The number of new drugs emerging in the U.S. pharmaceutical market is at a low point. The Food and Drug Administration (FDA) approved an average of 22.6 new drugs and biologics per year from 2005 through 2009, down from 37.2 a decade earlier (1995 through 1999). Paradoxically, this decrease in production has occurred despite billions of dollars in public and private funding for research and development, as well as consistently high revenues reported by the pharmaceutical industry. Meanwhile, demand for innovative therapeutic alternatives has been rising in numerous fields, including antibiotics for multi-drug resistant organisms and drugs for tropical diseases prevalent in low-income populations.

As a result, policymakers from academia, industry, and government have called for federal initiatives to stimulate drug development. Most proposals target the intellectual property environment, because market-exclusivity periods, usually supported by patents, foster revenue generation in the pharmaceutical market. For example, longer market exclusivity has been recommended for “first-in-class” products and for newly approved drugs. In 2008, the FDA Amendments Act authorized the sponsor of a drug for tropical disease to earn a transferable voucher entitling the company to expedited review of a different drug application, an incentive potentially worth $300 million. The recent health care reform legislation included 12 years of market exclusivity for biologic drugs (even if the drug’s patent expired before that time); anything less, industry advocates threatened, could hinder domestic innovation.

Such incentives are politically attractive because they offer support for drug innovation without direct allocation of taxpayer funds. Yet patients (or their insurers) bear the costs by paying higher prices for the products during market-exclusivity periods. These programs may also be subject to misuse if they are implemented in a way that permits the incentives to be earned for marginal innovations or in contexts beyond the intended scope of the legislation. Finally, hidden costs can emerge, such as the public health implications if market exclusivity makes essential drugs prohibitively expensive. This analysis critically reviews the origins and effects of five important pieces of legislation that support market-exclusivity incentive programs in pharmaceutical research and development (Table 1). The outcomes may provide important insights into the strengths and limitations of this policy strategy.

Drug development is closely entwined with the patent system. Pharmaceutical research and development require substantial technical knowledge, and trials demonstrating safety and efficacy necessitate considerable up-front investment. Drug manufacturers charge prices above the cost of production (“patent rents”) during the market-exclusivity period to recoup their initial costs and make a profit. Afterward, other manufacturers can sell their own versions at a price closer to the cost of production. Since generic drugs are widely substituted for brand-name drugs, the innovator quickly loses its pricing premium.

The combination of market exclusivity and patent rents drives private investment in innovation that contributes to new drug development. However, this system also has important implications for public health. For example, when patented products are prescribed, their high costs can reduce patient adherence to treatment regimens. The costs of brand-name drugs contribute to rising health care spending among public insurers such as Medicaid, which has responded by introducing coverage limitations and increasing patient copayments or deductibles. Such strategies reduce the use of clinically necessary drugs among
patients. Policy initiatives in this field, therefore, need to balance incentives for investment in research and development with assurances that the products will be available at a reasonable cost to patients.

**POLICY INITIATIVES PROMOTING RESEARCH AND DEVELOPMENT**

### THE BAYH–DOLE ACT

The Bayh–Dole Act of 1980 encouraged commercial development of government-sponsored research by allowing private control of inventions funded by federal grants, a policy that had not been in place formally before this time. Universities and the business community pointed to the government’s poor track record in licensing products; among 30,000 patents that had been awarded to the government for inventions arising from federally funded research, only 5% were used in the private sector. In the pharmaceutical sciences, patents on early-stage technologies were intended to give companies the incentive to invest in the clinical research needed to develop academic discoveries and bring drugs through the FDA approval process. Technology transfer was more common in the biologic sciences, where 75 of 325 government-held, health care–related patents (23%) were licensed as of 1976.

Table 1. Federal Legislative Programs Using Market-Exclusivity Incentives to Promote Pharmaceutical Research and Development.

<table>
<thead>
<tr>
<th>Legislation</th>
<th>Year</th>
<th>Intended Effect</th>
<th>Potential Collateral Effects with Important Public Health Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent and Trademark Act amendments (Bayh–Dole)</td>
<td>1980</td>
<td>Contribute to the patenting and development of discoveries in early-stage biomedical science made at universities and in other government-funded settings</td>
<td>Encourages the patenting of lower-quality inventions and investment in technology transfer by universities that may not be efficient managers of intellectual property. Increases the patenting of biomedical research that delays research and development in essential basic science and increases its cost.</td>
</tr>
<tr>
<td>Orphan Drug Act</td>
<td>1983</td>
<td>Increase the number of drugs developed to treat rare diseases</td>
<td>Encourages manufacturers to seek out orphan indications for drugs that could otherwise be tested in more general populations. Provides public subsidies for profitable products that might have been developed without the incentive. Leads to the approval of drugs then widely used off-label without supporting data.</td>
</tr>
<tr>
<td>Drug Price Competition and Patent Term Restoration Act (Waxman–Hatch)</td>
<td>1984</td>
<td>Increase the market-exclusivity period for brand-name drugs. Increase the number of generic drug manufacturers challenging weak patents on brand-name drugs</td>
<td>Allows the generic exclusivity incentive to be used to arrange settlements between generic and brand-name manufacturers that delay the market entry of viable lower-cost drugs.</td>
</tr>
<tr>
<td>Prescription Drug User Fee Act</td>
<td>1992</td>
<td>Increase the market-exclusivity period for brand-name drugs by reducing the FDA review period</td>
<td>Results in the approval of drugs with important safety concerns in order to meet the accelerated review deadline. Encourages the financial dependence of the FDA on the pharmaceutical industry, which may influence regulatory behavior.</td>
</tr>
<tr>
<td>FDA Modernization Act, Section 111 (Pediatric exclusivity extension)</td>
<td>1997</td>
<td>Increase the number of studies of approved drug products in pediatric patients</td>
<td>Leads manufacturers that want the incentive to support poor-quality studies that do not have substantial effects on public health. Overcompensates certain manufacturers of blockbuster drugs. Delays the availability of low-cost generic drugs for adult patients who need them.</td>
</tr>
</tbody>
</table>
may be biased by the self-interest of the respondents.

Another series of studies, however, has suggested that the influence of Bayh–Dole has been more modest. One study reported that university patenting was growing before 1980, although it also concluded that the legislation may have hastened patenting and licensing by universities that had previously avoided these practices. An analysis of subsequent citations received by academic patents — a measure of their value — showed that university patents declined in importance after 1980 relative to a random sample. Thus, universities may have been patenting less important inventions, although subsequent analyses have disputed this conclusion. A study of licensing income in universities reported that median net income from this source amounted to only $1.13 million per year. University licensing income is not distributed evenly; only a few institutions have earned large returns, and the expected licensing returns were modest when compared with research expenditures.

In addition, by encouraging universities to patent basic science work, Bayh–Dole may have contributed to slowing the progress of investigation and raising the costs of biomedical research. Surveys of biomedical scientists have documented data-withholding practices and delays in publication of results due to intellectual property considerations. These results remain controversial, since other more limited surveys have found no link between patenting and research delays.

Finally, the Bayh–Dole Act has been criticized for allowing private companies to derive patent rents from pharmaceutical technology and products discovered in publicly funded federal research facilities, meaning that patients were effectively paying twice for the drugs that emerged. Although the act has contributed to important technology transfer over the past few decades, its legacy also includes negative implications, such as a change in academic research culture.

THE ORPHAN DRUG ACT

The Orphan Drug Act of 1983 sought to encourage research into therapeutic agents that would treat rare diseases, for which a limited patient market could otherwise prevent recovery of the investment made in product development. The act provided manufacturers with federal grants, a tax credit for clinical trials, and an exclusive right to market the orphan drug for the approved use for 7 years from the date of FDA approval. The market-exclusivity provision — the key legislative incentive — is stronger than a patent but narrower in its application. Orphan market exclusivity cannot be interrupted by a competitor (even if the underlying patent has expired), but unlike a patent, the exclusivity applies only to the FDA-approved indication.

Many have hailed the act’s success. In the decade before 1982, the FDA approved 10 treatments for orphan diseases, but from 1983 through 2008, more than 325 approved products had been designated as orphans. In the past decade, orphan drugs accounted for 11% of new drug approvals and 24% of biologic drugs. Case studies have supported the opinion that the Orphan Drug Act has played an important role in the development of products aimed at medical conditions in limited populations. At the same time, many orphan products have been exceedingly profitable, calling into question the need for the legislative incentives providing direct government subsidies. Orphan drugs have also remained the most expensive products on the market, which may compromise patient access.

It has also become clear that manufacturers have used the incentives the act provides to strategically position drugs to earn incentives when those drugs could otherwise have been developed for larger populations. In these and other cases, orphan drugs are tested in a limited population and then used off-label once approved, an action that increases the risk that the drugs will later be found unsafe. For example, in 1989 epoetin alfa (Epogen, Amgen) was approved as an orphan drug to treat anemia associated with end-stage renal disease and was later approved for patients with cancer who become temporarily anemic during chemotherapy, but it has now also been used as long-term therapy for all types of anemia. Recently, use of Epogen has been reduced after studies linked overuse of the product to an increased risk of death from cardiovascular disease.

THE WAXMAN–HATCH ACT

In the Waxman–Hatch Act, passed in 1984, Congress sought to encourage innovation among pharmaceutical companies in the development of both brand-name and generic drugs. First, responding to concerns that the increasing length of time drugs spent in development had eroded market exclusivity for brand-name drugs and in-
hibited investment in research and development, Waxman–Hatch restored to manufacturers the time that had elapsed during the clinical development and FDA review periods. Second, the act gave the first generic manufacturer 180 days of generic-market exclusivity as a prize for successfully challenging the patent of an approved brand-name drug. This incentive was intended to encourage generic manufacturers to bring bioequivalent products to market sooner by helping them shoulder the expense of the litigation required to invalidate weak or illegitimate patents protecting brand-name drugs.

The Congressional Budget Office and other researchers have concluded that Waxman–Hatch effectively provided brand-name manufacturers with market-exclusivity extensions, with most estimates converging on 2 years; a more recent study has suggested that this increase stemmed primarily from shorter FDA reviews. Although guaranteed market-exclusivity time thus increased, other parts of the statute set up a regulatory process facilitating the entry of low-cost generic drugs after patent expiration. As a result, a greater number of drugs faced competition and prescriptions of generic drugs overall increased — from 19% in 1984 to more than 70% today.

The effect of the 180-day exclusivity period has been more controversial. The incentive had minimal effect through 1997, with only three manufacturers earning 180-day exclusivity periods for their generic products. More recently, the number of challenges brought by generic-drug manufacturers seeking to invalidate brand-name drugs' patents has increased. Nonetheless, the exclusivity period has not always been used as it was originally intended. A large number of generic-drug manufacturers have delayed or forfeited their 180-day exclusivity periods in settlement agreements with their brand-name counterparts. Abbott, for example, paid a potential generic competitor $4.5 million per month to delay the start of its exclusivity period for terazosin (Hytrin, Abbott Laboratories), which had annual sales of more than $500 million at the time. The 180-day exclusivity has been criticized as contributing to delays in bringing lower-cost, generic drugs to the market rather than encouraging their timely availability.

**The Prescription Drug User Fee Act**
The Prescription Drug User Fee Act (PDUFA), approved in 1992, was written in response to concerns about the FDA's review process. In the 1980s, lengthy evaluation times were targeted by both consumer activists, who sought earlier access to innovative drugs being developed for the treatment of the acquired immunodeficiency syndrome, and pharmaceutical manufacturers, who complained that delays increased the cost of research and development. In the PDUFA, Congress authorized the FDA to collect user fees from applicants, with the fees to be applied to the costs of drug review and approval. All new drug applications (NDAs) were to be acted on within a year of submission. By decreasing FDA review times, the PDUFA was intended to lower development costs and allow patent-protected new drugs to reach the market sooner.

The effect of the legislation was quickly noted. By 1994, the FDA had acted on 93% of NDAs within the anticipated time frame. The average duration of FDA review for drug applications submitted with user fees fell from 31.0 to 14.5 months. In the first 10 years of the program, user fees accounted for approximately $1.2 billion, ultimately constituting the majority of the agency's funding for NDA review activities. Recently, the PDUFA was adjusted so that some of this revenue could be devoted to improving surveillance of postapproval drug safety.

Despite these outcomes, concerns about unintended effects of the act have persisted, including its effect on the relationship between manufacturers and FDA reviewers. An unexpectedly large number of drugs approved between 1993 and 2000 were later withdrawn because of safety concerns. Although the FDA concluded in an evaluation of the approval process that shorter review times did not contribute to these withdrawals, some argued that the PDUFA had put increased pressure on the agency to approve new drugs. Controlled analyses of drug approvals have showed that drugs receiving faster reviews are associated with greater numbers of serious adverse reactions and that drugs approved closer to the legislative deadline were more likely to be associated with later concern about safety. However, these results remain controversial, and other research has reported no such association. Finally, a connection between the PDUFA and investment in pharmaceutical research and development has not been established. Internal manufacturer data suggest that a 10% reduction in FDA approval times could lead to a 1.7% increase in pharmaceutical spending on research and development, but such
speculative assessments have not been rigorously tested.

THE PEDIATRIC EXCLUSIVITY EXTENSION

The pediatric exclusivity legislation was designed to address the fact that few drugs were being developed or studied for pediatric patients, for whom only a small fraction of all prescriptions are written. Because their physiology is different from that of adults, pharmacodynamics of a drug originally tested in adults may not be the same in children. Prescription drugs were frequently used in pediatric patients without evidence of their effectiveness from supporting clinical trials. Consequently, in 1997 Congress authorized a 6-month extension of market exclusivity for patented drugs to accrue when the manufacturer conducted pediatric studies.

Pharmaceutical companies acted on the incentive, and by 2007 more than 300 studies had been conducted and more than 115 products had received labeling changes to account for pediatric use. New information was provided on dosing, pharmacokinetics, safety, and efficacy, and new formulations were developed.

Despite the growth in pediatric drug research, there have been questions about some of the trials conducted to earn the incentive. Pediatric trials have been conducted on a number of products with marginal public health importance for children, and the drugs most frequently used by children have been underrepresented; instead, pediatric exclusivity studies have tended to involve drugs that were both popular and profitable in the market for adults. In addition, some pediatric studies were of subpar quality or were not subject to peer review and publication in the medical literature. In these cases, the manufacturers' goal may have been to obtain the pediatric exclusivity bonus rather than to conduct clinically meaningful tests of their products in pediatric patients or to have the widest possible influence on public health. Finally, some manufacturers have delayed pediatric trials until late in the period of their product's market exclusivity, thereby increasing their return and minimizing the public health benefit.

At the same time, the pediatric exclusivity legislation has supported substantial profits. Among a selection of trials performed from 2002 through 2004, the median cost to the drug manufacturer per FDA written request was $12 million (range, $5 million to $44 million) and the median net economic benefit to the manufacturer was $134 million (range, −$9 million to $508 million), a profit ratio of more than 10 to 1. In specific drug classes, profit making could be even higher; for example, the ratio for antihypertensive drugs was 17 (range, 4 to 65).

Since Congress approved the pediatric exclusivity extension, a large number of pediatric trials have been performed, leading to some useful label changes. However, this incentive has also overcompensated many manufacturers without necessarily providing outcomes that are beneficial to children.

LESSONS FOR INCENTIVE PROGRAMS

A great deal of controversy remains about the overall effect of the legislation discussed above; few rigorous studies have determined whether the effect has been positive or negative. Reports charting the number of technology-transfer offices created after passage of the Bayh–Dole Act or the number of orphan drugs approved because of the Orphan Drug Act have been presented as definitive evidence of success, but such simple analyses are inherently limited. They may not address confounding factors that affect results, such as changes in the pharmaceutical market. Evaluation of policy on science and technology can be difficult, but at minimum any legislation offering a market-exclusivity incentive should be accompanied by an independent expert review of the incentive’s intended effectiveness and cost-effectiveness.

Although incentive programs have generated positive outcomes, misuse is common, leading to improper gains for manufacturers earned at a cost to patients or public insurers. In rare cases, as in the use of the Waxman–Hatch 180-day exclusivity period to allow companies producing generic drugs to negotiate lucrative settlements with brand-name manufacturers, it appears that such an outcome was an unintended and unexpected result. More often, however, the risk of waste was predicted during consideration of the legislation. For example, in the development of the final version of the Orphan Drug Act, Senator Orrin Hatch (R-UT) admitted that the legislative incentive would be available for drugs that, “because of their extremely high price, may well turn out to recover all their costs and become profitable.”

Until shortly before its passage, the Bayh–Dole Act
contained language to recoup public investment in commercialized technologies, but these provisions were dropped to obtain passage of the legislation.54

Therefore, past experiences suggest that incentive programs should be implemented in a way that encourages fairness and more closely links the incentive to the desired outcome. For example, in Europe, orphan drug legislation includes a reduced exclusivity period once use of the product expands. Another way to prevent manufacturers from taking undue advantage of incentive programs would be for them to return the government's initial investment with a reasonable rate of return if an orphan drug becomes exceedingly profitable. In the case of pediatric exclusivity, direct federal grant support (and perhaps a small bonus) could be provided to encourage researchers to conduct needed trials. Another possibility would be to calibrate the value of the incentive on the basis of the actual public health outcomes among pediatric patients. The failure to establish an appropriate link between incentive and outcome is evident in the FDA Priority Review Voucher, which accrues upon agency approval of the drug despite numerous instances in which manufacturers have not established easy access to essential medicines in resource-poor areas. A more appropriate incentive would be more closely tied to use of the drug or to improved health outcomes in patients suffering from the disease.95

Finally, using market exclusivity to encourage useful public health goals can lead to important secondary consequences. For example, the PDUFA has helped to accelerate drug review times, but accelerated time frames may also have contributed to the approval of drugs later found to have important safety problems. In some cases, the consequences of the act have emerged in a less direct fashion. The Bayh–Dole Act may have helped to commercialize some government-funded discoveries, but the effect of patenting and commercialization may also have slowed other aspects of the research process or changed the focus of basic science at universities. Pediatric exclusivity stimulated investment in studies of the effects of drugs on children, but the consequences for adult patients of the resulting delay in access to lower-cost generic versions of these drugs are unknown. It would be useful to consider such costs before enacting this kind of legislation — and at regular intervals afterward — so that policymakers can weigh these costs against any real benefits offered by the incentives.

Conclusions

Although use of market-exclusivity incentives to promote pharmaceutical innovation has potential benefits, future legislative efforts aimed at encouraging investment in drug research and development should be more precisely designed to avoid waste and misuse, and they should be linked to demonstration of positive public health outcomes. Without these limitations, making exclusivity incentives available to pharmaceutical manufacturers may not be worth the potential risks to public health.

Supported by the Public Health Law Research Program, the Robert Wood Johnson Foundation, a grant from the Harvard Clinical and Translational Science Center, and a Robert Wood Johnson Foundation Investigator Award in Health Policy Research.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Mary Kenneally for her research assistance and Kevin Outterson, Michelle Mello, Scott Burrell, Alex Wagenaar, Jeff Swanson, Jennifer Ibrahim, and Jennifer Wood for their comments on an earlier draft of the manuscript.

From the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital, and Harvard Medical School — both in Boston. Address reprint requests to Dr. Kesselheim at the Division of Pharmacoepidemiology and Pharmacoeconomics, 1620 Tremont St., Suite 3030, Boston, MA 02120, or at akessheim@partners.org.

1. PhRMA. Pharmaceutical industry profile 2009. (http://www.phrma.org/files/attachments/PhRMA%202009%20Profile%20FINAL.pdf.)
39. Idem. The Prescription Drug User Fee Act: is a faster


73. Pasquali SK, Sanders SP, Li JS. Oral antihypertensive trial design and analysis under the pediatric exclusivity provision. Am Heart J 2002;144:608-14.


