating and validating new methods.

By inviting the private sector to create consensus-based tools, the FDA clearly hopes to facilitate movement toward better, more efficient drug development. Still, individual firm incentives remain weak. Hence the main public vehicle in this effort, at least so far, is the Critical Path Institute, organized by University of Arizona pharmacologist Raymond Woosley, largely with public-sector funding (Werble 2006). How rapidly and how far this arrangement can proceed is very much unknown at present (again, see Usdin 2005).

The FDA leadership that created and launched Critical Path will someday move on, leaving the entire program to an uncertain fate. We should therefore think about what are likely to be the persistent features of a vigorous Critical Path or similar program. Certainly, we

could hope for faster and cleaner drug development at a lower cost both before and after approval, along with enhanced safety. Nonetheless, there are considerable downside risks. Industry-FDA collaboration would become even closer than it is now, especially in earlier stages. This could generate at least two adverse results. One is that drug development could be even more dependent than it is now on FDA staff expertise and attitudes. True, we can be encouraged by Gottlieb’s remarks at a February 7, 2006, AEI conference, when he

The FDA should take advantage of the simple fact that manufacturers face overwhelming market-driven incentives to maintain a reputation for product integrity regardless of what the FDA requires.

pointed out that the adoption of new technology can easily enhance both speed and safety in drug development. But FDA staff and their critics know that there will sometimes be tradeoffs between safety and faster drug development. Closer industry-agency collaboration could intensify existing pressures for excessive safety.

Another concern is that foreign regulatory agencies, including the European Union’s increasingly potent and competent European Medicines Agency, could find themselves even more reliant upon FDA leadership than they already are.⁶ This would weaken what has at times been an important counterweight to the FDA in the sense that the Europeans have sometimes been willing to approve

new drugs (and especially medical devices) even as the FDA hesitates for months or years. After all, it was the comparative speed of the various European drug-approval agencies that revealed in the 1960s and early 1970s the extraordinary “drug lag” that followed upon the 1962 changes in the FDA’s powers and mandates (Peltzman 1973, 1974; Wardell and Lasagna 1975).

What the FDA Should and Should Not Do

Quite aside from Critical Path, there is much the FDA can do on its own to make drug regulation more efficient and effective. First, the FDA can make greater use of European experience. That experience supplies ample examples of how to get safe products to market faster and with far less stringent manufacturing regulation.

Second, the FDA can begin to deregulate manufacturing. There has to be a way to move toward validating output—are the pills and capsules what they are supposed to be?—instead of regulating every detail at every stage of manufacturing. The FDA should take advantage

of the simple fact that manufacturers face overwhelming market-driven incentives to maintain a reputation for product integrity regardless of what the FDA requires. Indeed, the very intricacy of FDA regulation relieves manufacturers of market pressure to keep up with traditional progress in terms of both safety and costs.

Third, the FDA can expand its policy of approving drugs on the basis of what, by traditional standards, is incomplete (but often compelling) information. In “accelerated approval,” for example, a drug is approved on the basis of surrogate markers—such as HIV virus counts—rather than on clinical benefits such as delayed death or disability. Often used for AIDS and cancer drugs, accelerated approval could be usefully applied to other conditions such as Alzheimer’s disease (see Rawson 2006 and American Enterprise Institute 2006). Also promising is the prospect of approving more drugs in the middle of the phase 3 clinical trials that normally must be completed before filing a new drug application. Phase 3 trials would continue even as commercial use commences and the results would be used to reassess the approval decision.

Fourth, the agency can continue to experiment with more flexible clinical trial structures. A welcome start is the FDA’s recent “phase 0” proposal, which removes some of the barriers to small-scale safety testing of new drugs (FDA 2006). Much more is possible. In his March 7 speech at the Cancer Progress Conference, Gottlieb listed a variety of ways to make greater use of innovative biomarkers, toxicity tests, and diagnostics, with special provision for testing preventatives (as opposed to treatments) (Gottlieb 2006b).

Finally, there are actions the FDA should not take. It should not create an independent drug safety board despite the urgings of some members of Congress. This proposal is based on the idea that FDA regulators are too reluctant to remove or restrict drugs they previously approved. But the safety board would have the same problem as soon as it permitted a drug to remain on the market in the face of new safety concerns, which is inevitable for most drugs. Worse, there is no reason to think an independent board would be better than FDA staff at the real task: balancing the continuing stream of new evidence on both risks and benefits of newly approved drugs. A safety board would reinforce the excessive safety incentives that already plague the FDA.

The agency should also continue to dismiss proposals (Avorn 2005) to require new drugs to be superior to existing drugs rather than simply safe and effective.

Demonstrating a difference between two effective drugs is far more difficult than demonstrating advantage over a placebo. In addition, competing drugs are usually developed simultaneously rather than one after another (DiMasi and Paquette 2004). This means that a superiority requirement would force every developer to mount far larger and costlier clinical trials because they might have to demonstrate superiority over a competing drug that unexpectedly reaches market first. Moreover, the superiority requirement would increase prices by limiting competition from biologically similar drugs.

A Turning Point?

FDA pharmaceutical regulation has gyrated widely. The infamous drug lag of the 1960s and early 1970s was followed by the move toward faster approvals during the early years of the AIDS epidemic in the late 1980s, and then by a more conservative approach in the 1990s leading to congressional pressure and the 1997 FDA Modernization Act (which modestly liberalized drug development regulation). In the past two years or so, there has been an unprecedented wave of academic criticism of FDA staff actions on drug safety. Underlying these fluctuations, however, has been the relentless institutionalization of excessive caution and the undermining of industry incentives to advance the science of drug regulation itself. All the while, the dynamics of technological progress in molecular biology and allied fields have been creating the biotechnology drug industry. The new science requires innovation in both drug development and public policy even as regulatory forces have, to an unknown degree, retarded progress in both areas. The FDA is now engaged in significant efforts to ameliorate these problems. Progress will be difficult; it will depend on the energy and persistence of current leadership and, far more important, the extent to which the FDA revises the incentives facing its own staff and the pharmaceutical industry.

Elizabeth DuPré provided research assistance and Nicole Passan worked with Mr. Calfee to edit and produce this Health Policy Outlook.

References

- American Enterprise Institute. 2006. Getting the most innovative drugs to market: What can the FDA do? February 7. www.aei.org/event1257/.
- Associated Press. 2002. F.D.A. to update rules on drug factories. August 22.

- Angell, Marcia. 2004. *The truth about the drug companies: How they deceive us and what to do about it*. New York: Random House.
- Avorn, Jerry. 2004. *Powerful medicines: The benefits, risks, and costs of prescription drugs*. New York: Knopf.
- Avorn, Jerry. 2005. FDA standards—Good enough for government work? *New England Journal of Medicine* 353 (10): 969–972.
- Berndt, Ernst R., Adrian H. B. Gottschalk, Tomas Philipson, and Matthew W. Strobeck. 2004. Assessing the impacts of the prescription drug user fee acts (PDUFA) on the FDA approval process. NBER Working Paper 10822, National Bureau of Economic Research, Cambridge, Mass.
- Burton, Thomas M. 2002. Abbott labs' 4th-quarter earnings fell, but its regulatory woes may end soon. *Wall Street Journal*, January 17.
- Burton, Thomas M., Geeta Anand, and Gardiner Harris. 2002. Abbott, Schering stock fall sharply as FDA comes down hard on both. *Wall Street Journal*, May 16.
- Calfee, John E. 2002. Public policy issues in direct-to-consumer advertising of prescription drugs. *Journal of Public Policy and Marketing* 19 (2) (Fall): 174–194.
- Calfee, John E. 2005. The Vioxx fallout. *AEI Health Policy Outlook*, September–October.
- Calfee, John E., Elizabeth DuPré, and Mario Villarreal. 2006. An exploratory analysis of pharmaceutical price disparities and their implications among six developed nations. Working Paper, American Enterprise Institute, Washington, D.C.
- DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski. 2003. The price of innovation: New estimates of drug development costs. *Journal of Health Economics* 22 (2): 151–185.
- DiMasi, Joseph A., and Cherie Paquette. 2004. The economics of follow-on drug research and development: Trends in entry rates and timing of development. *Pharmacoeconomics* 22 (2): 1–14.
- Flanagan, Michael. 2006. Avastin's progression. *BioCentury*. March 6: A1–A7.
- Food and Drug Administration. 2003. "Strategic action plan: Protecting and advancing America's health." www.fda.gov/oc/mcclellan/FDAStrategicPlan.pdf (accessed February 6, 2006).
- Food and Drug Administration. 2004a. "Center for Drug Evaluation and Research (CDER) report to the nation: 2004." www.fda.gov/cder/reports/rtn/2004/rtn2004-1.htm (accessed February 6, 2006).
- Food and Drug Administration. 2004b. "FDA White Paper: Challenge and opportunity on the critical path to new medical products." March 2004. www.fda.gov/oc/initiatives/criticalpath/whitepaper.html.
- Food and Drug Administration. 2005. CDER drug and biologic approval reports. www.fda.gov/cder/rdmt/default.htm.
- Food and Drug Administration. 2006. "Guidance for industry, investigators, and reviewers. Exploratory IND studies." www.fda.gov/cder/guidance/7086fml.htm.
- Friedman, Michael A., Janet Woodcock, Murray M. Lumpkin, Jeffrey E. Shuren, Arthur E. Hass, and Larry J. Thompson. 1999. The safety of newly approved medicines: Do recent market removals mean there is a problem? *The Journal of the American Medical Association* 281 (18): 1728–1734.
- Goozner, Merrill. 2004. *The \$800 million pill: The truth behind the cost of new drugs*. Berkeley, Calif.: University of California Press.
- Gottlieb, Scott. 2006a. Modernizing development science to unlock new treatments. Remarks at the American Enterprise Institute, Washington, D.C., February 7.
- Gottlieb, Scott. 2006b. Remarks before the 17th annual Cancer Progress Conference, New York, N.Y., March 7.
- Henderson, Diedtra, and Christopher Rowland. 2005. Once 'too slow,' FDA approvals called 'too fast.' *Boston Globe*, April 10.
- Holden, Constance. 2003. Future brightening for depression treatments. *Science* 302 (5646): 810–813.
- Kassirer, Jerome. 2004. *On the take: How medicine's complicity with big business can endanger your health*. New York, Oxford University Press.
- Kibbe, Arthur. 2002. Speech at the meeting of the Advisory Committee for Pharmaceutical Science, October 21, transcript, 63.
- Lancet*. 2004. Editorial: Vioxx, the implosion of Merck, and aftershocks at the FDA. 364 (9450): 1995–1996.
- Los Angeles Times*. 2001. The *Times* wins Pulitzer for FDA investigative stories. April 17.
- Lutter, Randall. 2005. Remarks on Berndt, Gottschalk, Philipson, and Strobeck's "Assessing the impacts of the Prescription Drug User Fee Acts on the FDA approval process," American Enterprise Institute, Washington, D.C., February 26.
- Moses, Hamilton III, E. Ray Dorsey, David H. M. Matheson, and Samuel O. Their. 2005. Financial anatomy of biomedical research. *The Journal of the American Medical Association* 294 (11): 1333–1342.
- Peltzman, Sam. 1973. An evaluation of consumer protection legislation: The 1962 Drug Amendments. *Journal of Political Economy* 81 (5) (September–October): 1049–1091.
- Peltzman, Sam. 1974. *Regulation of pharmaceutical innovation: The 1962 Amendments*. Washington, D.C.: American Enterprise Institute for Public Policy Research.

- Rawson, Kate. 2006. Rethinking Alzheimer's: Mapping out an approval process. *RPM Report*. February.
- Rucker, T. Donald. 2001. Prescription drugs under Medicare: The legacy of the task force on prescription drugs, part I. *Journal of Research in Pharmaceutical Economics* 10 (2, 3).
- Topol, Eric J. 2004. Failing the public health: Rofecoxib, Merck, and the FDA. *New England Journal of Medicine* 351 (17): 1707–1709.
- Usdin, Steve. 2005. Starting down the path. *BioCentury*. November 14: A1–A5.
- Usdin, Steve. 2006. Diminishing returns. *BioCentury*. February 13: A1–A7.
- U.S. Department of Health, Education and Welfare (USDHEW). 1968. "The drug makers and the drug distributors," Task Force on Prescription Drugs, background papers, December.
- Wardell, William M., and Louis Lasagna. 1975. *Regulation and drug development*. Washington, D.C.: American Enterprise Institute for Public Policy Research.
- Werble, Cole. 2006. A critical test for FDA's Critical Path Initiative. *RPM Report*. February.

Notes

1. The term "chemical" is increasingly a misnomer and is being replaced by "molecular" because of the growing 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 than 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. This separation is being rapidly attenuated by organizational changes. Almost all the numbers cited here are for traditional drugs, but the issues I discuss pertain to all pharmaceuticals, including biotech products, vaccines, and diagnostic tests.
2. Many of these points were emphasized in an October 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" (Kibbe 2002).
3. 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* (2001). Rezulin was in fact pulled after safer alternatives became established.
4. On Critical Path, see FDA (2004b) and Gottlieb (2006a). FDA leadership is certainly aware that FDA regulation has often been suboptimal, as evidenced by the quotations attributed to Janet Woodcock in Usdin (2005).
5. As quoted by Usdin (2006) in his coverage of an AEI conference, Getting the Most Innovative Drugs to Market: What Can the FDA Do? February 7, 2006.
6. Deputy FDA commissioner Janet Woodcock has pointed out that trying to advance Critical Path through formal international harmonization would be intolerably slow; see Usdin (2005), A3.