

Health Affairs

At the Intersection of Health, Health Care and Policy

Cite this article as:

Henry G. Grabowski, Joseph A. DiMasi and Genia Long
The Roles Of Patents And Research And Development Incentives In
Biopharmaceutical Innovation
Health Affairs 34, no.2 (2015):302-310
doi: 10.1377/hlthaff.2014.1047

The online version of this article, along with updated information and services, is available at:

<http://content.healthaffairs.org/content/34/2/302>

For Reprints, Links & Permissions :

http://content.healthaffairs.org/1340_reprints.php

Email Alertings : <http://content.healthaffairs.org/subscriptions/etoc.dtl>

To Subscribe : <https://fulfillment.healthaffairs.org>

Health Affairs is published monthly by Project HOPE at 7500 Old Georgetown Road, Suite 600, Bethesda, MD 20814-6133. Copyright © by Project HOPE - The People-to-People Health Foundation. As provided by United States copyright law (Title 17, U.S. Code), no part of may be reproduced, displayed, or transmitted in any form or by any means, electronic or mechanical, including photocopying or by information storage or retrieval systems, without prior written permission from the Publisher. All rights reserved.

Not for commercial use or unauthorized distribution

By Henry G. Grabowski, Joseph A. DiMasi, and Genia Long

DOI: 10.1377/hlthaff.2014.1047
HEALTH AFFAIRS 34,
NO. 2 (2015): 302-310
©2015 Project HOPE—
The People-to-People Health
Foundation, Inc.

The Roles Of Patents And Research And Development Incentives In Biopharmaceutical Innovation

Henry G. Grabowski (grabow@econ.duke.edu) is a professor of economics at Duke University, in Durham, North Carolina.

Joseph A. DiMasi is director of economic analysis at the Tufts Center for the Study of Drug Development, Tufts University, in Boston, Massachusetts.

Genia Long is a senior advisor at the Analysis Group, in Boston, Massachusetts.

ABSTRACT Patents and other forms of intellectual property protection play essential roles in encouraging innovation in biopharmaceuticals. As part of the “21st Century Cures” initiative, Congress is reviewing the policy mechanisms designed to accelerate the discovery, development, and delivery of new treatments. Debate continues about how best to balance patent and intellectual property incentives to encourage innovation, on the one hand, and generic utilization and price competition, on the other hand. We review the current framework for accomplishing these dual objectives and the important role of patents and regulatory exclusivity (together, the patent-based system), given the lengthy, costly, and risky biopharmaceutical research and development process. We summarize existing targeted incentives, such as for orphan drugs and neglected diseases, and we consider the pros and cons of proposed voluntary or mandatory alternatives to the patent-based system, such as prizes and government research and development contracting. We conclude that patents and regulatory exclusivity provisions are likely to remain the core approach to providing incentives for biopharmaceutical research and development. However, prizes and other voluntary supplements could play a useful role in addressing unmet needs and gaps in specific circumstances.

Technological innovation is widely recognized as a key determinant of economic and public health progress.^{1,2} Patents and other forms of intellectual property protection are generally thought to play essential roles in encouraging innovation in biopharmaceuticals. This is because the process of developing a new drug and bringing it to market is long, costly, and risky, and the costs of imitation are low. After a new drug has been approved and is being marketed, its patents protect it from competition from chemically identical entrants (or entrants infringing on other patents) for a period of time. For firms to have an incentive to continue to invest in innovative development

efforts, they must have an expectation that they can charge enough during this period to recoup costs and make a profit. After a drug’s patent or patents expire, generic rivals can enter the market at greatly reduced development cost and prices, providing added consumer benefit but eroding the innovator drug company’s revenues.

The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act) was designed to balance innovation incentives and generic price competition for new drugs (generally small-molecule chemical drugs, with some large-molecule biologic exceptions) by extending the period of a drug’s marketing exclusivity while providing a regulatory framework for generic drug approval.

This framework was later changed to encompass so-called biosimilars for large-molecule (biologic) drugs through the separate Biologics Price Competition and Innovation Act of 2009. Other measures have been enacted to provide research and development (R&D) incentives for antibiotics and drugs to treat orphan diseases and neglected tropical diseases.

Discussion continues about whether current innovation incentives are optimal or even adequate, given evolving public health needs and scientific knowledge. For instance, the House Energy and Commerce Committee recently embarked on the “21st Century Cures” initiative,³ following earlier recommendations by the President’s Council of Advisors on Science and Technology on responding to challenges in “propelling innovation in drug discovery, development, and evaluation.”⁴

In this context, we discuss the importance of patents and other forms of intellectual property protection to biopharmaceutical innovation, given the unique economic characteristics of drug research and development. We also review the R&D incentives that complement patents in certain circumstances. Finally, we consider the pros and cons of selected voluntary (“opt-in”) or mandatory alternatives to the current patent- and regulatory exclusivity-based system (such as prizes or government-contracted drug development) and whether they could better achieve the dual goals of innovation incentives and price competition.

The Role Of Patents In Biopharmaceutical Innovation

The essential rationale for patent protection for biopharmaceuticals is that long-term benefits in the form of continued future innovation by pioneer or brand-name drug manufacturers outweigh the relatively short-term restrictions on imitative cost competition associated with market exclusivity. Regardless, the entry of other branded agents remains an important source of therapeutic competition during the patent term.

Several economic characteristics make patents and intellectual property protection particularly important to innovation incentives for the biopharmaceutical industry.⁵ The R&D process often takes more than a decade to complete, and according to a recent analysis by Joseph DiMasi and colleagues, per new drug approval (including failed attempts), it involves more than a billion dollars in out-of-pocket costs.⁶ Only approximately one in eight drug candidates survive clinical testing.⁶

As a result of the high risks of failure and the

high costs, research and development must be funded by the few successful, on-market products (the top quintile of marketed products provide the dominant share of R&D returns).^{7,8} Once a new drug’s patent term and any regulatory exclusivity provisions have expired, competing manufacturers are allowed to sell generic equivalents that require the investment of only several million dollars and that have a high likelihood of commercial success. Absent intellectual property protections that allow marketing exclusivity, innovative firms would be unlikely to make the costly and risky investments needed to bring a new drug to market.

Patents confer the right to exclude competitors for a limited time within a given scope, as defined by patent claims. However, they do not guarantee demand, nor do they prevent competition from nonidentical drugs that treat the same diseases and fall outside the protection of the patents.

New products may enter the same therapeutic class with common mechanisms of action but different molecular structures (for example, different statins) or with differing mechanisms of action (such as calcium channel blockers and angiotensin receptor blockers).⁹ Joseph DiMasi and Laura Faden have found that the time between a first-in-class new drug and subsequent new drugs in the same therapeutic class has been dramatically reduced, from a median of 10.2 years in the 1970s to 2.5 years in the early 2000s.¹⁰ Drugs in the same class compete through quality and price for preferred placement on drug formularies and physicians’ choices for patient treatment.

Patents play an essential role in the economic “ecosystem” of discovery and investment that has developed since the 1980s. Hundreds of start-up firms, often backed by venture capital, have been launched, and a robust innovation market has emerged.¹¹ The value of these development-stage firms is largely determined by their proprietary technologies and the candidate drugs they have in development. As a result, the strength of intellectual property protection plays a key role in funding and partnership opportunities for such firms.

Universities also play a key role in the R&D ecosystem because they conduct basic biomedical research supported by sponsored research grants from the National Institutes of Health (NIH) and the National Science Foundation (NSF). The Patent and Trademark Law Amendments Act of 1980 (commonly known as the Bayh-Dole Act) gave universities the right to retain title to patents and discoveries made through federally funded research. This change was designed to encourage technology transfer

through industry licensing and the creation of start-up companies. Universities received only 390 patents for their discoveries in 1980,¹² compared to 4,296 in 2011, with biotechnology and pharmaceuticals being the top two technology areas (accounting for 36 percent of all university patent awards in 2012).¹³

University licensing trends have generated debate. For instance, there have been recent proposals to encourage the federal government to “march in” and require a university to license a patent or enforce reduced pricing or other terms.¹⁴ The percentage of approved drugs with public-sector patents is relatively small.¹⁵ Nevertheless, if the government exercised its march-in rights in this way, that action could have adverse effects on technology transfer activities and early-stage company investment, particularly if it were to disrupt existing expectations of grantees, licensees, and investors.¹² There have been four petitions to the NIH requesting it to exercise march-in rights on behalf of the federal government; none has been granted.¹⁶

Patents And Exclusivity Provisions For Drugs And Biologics

The Hatch-Waxman Act created a low-cost regulatory mechanism for generic drug manufacturers to obtain marketing approval from the Food and Drug Administration (FDA) by submitting an abbreviated new drug application and

demonstrating the drug’s bioequivalence to the innovative “reference” product. For innovators, the act restores some of the “patent clock” time lost during lengthy clinical trials and FDA review periods. It also provides a five-year regulatory exclusivity period for new molecular entities that runs concurrently with patent term protection, during which time an abbreviated new drug application cannot be submitted (four years in the case of a patent challenge).

The act also encourages generic manufacturers to challenge brand-name patents, in that the first company to file an abbreviated new drug application with a patent challenge is eligible to receive 180 days of generic drug market exclusivity, during which time no other generic competitor can enter the market. As a result, patent challenges have become a major factor in generic competition. Exhibit 1 summarizes the main provisions of the Hatch-Waxman Act. The act’s effects have been extensively analyzed elsewhere.^{17,18}

Since the 1980s, biologics (large-molecule products such as vaccines, blood or blood components, proteins, and living cells created or modified through a biologic process) have become increasingly significant, both clinically and economically. New chemical drugs receive five years of marketing exclusivity under the Hatch-Waxman Act. In contrast, new biologic products enjoy twelve years of regulatory exclusivity under the Biologics Price Competition and

EXHIBIT 1

Provisions Related To Intellectual Property (IP) In The Hatch-Waxman Act Of 1984 And The Biologics Price Competition And Innovation Act (BPCIA) Of 2009

Provision	Hatch-Waxman Act	BPCIA
Patent term restoration for new molecular entities	One of innovator’s drug patents is eligible for partial patent term restoration based on time lost in FDA review and half of time lost during clinical development Restoration is capped at 5 years; extended patent term cannot exceed 14 years from FDA approval (including restoration)	Same provisions apply for patents on biologics
Exclusivity for new molecular entities	Exclusivity period is 5 years An ANDA can be submitted after 5 years (or 4 years, in the case of a patent challenge)	Exclusivity period before a biosimilar application can be approved is 12 years after reference biologic is first licensed A biosimilar application can be filed 4 years after reference biologic is first licensed
Patent challenges by generic firms	Stay of FDA generic approval of up to 30 months to allow courts to resolve patent challenges; a generic can enter “at risk” of damages if district court litigation is ongoing after 30 months and later finds in favor of branded drug First-filing generic firm has 180-day generic exclusivity period if it gains the right to enter prior to patent expiration through litigation or a patent settlement, or if innovator does not sue when generic files	FDA acceptance of a biosimilar application triggers exchange of information on patents and potential litigation in accordance with specific timelines No 180-day exclusivity awarded for patent challenges; no 30-month stay of approval associated with patent challenges

SOURCE Authors’ analysis of legislation. **NOTES** The Hatch-Waxman Act is the Drug Price Competition and Patent Term Restoration Act of 1984. FDA is Food and Drug Administration. ANDA is abbreviated new drug application.

Innovation Act (patents may provide lesser or greater protection). The latter act also created an abbreviated regulatory pathway for so-called biosimilars, with applications under it relying in part on the innovator drug's data on safety and efficacy, together with a framework of provisions regarding regulatory exclusivity and patent challenges (Exhibit 1).¹⁹ There are no 180-day exclusivity periods for patent challenges by biosimilar applicants. Instead, the Biologics Price Competition and Innovation Act mandates an information exchange between the parties and specifies timelines for filing lawsuits and responses after an application is submitted.¹⁹

Several biosimilars have been approved in Europe.²⁰ However, biosimilar regulation, development, and competition in the United States are still in the early stages. The FDA recently accepted its first biosimilar application (for Sandoz's filgrastim), and its Oncologic Drugs Advisory Committee has recommended approval.²¹ The FDA has not yet issued its decision on whether to approve the drug given the evidence submitted and, if so, whether it will designate it as interchangeable with the reference drug.

The different regulatory exclusivity provisions of the Biologics Price Competition and Innovation Act and the Hatch-Waxman Act have stimulated discussions regarding the potential implications of different incentives for R&D investments for small-molecule versus large-molecule projects.²² Another concern is whether, even after taking account of the patent restoration provisions applicable to all new drugs, there are adequate incentives for innovator companies to develop therapies that require particularly large and risky investments, such as oncology therapies for which the FDA requires long-term survival data instead of more easily obtainable surrogate endpoint data for approval.²³

Generic Competition And Market Exclusivity Periods

Since the passage of the Hatch-Waxman Act, generic competition has flourished, and generics quickly capture dominant shares of prescriptions when patent protection of branded products ends.^{17,18} Generic drugs accounted for 86 percent of US prescriptions in 2013, compared with only 19 percent in 1984.²⁴

Patent and regulatory exclusivity terms, together with market entry decisions by generic drug firms, determine the market exclusivity period of a new branded drug (the time between the launch of the drug and the launch of its first generic competitor). Because of the time required to conduct clinical trials and earn FDA approval, the market exclusivity period for drugs

is generally much shorter than the statutory twenty-year patent life. The most recently calculated average market exclusivity period for new small-molecule drugs that experienced initial generic drug entry in 2011–12 was 12.9 years.¹⁷

The average market exclusivity period remained relatively constant between 1995 and 2012, varying between 12.2 and 13.7 years.¹⁷ However, other factors have changed, which may lead to reductions over time. For example, patent challenges have become more common in recent years and have occurred much sooner after the originator product's launch date. Specifically, 81 percent of new small-molecule drugs that experienced first generic entry in 2012 had had their patents challenged by potential generic competitors, compared to only 9 percent in 1995.¹⁷ There are some indications that this trend may be causing a reduction in market exclusivity periods, especially for higher-revenue drugs.^{25,26}

With the increase in patent challenges, settlements between generic and innovator or brand-name firms have permitted the parties to enter into agreements that allow generic entry prior to the patent's expiration and avoid the uncertainties associated with litigation. However, some of these settlements have raised antitrust concerns on the part of the Federal Trade Commission (FTC).

After conflicting US district court rulings, in 2013 the US Supreme Court decided in *FTC v. Actavis, Inc.*, that agreements according to which innovator firms provide something of value to generic firms (sometimes referred to as “pay for delay” or “reverse payment” agreements) are neither presumptively lawful nor presumptively unlawful. Instead, they must be evaluated using a “rule of reason” standard.²⁷ Evolving case law on patent challenges and settlements could have important effects on the future behavior of innovator and generic firms.

Under the America Invents Act of 2011, the US patent system has transitioned from a “first-to-invent” to a “first-to-file” system, aligning itself with the patent systems in most other countries. The act also provides an additional postpatent grant review pathway for generic firms to challenge the validity of innovators' patents. The impact of these changes on competition is not yet known and remains an important issue for further research.

Targeted Exclusivity And Complementary Incentives

Congress expanded the innovation policy “tool kit” by enacting special exclusivity incentives to stimulate the development of new drugs and to encourage additional clinical studies in pediatric

populations, studies of “orphan” drugs, and studies of antibiotics that address life-threatening illnesses associated with drug-resistant bacteria. These periods supplement baseline patent and regulatory exclusivity periods with additional incentive mechanisms (Exhibit 2).

PEDIATRIC STUDIES Patent and regulatory exclusivity periods may be extended by six months under what is known as “pediatric exclusivity.” Historically, many drugs commonly prescribed for children had not been studied extensively in pediatric populations, given limited patient populations, recruitment difficulties, and other challenges. As a result, dosing, safety, efficacy, and side-effect information specific to children was largely unavailable to regulators, clinicians, patients, and their families.

As part of the Food and Drug Administration Modernization Act of 1997, Congress enacted a six-month exclusivity incentive for pediatric clinical studies that are conducted in response to a written request from the FDA (Exhibit 2). The program has been successful in increasing

clinical trial evidence on pediatric outcomes, although some delays in generic entry associated with the extra six months of market exclusivity have been criticized.²⁸ Pediatric exclusivity incentives had been subject to annual five-year evaluations and sunset provisions, but Congress made the incentives permanent in 2012.

ORPHAN DRUGS Recognizing that high R&D costs create financial disincentives when the number of potential patients is small, Congress passed the Orphan Drug Act of 1983 (Exhibit 2). The act increases incentives for developing drugs to treat rare diseases (those affecting fewer than 200,000 people in the United States each year). Orphan drug designation provides exclusive marketing rights for seven years from approval, tax credits, government grants, and access to special technical advice from the FDA.

The program has been highly successful in increasing the level of drug development investment in rare diseases. Between 1984 and 2011 the FDA granted 2,626 orphan designations for drugs in development, and it approved for mar-

EXHIBIT 2

Targeted Incentives For Research And Development (R&D), By Public Health Area

Legislation or policy	Target	“Push” incentives	“Pull” incentives
PEDIATRIC STUDIES			
Food and Drug Administration Modernization Act of 1997 (reauthorized every five years, made permanent in 2012)	Limited patient populations, recruitment challenges create gap in testing of drugs in pediatric populations	— ^a	6 months added to existing exclusivities and expiration dates of patents listed in FDA “Orange Book”
ORPHAN DRUGS			
Orphan Drug Act of 1983	High costs of drug development create disincentive for drugs for rare diseases with limited patient populations	Tax credits of up to 50% of qualified clinical development spending Exemption from certain FDA fees Government grants Access to special FDA technical advice	FDA may not approve an application for the same drug for the same orphan indication for 7 years
ANTIBIOTICS			
Generating Antibiotic Incentives Now (GAIN) Act of 2012	Growing antibiotic resistance and threat of “super bugs”	FDA Fast Track and Priority Review status	5-year exclusivity extension
NEGLECTED TROPICAL AND RARE PEDIATRIC DISEASES			
Food and Drug Administration Amendments Act of 2007	Insufficient demand to attract private R&D investment in poor countries	— ^a	Priority Review vouchers may be transferred or sold and applied to other drugs in developed markets
Public-private consortia price-volume purchase guarantees	Insufficient demand to attract private R&D investment in poor countries	— ^a	Advance market commitments provide long-term market purchase pledges
BIOTERRORISM			
Project BioShield Act of 2004 (reauthorized in 2013)	No existing market	New regulatory models and processes to streamline review and approval	Government contracts for R&D and medical countermeasures to combat bioterrorism

SOURCE Authors’ analysis of legislation. **NOTES** “Push” incentives are those that are designed to reduce development costs. “Pull” incentives are those that are designed to increase revenues. FDA is Food and Drug Administration. ^aNot applicable.

The average market exclusivity period remained relatively constant between 1995 and 2012.

keting more than 350 drugs with orphan designations. In contrast, during the ten years before the law's passage, fewer than ten such products were approved and marketed.²⁹ Frank Lichtenberg found that the increase in new orphan drug approvals resulted in a significant reduction in potential years of life lost before age sixty-five resulting from rare diseases in France and the United States.³⁰

ANTIBIOTICS Since the 1990s various health agencies have identified growing antibiotic resistance as a major health threat, but few new antibiotics have been introduced.³¹ Concerns about resistance have increased. However, reserving new antibiotics as drugs of “last resort” constrains their sales. Together with rising R&D costs and other challenges, this created a disincentive to investment in developing new antibiotics.

The Generating Antibiotic Incentives Now (GAIN) Act of 2012 was designed to strengthen the pipeline of antibiotic and antifungal drugs for life-threatening or other serious infections by providing several economic incentives (Exhibit 2). These include a five-year extension of regulatory exclusivity from generic competition (supplementing the five years of exclusivity for new small-molecule drugs under the Hatch-Waxman Act and any applicable orphan drug and pediatric exclusivity). These drugs are also eligible for the FDA's Fast Track and Priority Review programs. Fast Track status provides more frequent interactions with FDA review teams and the opportunity for a “rolling review,” or review of portions of the application before the complete application is submitted. Priority reviews are expected to be completed by the FDA within six months—substantially faster than the ten months required for a standard review.

Thirty-five antibiotics have been designated as qualified infectious disease products under the GAIN Act, making them eligible for these incentives, including extended regulatory exclusivity, if the FDA approves them.³² As of December 2014, four had been approved: dalbavancin,

tedizolid, oritavancin, and a combination of cef-
tozane and tazobactam.³³ The FDA is also developing guidance for antibacterial drug development, as called for in the GAIN Act.

NEGLECTED DISEASES In cases where an inadequate market exists for a developed drug because of insufficient demand, other mechanisms have been proposed or implemented. These cases include neglected tropical diseases in less developed countries and rare pediatric diseases.

► **TRANSFERABLE PRIORITY REVIEW VOUCHERS:** The Food and Drug Administration Amendments Act of 2007 authorizes the FDA to award a Priority Review voucher to the manufacturer of a newly approved drug or biologic application that targets any of sixteen specific neglected tropical diseases and that offers major advances in treatment or provides treatment where no adequate therapy has existed (Exhibit 2).³⁴ A bill adding Ebola to the list—the Adding Ebola to the FDA Priority Review Voucher Program Act—was passed by Congress in 2014 and signed into law.

The voucher may be transferred or sold to another manufacturer. It entitles the holder to a Priority Review for another product that would not otherwise be eligible for one. To ensure that the additional Priority Review does not displace another drug's Priority Review, the FDA also is paid a user fee by the voucher recipient (approximately \$2.3 million in 2014). In 2012 the program was modified to add rare pediatric diseases on a trial basis, among other changes.

Four products (for malaria, tuberculosis, Morquio A syndrome, and leishmaniasis) have thus far earned transferable vouchers. Confirming the potential economic value of a voucher, Gilead Sciences recently announced that it is paying \$125 million for the voucher received by Knight Therapeutics, but it has not yet announced for which drug it will be used.³⁵ This follows an earlier announcement by Regeneron and Sanofi that they had purchased a voucher received by BioMarin for \$67.5 million and would use it for their injectable cholesterol drug.³⁶

► **ADVANCE MARKET COMMITMENTS:** In an advance market commitment (a concept developed by Michael Kremer and others), donors make a long-term contractual pledge to pay a “top-up” price for unit sales of a new vaccine when it is successfully developed and if target countries are willing to pay modest copayments per unit (Exhibit 2).³⁷ In this way, the guarantee of an attractive sustained market is intended to attract sufficient R&D investment and capacity construction.

In an initial test in 2007, a number of countries and the Bill & Melinda Gates Foundation committed a combined total of \$1.5 billion for pneu-

mococcal disease vaccines in late-stage development. And in 2010 GlaxoSmithKline and Pfizer signed commitments to provide thirty million doses of their respective second-generation multistrain pneumococcal vaccines each year during a ten-year contract, which is expected to prevent more than 500,000 child deaths over the decade.³⁸

Alternatives To The Patent-Based System

Some critics of the patent-based system have advocated replacing it with prize systems, government contracting, or other options that they argue could better balance the dual objectives of price competition and innovation incentives.³⁹ For instance, legislation—the Medical Innovation Prize Act—was introduced in Congress in 2005 that would substitute a prize approach for patents.

As proposed alternatives to the patent system, government spending could be substituted for private R&D spending, directly through government contracts or through a prize system for specified drug innovations.⁴⁰ Through either method, government expenditures would be funded by additional federal taxes. These would be theoretically offset, at least in part, by lower prices from the immediate “genericization” of all drugs covered by these programs at launch. Proponents of the prize system approach contend that pharmaceutical prices remain significantly above the marginal costs of production (which exclude the high fixed costs of R&D and other up-front investments) and that, as a result, health care costs are higher than they would be in the absence of patents and regulatory exclusivity (at least temporarily, and for drugs that would be developed and launched under such a regime). This means that some patients in need of certain medicines are unable to afford them.

These proposals present both theoretical and practical problems, depending on their design and on whether they would be mandatory alternatives or voluntary supplements to the existing intellectual property system. As mandatory alternatives, they would introduce more immediate generic price competition but also risks of reduced innovation incentives, R&D delays, and therefore fewer new therapies’ being developed and coming to market. As supplements, depending on their design, they might address important unmet needs and gaps.³⁸

A detailed analysis of alternatives is beyond the scope of this article. However, some of the key issues are summarized briefly below.

GOVERNMENT-CONTRACTED DRUG DEVELOPMENT

As a widespread replacement for private-

Debate continues regarding how best to design incentives to foster continued biopharmaceutical innovation.

sector later-stage R&D investment, direct government purchase through grants and contracts generally would require a degree of centralized information and decision making that critics say would introduce uncertainties and delays into biotechnology’s scientific and business environment. Program administrators would face challenges in “picking winners” among constantly changing scientific opportunities and competing organizations. In comparison, NIH grants have focused on basic research and technology transfer, instead of on late-stage drug development, and the grants amount to a fraction of private-sector investment.¹²

In some cases, however, no effective market exists, and government contracting might provide a necessary complementary incentive to patents. For example, in response to bioterrorism threats, the government has developed funding programs and other initiatives to encourage research and development in the absence of a developed market (Exhibit 2).⁴¹ The importance of consistent and adequate investment in underdeveloped therapies and the public health linkage between developed and less-developed regions is highlighted by recent developments in the spread of Ebola.

PRIZE SYSTEMS Prizes have the advantage of rewarding outputs instead of funding inputs (they only pay for success), and in some instances they may attract a wider set of options and market participants, compared to current market incumbents. However, there would be several challenges if they were mandatory replacements for patents.

First, prizes generally require clear, prespecified performance criteria, which might not always be possible to define. Second, given that the biopharmaceutical R&D process is particularly long and costly, prizes could be subject to “hold-up” problems. As a result, innovators might fear that, having made substantial non-recoverable investments over many years, they

could see their prizes reduced by legislatures or government agencies because of budget constraints or cost reduction efforts. Early-stage venture-supported research and development would be particularly vulnerable.

Third, biomedical progress often occurs incrementally, as successive “best-in-class” drugs are introduced.⁴² It is also clinically desirable that a variety of agents be available, given sometimes idiosyncratic patient response. Unless an ongoing series of prizes were offered to simulate the effects of such dynamic competition, the benefits of therapeutic on-patent competition would be lost in a “winner-take-all” competition.

Voluntary prizes that supplemented the patent system could mitigate many of these problems and maintain market incentives. Noting that prizes are often focused on demonstration projects instead of on widespread access to valued new technologies, Michael Kremer and Heidi Williams suggest incorporating market acceptance features (as in an advance market com-

mitment). They also observe that having voluntary programs supplement patents instead of replacing them would limit the risk of undermining investors’ long-term expectations of future rewards, which is critical to current innovation incentives.³⁸

Conclusion

Debate continues regarding how best to design intellectual property and other incentives to foster continued biopharmaceutical innovation, and how to balance these incentives with benefits from price competition. A system of patent and regulatory intellectual property provisions and targeted R&D incentives to address unmet needs when market incentives are inadequate, alongside policies encouraging price competition and the use of generics, is likely to remain the core approach for achieving these objectives. ■

The research was supported in part by Pharmaceutical Research and Manufacturers of America. The design,

analysis, and composition of the analysis and manuscript were conducted independently and entirely by the

authors, who are solely responsible for any errors.

NOTES

- 1 Cutler D, Deaton A, Lleras-Muney A. The determinants of mortality. *J Econ Perspect*. 2006;20(3):97–120.
- 2 Lichtenberg FR, Virabhak S. Pharmaceutical-embodied technical progress, longevity, and quality of life; drugs as “equipment for your health.” *MDE Manage Decis Econ*. 2007;28(4–5):371–92.
- 3 US House of Representatives Energy and Commerce Committee. 21st Century Cures: an update on the President’s Council of Advisors on Science and Technology 2012 report on propelling innovation [Internet]. Washington (DC): House of Representatives; [cited 2014 Dec 9]. Available from: <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/analysis/21stCenturyCures/20140512PCASTWhitePaper.pdf>
- 4 President’s Council of Advisors on Science and Technology. Report to the president on propelling innovation in drug discovery, development, and evaluation [Internet]. Washington (DC): Executive Office of the President; 2012 Sep [cited 2014 Dec 9]. Available from: <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf>
- 5 Previous studies have confirmed that the pharmaceutical industry places unique importance on patents, relative to other mechanisms to protect intellectual property investments such as trade secrets, complementary sales and service or manufacturing capabilities, and being first to market. See, for example, Cohen WM, Nelson RR, Walsh JP. Protecting their intellectual assets: appropriability conditions and why U.S. manufacturing firms patent (or not) [Internet]. Cambridge (MA): National Bureau of Economic Research; 2000 Feb [cited 2014 Dec 9]. (NBER Working Paper No. 7552). Available from: <http://www.nber.org/papers/w7552.pdf>
- 6 DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. Briefing: Cost of Developing a New Drug; 2014 Nov 18 [Internet]. Boston (MA): Tufts University, Tufts Center for the Study of Drug Development; [cited 2014 Dec 15]. Available from: http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf
- 7 Grabowski H, Vernon J, DiMasi JA. Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics*. 2002; 20(Suppl 3):11–29.
- 8 Scherer FM. Pharmaceutical innovation. In: Hall B, Rosenberg N, editors. *Handbook of the economics of innovation*. Vol. 1. Amsterdam: North-Holland; 2010. p. 539–74.
- 9 Lichtenberg F, Philipson TJ. The dual effects of intellectual property regulations: within- and between-patent competition in the U.S. pharmaceuticals industry. *J Law Econ*. 2002;45(S2):643–72.
- 10 DiMasi JA, Faden L. Competitiveness in follow-on drug R&D: a race or imitation? *Nat Rev Drug Discov*. 2011;10(1):23–7.
- 11 Cockburn IM. The changing structure of the pharmaceutical industry. *Health Aff (Millwood)*. 2004;23(1):10–22.
- 12 Schacht WH. The Bayh-Dole Act: selected issues in patent policy and the commercialization of technology [Internet]. Washington (DC): Congressional Research Service; 2012 Mar 16 [cited 2014 Dec 9]. p. 9. Available from: https://www.autm.net/Bayh_Dole_Act_Report.htm
- 13 National Science Board. Science and engineering indicators, 2014, appendix tables 5-64 and 5-63 [Internet]. Washington (DC): National Science Foundation; 2014 Apr [cited 2014 Dec 14]. Available for download from: <http://www.nsf.gov/statistics/seind14/index.cfm/appendix>
- 14 Treasure CL, Avorn J, Kesselheim AS. What is the public’s right to access medical discoveries based on federally funded research? *JAMA*. 2014;311(9):907–8.
- 15 Nine percent of the drugs approved by the Food and Drug Administration during 1988–2005 (excluding most biologics) had public-sector patents, defined as those that were

- assigned to a government agency or that had a government interest statement, acknowledging government funding. Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Aff (Millwood)*. 2011;30(2):332–9.
- 16 See Zerhouni EA. In the case of Xalatan manufactured by Pfizer, Inc. [Internet]. Bethesda (MD): National Institutes of Health; [cited 2014 Dec 9]. Available from: <http://www.ot.nih.gov/sites/default/files/documents/policy/March-in-xalatan.pdf>
 - 17 Grabowski H, Long G, Mortimer R. Recent trends in brand-name and generic drug competition. *J Med Econ*. 2014;17(3):207–14.
 - 18 Berndt ERF, Aitken ML. Brand loyalty, generic entry, and price competition in pharmaceuticals in the quarter century after the 1984 Waxman-Hatch legislation. *Int J Econ Bus*. 2011;18(2):177–201.
 - 19 Grabowski HG, Long G, Mortimer R. Biosimilars. In: Culyer AJ, editor. *Encyclopedia of health economics*. Vol. 1. San Diego (CA): Elsevier; 2014. p. 86–97.
 - 20 Grabowski H, Guha R, Salgado M. Biosimilar competition: lessons from Europe. *Nat Rev Drug Discov*. 2014;13(2):99–100.
 - 21 James D. FDA committee recommends first biosimilar approval. *Pharmacy Times* [serial on the Internet]. 2015 Jan 7 [cited 2015 Jan 12]. Available from: <http://www.pharmacytimes.com/product-news/FDA-Committee-Recommend-First-Biosimilar-Approval>
 - 22 For example, a model that extended the data exclusivity period for all small-molecule drugs to twelve years found long-term benefits in terms of increased innovation that would benefit future generations. Goldman DP, Lakdawalla DN, Malkin JD, Romley J, Philipson T. The benefits from giving makers of conventional “small molecule” drugs longer exclusivity over clinical trial data. *Health Aff (Millwood)*. 2011;30(1):84–89.
 - 23 Budish E, Roin BN, Williams H. Do fixed patent terms distort innovation? Evidence from cancer clinical trials [Internet]. Cambridge (MA): National Bureau of Economic Research; 2013 Sep [cited 2014 Dec 9]. (NBER Working Paper No. 19430). Available from: <http://www.nber.org/papers/w19430.pdf>
 - 24 Aitken M, Kleinrock M. Medicine use and shifting costs of healthcare: a review of the use of medicines in the United States in 2013 [Internet]. Parsippany (NJ): IMS Institute for Healthcare Informatics; 2014 Apr [cited 2015 Jan 12]. (Free registration required). Available for download from: <http://www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c71ad8c22a/?vgnnextoid=2684d47626745410VgnVCM10000076192ca2RCRD>
 - 25 An earlier study found that challenges by potential generic competitors shortened market exclusivity periods by at least 1.5 years, regardless of whether or not the challenges were successful. Grabowski HG, Kyle M. Generic competition and market exclusivity periods in pharmaceuticals. *MDE Manage Decis Econ*. 2007;28(4–5):491–502.
 - 26 For a contrasting view, see Hemphill CS, Sampat BN. Evergreening, patent challenges, and effective market life in pharmaceuticals. *J Health Econ*. 2012;31(2):327–39.
 - 27 *FTC v. Actavis, Inc.*, 133 S. Ct. 2233 (2013).
 - 28 Li JS, Eisenstein EL, Grabowski HG, Reid ED, Mangum B, Schulman KA, et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA*. 2007;297(5):480–8.
 - 29 Long G, Works J. Innovation in the biopharmaceutical pipeline: a multi-dimensional view [Internet]. Boston (MA): Analysis Group; 2013 Jan [cited 2014 Dec 9]. Available from: http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf
 - 30 Lichtenberg FR. The impact of new (orphan) drug approvals on premature mortality from rare diseases in the United States and France, 1999–2007. *Eur J Health Econ*. 2013;14(1):41–56.
 - 31 Powers JH. Antimicrobial drug development—the past, the present, and the future. *Clin Microbiol Infect*. 2004;10(Suppl 4):23–31.
 - 32 Cox EM. FDA’s multi-pronged approach helps meet the challenge of bringing new and innovative antibiotics to patients who need them. *FDA Voice* [serial on the Internet]. 2014 Jul 28 [cited 2014 Dec 9]. Available from: <http://blogs.fda.gov/fdavoic/index.php/tag/cder/>
 - 33 Food and Drug Administration [Internet]. Silver Spring (MD): FDA. News release, FDA approves new antibacterial drug Zerbaxa: fourth new antibacterial drug approved this year. 2014 Dec 19 [cited 2015 Jan 12]. Available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427534.htm>
 - 34 Ridley DB, Grabowski HG, Moe J. Developing drugs for developing countries. *Health Aff*. 2006;25(2):313–324.
 - 35 Knight Therapeutics [Internet]. Montreal: Knight. Press release, Knight sells Priority Review Voucher to Gilead; 2014 Nov 19 [cited 2014 Dec 14]. Available from: <http://www.gud-knight.com/en/knight-sells-priority-review-voucher-to-gilead>
 - 36 Regeneron [Internet]. Tarrytown (NY): Regeneron. Press release, Regeneron and Sanofi announce plan to use priority review voucher for Alirocumab U.S. FDA submission; 2014 Jul 30 [cited 2014 Dec 9]. Available from: http://investor.regeneron.com/common/download/download.cfm?companyid=REGN&fileid=772356&filekey=1e721856-2d62-4be1-a834-acd4812d9acc&filename=REGN_News_2014_7_30_General_Releases.pdf
 - 37 Kremer M. Pharmaceuticals and the developing world. *J Econ Perspect*. 2002;16(4):67–90.
 - 38 Kremer M, Williams H. Incentivizing innovation: adding to the tool kit. In: Lerner J, Stern S, editors. *Innovation policy and the economy*. Vol. 10. Chicago (IL): University of Chicago Press; 2010. p. 1–17.
 - 39 Stiglitz JE. Scrooge and intellectual property rights. *BMJ*. 2006;333(7582):1279–80.
 - 40 Wright BD. The economics of invention incentives: patents, prizes, and research contracts. *Am Econ Rev*. 1983;93(4):691–707.
 - 41 Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response. Project BioShield annual report to Congress: January 2012–December 2012 [Internet]. Washington (DC): HHS; [cited 2014 Dec 9]. Available from: https://www.medicalcountermeasures.gov/media/33065/pbs_report_2012_hires_final2_508.pdf
 - 42 Booth B, Zimmel R. Quest for the best. *Nat Rev Drug Discov*. 2003;2(10):838–41.