

White Paper

Sustaining Innovation While Ensuring Affordability for Specialty Pharmaceuticals

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Overview

Efforts by public and private insurers to moderate the escalation of specialty drug prices encounter the objection that industry revenues are essential to fund research and development. High prices and profits indeed have generated an impressive pipeline of treatments for previously intractable conditions and have supported over half of total research investments over the past decade. However, prices set at levels sufficient to fund continued innovation are exerting severe financial pressure on insurers, who in turn are defending their budgets through ever more strict formulary exclusions, prior authorization requirements, step therapy, and consumer cost sharing.

Industry profits are only one of several mechanisms available for funding pharmaceutical R&D. Others include governmental, philanthropic, and crowdsourced research grants; targeted tax incentives; innovation prizes for successful product launch or the achievement of development milestones; and licensebased pricing methods such as those negotiated by pharmaceutical firms with low-income nations and proposed for selected classes of drugs in the US.

This white paper describes the challenges created by the current reliance on industry prices and profits to fund pharmaceutical R&D, analyzes the other available mechanisms, and proposes reforms to incrementally expand reliance on the alternatives and thereby reduce the threat to innovation investments that may occur as a byproduct of downward pressure on drug prices.

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Introduction

The remarkable pharmaceutical innovation of recent decades has flowed from sustained investments in research and development (R&D), half of which has been supplied by pharmaceutical industry itself.¹² To sustain these investments, however, manufacturers have imposed dramatic increases in product prices, creating great strain on the governmental programs, insurers, employers, and households. To protect their budgets, purchasers have been erecting administrative and financial barriers to drug utilization. Physicians now labor under onerous requirements for prior authorization, while patients pay high cost shares or forgo treatment altogether. The pushback against rising pharmaceutical prices is gaining sufficient momentum to threaten the flow of funds into the industry and thereby its research investments. Many pharmaceutical firms are pulling back from research on the large therapeutic classes and focusing their efforts on orphan conditions and other niches less subject to competition. Legislators and regulators feel pressure to 'do something' but are unsure whether to criticize the drug industry for high prices or the insurance industry for impeding access.

Resistance to rising drug prices is important to assure the affordability of health care, but must not be done in a manner that undermines the dynamic of research and development. In order jointly to pursue the social goals of affordability and innovation, two complementary strategies must be pursued.

First, it is important to expand alternative funding mechanisms, including governmental grants, tax incentives, and innovation prizes. These mechanisms support forms of research that attract insufficient industry investment and reduce the access problems created by high prices and payer pushback. Unfortunately, these alternatives have struggled to sustain past levels of funding, much less replace industry profits. Governmental support for the National Institutes for Health (NIH) has eroded in inflation-adjusted terms, and even with the new appropriations authorized under the 21st Century Cures Act will not regain 2004 levels. Tax credits for pharmaceutical research have been trimmed rather than expanded. Prize mechanisms have difficulty recruiting potential donors. Alternative funding mechanisms deserve to be expanded but, as a practical matter, will supplement rather than substitute for industry profits.

Second, it is important to change the structure of drug pricing in such a manner as to reduce the burdens imposed on physicians and patients. Alternative pricing structures already are being used in limited circumstances and could be adopted more widely. Some purchasers offer the manufacturer a license fee for access to its drug, supplemented by a per-prescription price set at low generic levels. This 'two-part pricing' structure provides to the manufacturer a return on its research investment while changing the payer's incentive from one of impeding to one of promoting access. Outside the US, some payers and manufacturers agree on a target sales volume for each drug, negotiating one price to be paid per prescription until that target is reached and a lower price to be paid thereafter. This 'budget-based pricing' offers financial predictability to payers while assuring manufacturers a return on their research investments. In the US, some manufacturers agree to set prices at independently-defined 'value-based' levels in exchange for insurer commitments to support appropriate prescription and adherence. This 'access-based pricing' generates a revenue stream to manufacturers equivalent to the status quo of low volumes at high prices.

This paper addresses the serious possibility that high prices and the resulting purchaser pushback will erode the principal funding source for pharmaceutical research, thereby slowing much-needed innovation. It begins by describing the alternative mechanisms for financing R&D, including governmental grants, tax incentives, and innovation prizes, and compares them to the contemporary reliance on product prices and industry profits. It then examines two-part, budget-based, and access-based pricing structures and the incentives they create. In its final section the paper makes recommendations on how the alternative funding sources can be expanded, thereby relieving some of the pressure on profits to finance research, and how the alternative pricing structures can be promoted, thereby reducing the administrative costs of existing market dynamics.



PART 1 Prices and Profits to Fund Pharmacuetical Research



Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2015

Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center

Innovation in the life sciences has been financed so extensively by the industry itself that it is easy to forget that market prices and profits often are insufficient to support investments in research and development. In a competitive industry, there is nothing stopping one firm from imitating and appropriating the results of another's research. The follow-on firm will be able to price its product below that of the innovator, as it has no research expenditures to cover, which will force the innovator to reduce its prices in response. Absent barriers to entry, more competitors will enter the market until prices are driven down to the marginal cost of manufacturing and distribution. At this point no profits remain to finance research, and there is no incentive to invest in the hope of future profits. The fundamental dilemma facing a competitive economy is how to overcome under-investment in research and innovation.³

As a practical matter, many industries do finance R&D from prices and profits, but they do so in ways very different from those observed in the pharmaceutical sector. Firms are able to price above costs, and devote the resulting profits to research, if they can keep the new knowledge secret from would-be competitors or, alternatively, if they can outrun competitors by quickly embodying new techniques into better products that can be sold at premium prices. Trade secrecy and first mover advantages are major sources of research funding in most industries.^{4 5} Trade secrecy and first mover strategies are of only limited effectiveness in the pharmaceutical sector. Restricting information on drug structure and performance would prevent physicians from understanding the product's risks and benefits and thereby would endanger patients. Secrecy would impede the ability of each generation of researchers to build on the insights of those going before, slowing rather than stimulating progress in science and clinical care. For their part, first mover advantages are of limited value where products, including drug molecules, are stable after initial discovery rather than subject to continual modification.

Pharmaceutical research and development has been financed largely by the industry based on special institutional features designed by public policy.⁶ Most important are patent protections against product copying, which permit firms to set prices above costs, and publicly subsidized insurance, which enables patients to access high-priced drugs without personally paying most of the charge.

Policy-based protections for intellectual property prevent firms from reproducing each other's patented discoveries, thereby allowing innovators to price their products at monopolistic rather than competitive levels. All pharmaceuticals, including small molecule chemical and large molecule biologic products, are protected from imitation for 20 years after the original patent filing. This patent protection is extended by special features of the pharmaceutical market. The FDA can extend the term of a drug's patent protection to indemnify the innovator for the years after patent filing that were devoted to satisfying the agency's requirements for market authorization. Additional legislative protections apply to drugs addressing small orphan conditions, where competitors are banned for a period of time from launching a drug addressing the same condition even if it does not violate the incumbent firm's patents.

High prices will only result in high profits, and hence be able to fuel investments in research, to the extent consumers purchase the expensive products. But many specialty drugs target small patient populations and must be priced at high levels per patient to amortize development costs. These prices are far above what most patients can afford to pay. The price mechanism therefore is only able to support research and development to the extent non-patients are willing to pay for the drugs used by patients. They do this by purchasing health insurance, which obtains the bulk of its revenues from premiums charged to healthy enrollees and incurs most of its costs paying for care provided to very sick enrollees. Health insurance only is able keep its premiums low enough to attract healthy enrollees due to taxpayer subsidies and supportive regulations.

The acceleration of price increases

Ironically, the success of industry-funded R&D has created serious challenges for the innovators. Pharmaceutical firms have expanded their research, regulatory compliance, marketing, and distribution capabilities in anticipation of continued innovation and the revenues that flow from them. For as long as new products could be developed in-house or licensed from outside startups, they would generate the profits needed to fund these operations and the financial return expected by investors. Any slowdown, however, would squeeze revenues and imperil growth. Faced with the choice between raising prices and disappointing their investors, pharmaceutical firms have chosen to raise prices, both at the time of new product launch and in annual post-launch increases.

Prices have increased dramatically in the past decade. Between 2005 and 2013, for example, the launch price of new oncology products increased 12% per year without commensurate increases in efficacy, implying an increase in cost per life year gained from \$139,000 to \$207,000.7 Between 2009 and 2015 the prices charged for 30 major specialty drugs more than doubled, with the greatest increases imposed for products facing the least competition or where patients were most reluctant to switch.⁸ Manufacturers have been able to charge substantially higher prices in the United States than in countries where the single governmental payer or tightly regulated private payers are willing to sacrifice access unless they obtain lower rates. ⁹10

The ability to charge prices higher than costs gives pharmaceutical firms incentives to promote their products to physicians and patients, since each pill or vial sold contributes to covering fixed costs and increasing the firm's financial return on its investments. Vigorous promotion is socially desirable for effective products plagued with failures of physician adoption and patient adherence, which constitute a major source of avoidable mortality and morbidity. ¹¹ ¹² But financial incentives can induce pharmaceutical firms to promote their products to patients where the evidence of benefit is weak, since the markup of price over cost is the same for all prescriptions. Pharmaceutical firms often 'detail' their products to physician offices, sponsor advertisements in clinical journals, subsidize professional education programs, and offer honoraria to physicians willing to speak at professional meetings. Products are promoted to patients through 'direct-to-consumer' advertising, free samples, and subsidies for advocacy organizations.

The purchaser pushback

The revenues from high prices and aggressive promotion support manufacturers' investments but, simultaneously, raise expenditures for purchasers. Private insurers and PBMs closely monitor trends in pharmaceutical claims since their profits derive from the difference between the premiums they charge to their customers and the spending they are required to make for covered services. The purchasers' attention to pharmaceutical price and utilization is sharpened by the uneven distribution of patient spending, especially for rare conditions requiring high-priced specialty drugs. Insurers that offer generous coverage for specialty drugs find themselves attracting the sickest enrollees who are most in need of those products. This 'adverse selection' forces them to raise premiums to cover their higher claims costs and, in turn, threatens their ability to compete with insurers who attract fewer patients needing expensive drugs. As some insurers raise barriers to patient access, others are forced to follow suit or face a spiral of rising costs and declining enrollment. Under provisions of federal law, insurers are prohibited from denying coverage to individuals with serious medical conditions, but they achieve the same result through prior authorization and cost sharing requirements that apply to all enrollees but disproportionately affect those needing expensive medications.

Purchasers initially imposed cost sharing on consumers with the intent of inducing them to shift from expensive brands to cheaper generics, focusing on therapeutic classes where products had lost their patent exclusivity. This now has extended to specialty drugs facing few competitors. Patient self-administered drugs managed through the pharmacy benefit now often are placed in formulary 'tiers' that require 20-50% coinsurance rather than the modest dollar amounts required for non-specialty drugs. Coinsurance requirements are limited by annual out-of-pocket maximums, but these have risen rapidly in recent years and are absent altogether for many Medicare beneficiaries. Physician-administered drugs managed through the medical benefit often face both coinsurance and deductibles whose levels also have been rising rapidly. In 2016, 48% of Medicare enrollees were subject to percentage coinsurance and 23% of individuals with employment-based insurance faced an annual deductible of \$2000 or more.^{13 14} These cost sharing requirements are linked to the list price of the drug rather than to the net price that the insurers pay after negotiating rebates from manufacturers. Cost sharing has been associated with drug abandonment, discontinuation, and gaps in treatment for patients suffering from rheumatoid arthritis,¹⁵¹⁶ multiple sclerosis,17 psoriasis,18 chronic myeloid leukemia 19, and a broad range of cancers treatable by oral oncolytic agents.²⁰ Cost sharing also influences the financial wellbeing of patients, with detrimental effects on household finances as well as the ability to afford medical services. 21

Consumer cost sharing has been supplemented by increasingly rigorous administrative oversight of physician prescription choices. In 2016, for example, 82% of firms with 200 or more employees required prior authorization and 68% required step therapy for specialty drugs.²² Some forms of utilization oversight and management are appropriate to ensure that the right patient is the one getting the drug. This may include requirements that the patient falls within the FDA-authorized indication (e.g., is on-label) or within the clinical guidelines developed by authoritative professional societies. Driven by the pressure to stay within their budgets and not succumb to adverse selection, however, purchasers have been pushing

utilization management beyond the domain of clinical appropriateness. Some policies deny coverage to patient populations that fall within the FDA label or evidence-based guidelines. For example, 69% of prior authorization policies for rheumatoid arthritis and 46% of policies for multiple sclerosis used by the 10 largest health insurers were found to be tighter than the corresponding FDA label.²³²⁴ Other policies deny coverage by age (e.g., children) or severity of illness (e.g., advanced liver disease for patients infected by Hepatitis C).

The importance of the criteria used for prior authorization is matched by the importance of the process and documentation required. Many purchasers rely on telephone and fax requests, inevitably a cumbersome and error-prone process. Demands that physicians document their authorization requests with laboratory tests, photographs, radiographs, and medical records impose significant administrative burdens and reduce physician willingness to prescribe expensive drugs. A survey of 1000 medical practices conducted in December 2017 found 84% to report the burden of prior authorization to be high or extremely high. One third reported that the burden had increased somewhat in the previous five years and half reported the burden had increased significantly. ²⁵

These financial and administrative controls on specialty drugs can be very effective. For example, half of authorization requests by physicians for PCKS9 inhibitor drugs, which reduce harmful cholesterol for patients intolerant or non-responsive to traditional statin medications, were denied by the prior authorization systems. Of those prescriptions that did meet the purchasers' criteria and were authorized, one third were never filled by the patient due to cost sharing requirements. ^{26 27}

The war of all against all

The purchaser pushback against high drug prices has engendered its own pushback from pharmaceutical firms to support their sales volumes and revenues. Manufacturers support consumers' financial access through copay cards and other financial initiatives that negate some of the cost sharing obligations. Medicare prohibits direct industry subsidies for its beneficiaries, viewing it as a financial inducement, and so manufacturers donate funds to independent foundations that subsidize Medicare beneficiaries. Manufacturers' support physicians' ability to navigate prior authorization and step therapy requirements by researching each insurer's criteria and the documentation needed to satisfy them. These consumer and physician support programs are expensive, and must be financed by manufacturers from their next round of price increases. The vicious cycle of high prices and product promotion, utilization management, consumer cost sharing, and further price increases is drawing ever more negative attention. Polls now consistently identify drug prices, consumer cost sharing, and utilization management as sources of popular discontent. Not surprisingly, legislators and regulators are proposing increasingly harsh interventions.

The traditional framework for funding pharmaceutical research and development, based on prices and profits, clearly is under pressure. In seeking an alternative approach to sustaining innovation, it is important to consider alternative sources of funding and changes in the structure of pricing itself.

PART 2 Alternative Mechanisms for Funding Research



Industry profits are the largest but by no means the sole source of funding for pharmaceutical research, and market exclusivity is not the only policy framework designed to promote innovation. Three other funding mechanisms, each based on its own set of policy principles, complement the exclusivity framework. These include governmental and philanthropic grants, tax credits and targeted tax reductions, and innovation prizes. In recent years, these alternative funding sources have declined in relative importance and the innovation ecosystem has tilted towards greater reliance on industry. Some policy analysts have proposed a radical tilt in the other direction, towards a complete 'de-linkage' between research funding and industry revenues. Others support an expansion of non-price funding to better supplement, rather than substitute for, industry profits. For its part, economic theory argues that patents, grants, tax incentives, and prizes offer distinctive advantages for supporting innovation in different circumstances.²⁸²⁹

RESEARCH GRANTS

Grants made to universities, scientific institutes, and teaching hospitals constitute the largest source of pharmaceutical R&D funding after the profits earned by industry. The majority are devoted to basic science, which constitutes the foundation for all subsequent innovation. Indeed, increased public grant-making stimulates increased industry investments. ³⁰ Every one of the 210 new drugs approved by the FDA between 2010 and 2016 was derived at least in part from published scientific research supported by the National Institutes for Health (NIH).³¹

In addition to funding basic science, NIH supports 'applied', 'clinical,' and 'translational' projects.³² The definitions of these categories overlap, but they all constitute incremental moves from research towards development. In 2017 half of the total NIH budget was devoted to basic biomedical and behavioral research and half to 'applied' research, implying \$16.4B and \$15.1B in funding for each.³³ Separately, the NIH reported that that it devoted \$12.7B to clinical research and an additional \$3.6B to clinical trials.³⁴ In 2017 the various NIH centers and institutes reported that they invested \$2.2B in 'translational' as distinct from 'basic' research.³⁵

Total grant funding has continued to grow, but at a slowing rate, and since 2004 has declined in inflation-adjusted terms. Governmental grants have fallen behind industry investments, declining from 54% of the total in 1994 to 42% in 2012.³⁶ The 21st Century Cures Act authorized additional NIH funding but will only slow and not stem this erosion.³⁷ Philanthropic investments in medical research have grown but will never achieve the scale achieved from federal sources.

The erosion of NIH and other governmental support puts at risk the historical US dominance in the global life sciences industry.^{38 39} Some nations, especially China, have increased research grant-making in recent years as part of their efforts to expand their pharmaceutical industries.⁴⁰ The combination of declining US and increasing foreign grant-making has led to a decline in the US share of global health-related investments in research and development from 57% in 2004 to 49% in 2012.⁴¹

Research grants offer some important advantages over industry profits for funding research. Most obviously, grants can be targeted at questions in basic science, where answers typically are difficult to obtain and commercial applications are uncertain. These projects obtain little industry support because investors would require an unachievable rate of return to compensate for the high risk and delayed reward. Private funding for these projects suffers from collective action failure, with no one firm willing to invest because its competitors will have access to the findings without contributing the financing. In economic parlance, investments in basic research are a public good, and best are funded by governmental and philanthropic sources.

However, research grants need not focus exclusively on basic science, as evidenced in the substantial NIH funding for applied, clinical, and translational projects. They can fund the development of products that have limited commercial value, and hence will generate little industry investment. These can include treatments and preventive measures for illnesses predominately afflicting low-income nations, such as malaria and dengue fever. They can target products that will only be used in very low volumes or held in reserve altogether, such as vaccines for global pandemics or antibiotics for drug-resistant infections.

Research grants are of value not merely for some types of conditions but for some types of firms. Whereas large and diversified pharmaceutical corporations can fund the development of tomorrow's innovation from profits off yesterday's, universities and the startup firms launched from universities typically lack an analogous cash flow. Startups can obtain cash infusions from venture capital investors, but these demand substantial equity in exchange, whereas grants constitute 'non-dilutive' cash injections. Research grants support the nation's life sciences ecosystem in its competition with other nations for firms, jobs, sales, and tax revenues. Grants typically are made to organizations and institutions based in the United States, even if the research projects themselves include global components.

Research grants suffer from important limitations as a source of funding, which explains why they have not displaced other sources. Their major challenge is to sustain taxpayer support in the context of competing priorities and budgetary fatigue. Moreover, the responsiveness of grant funding to governmental rather than market priorities can be a liability as well as an advantage. NIH grant-making at times seems to prioritize topics that catch the imagination of Congressional entrepreneurs, often expressed as 'wars' or 'moonshots' or 'imperatives', rather than reflecting a sober assessment of the state of the science.

Grants reimburse the inputs rather than reward the outputs of research. Grant recipients often define success for one project as obtaining a foot up on obtaining subsequent grant funding, generating peer-reviewed publications rather than developing safe and effective drugs. Funding agencies are subject to capture by politically-potent recipient organizations, such as academic medical centers, and by established researchers to the detriment of new researchers pursuing potentially disruptive ideas.

TAX INCENTIVES

In addition to directly supporting pharmaceutical research thru grant-making activities, the government supports it indirectly through the tax code. Tax incentives have a political advantage in that they do not need to be appropriated anew each year. However, they reduce revenues and hence indirectly require that additional taxes be raised, expenditures on other programs be reduced, or the budget deficit be allowed to increase. But these downstream implications are not clearly visible to the skeptical taxpayer.

The principal distinction in tax incentives is between credits for research-related expenditures and reductions in tax rates on profits derived from those expenditures. A secondary distinction is between policies that target the pharmaceutical sector and those that affect all industries.

Tax credits for research expenditures

Tax credits offset some of the costs of research and development without those expenditures needing to have resulted in a successful new drug launch. In this sense tax credits resemble research grants more than to innovation prizes, because prizes typically are awarded to successful innovations. Tax credits are of particularly high value to startup firms that cannot fund research from profits because they lack profitable products.

The federal research and experimental tax credit rewards businesses for an increase in their spending on research. A US corporate taxpayer must determine the increment of its current-year qualified research expense (QRE) over a computed base amount and is able to claim 50% of these expenses for special tax treatment. QREs cover the full value of wages and supplies devoted to research by the taxpaying firm itself, plus 65% of any research expenditures made by outside firms (such as Contract Research Organizations in the case of pharmaceutical firms). All the claimed expenditures must be for work done in the United States. Some individual states also provide a tax credit for research expenditures incurred within their boundaries. For example, California offers a 15% credit for research expenditures made within that state. ⁴²

The Orphan Drug Act (ODA) of 1984 included a 50% targeted tax credit for clinical testing and other expenditures related to the development of drugs addressing conditions affecting fewer than 200,000 patients in the United States. There have been various legislative attempts to create analogous credits for research related to the development of antibiotics, given the dearth of investment and the rise of drug-resistant bacterial strains, but to date they have not been adopted.

Supporters of the ODA tax credit claim that it has contributed significantly to the blossoming of research and to new product launches. Whereas there were almost no drugs developed for orphan conditions in the years prior to passage of the Act, the following decades have witnessed FDA approval of 3,976 orphan product designations (one drug may have indications for several orphan conditions). Global orphan drug revenues summed to \$60 billion in 2008 and are expected to climb to \$209 billion by 2022, at which point they will account for 21% of global pharmaceutical sales.43 It is unclear how much of the surge in orphan drug development can be attributed to the targeted tax credit as distinct from other supportive policies. The ODA also offered research grants, waived FDA product registration fees, and, most importantly, extended the period of regulatory market exclusivity from five to seven years. Market exclusivity has permitted manufacturers to set prices for orphan drugs at levels five times higher than those for other branded medications.

The orphan drug credit has been very popular with the pharmaceutical industry. Tax claims submitted under the ODA increased five-fold between 2005 (\$280 million) and 2014 (\$1.5 billion).⁴⁴ Targeted credits do face opposition. Conservative critics argue that targeted credits constitute an example of the government picking winners and losers among industries, and should be replaced by non-targeted credits and rate reductions.⁴⁵ Liberal critics argue that the

vague criteria for claiming ODA credits have allowed drug firms to gain significant tax advantages for drugs that went on to be used by millions of patients.⁴⁶ In the 2017 tax reform legislation, the ODA tax credit was reduced from 50% to 25% and was almost eliminated altogether, as the Republican Congressional majority sought savings with which to finance the more general corporate tax reduction. ⁴⁷

Tax reductions: the patent box

Some policy analysts favor reductions in the taxes levied on corporate profits derived from innovation-related products. ⁴⁸ Many nations outside the US have sought to attract firms conducting pharmaceutical research and manufacturing by offering a significantly lower tax rates on their profits. ^{49,50} The definition of innovation-related profits varies considerably, from narrow versions explicitly linked to patent royalties to broad versions encompassing almost any spending that develops or improves products. As these lower tax rates typically are represented on corporate tax forms as a special box to be checked, they often are referred to as a patent or innovation 'box.'

Innovation and patent boxes enjoy bipartisan support in the United States but have yet to be broadly adopted. Patent boxes face opposition from industries that do not invest in research and fear that targeted reductions will render more difficult the passage of across-the-board tax cuts. In contrast, the pharmaceutical industry has consistently supported the adoption of a patent box.⁵¹ In 2018 the US tax code was revised to reduce taxes on the profits derived from patents domiciled in other nations, as part of an effort to encourage US firms to repatriate overseas profits and the commercial activities that generate them. ⁵²

Patent box skeptics argue that targeted cuts today will necessitate tax increases or expenditure decreases tomorrow, and will reward most handsomely those firms that have aggressively domiciled patents in low-tax nations. These skeptics favor expansion of the tax credit over reductions in the tax rate.⁵³ The European Union has sought to limit the adoption of targeted corporate tax cuts in the effort to dampen competition among member nations for research and manufacturing jobs.

INNOVATION PRIZES

Innovation prizes historically have been used as both a substitute for and a complement to intellectual property rights to reward and stimulate innovation, not merely in the pharmaceutical sector but across the economy. Prizes differ from research grants and tax credits in that they are awarded for the successful output of research activities, not as reimbursement for initial investments. As a mechanism for encouraging research, innovation prizes differ from industry profits in that they are awarded independently of the volume of sales. They do not create incentives for recipient firms to promote their product nor for purchasers to erect barriers to utilization. Reliance on innovation prizes favors pharmaceutical firms with capabilities in research and development, whereas reliance on industry profits favors those with capabilities in sales and marketing. A reliance on profits to fund investments induces research-oriented startups on sell or license their innovations to marketingoriented incumbent firms, with a potential dampening of the startups' entrepreneurial zeal and ethos of experimentation. Prize does not affect prices etc.

Prize mechanisms require clear success criteria for the prize to be awarded, limiting their use for early stage and blue-sky initiatives where goals are unclear but ambitious. The criteria must be clear to potential recipients and to judges in the case of disagreement and litigation. This challenge can be mitigated by linking prizes to developmental milestones rather than to final products.

The paradigmatic innovation prize is a sum promised by a governmental or philanthropic organization to any biotechnology or pharmaceutical firm that successfully achieves a pre-defined target, such as FDA approval of a drug for a previously untreatable condition. These prizes typically are made for treatments where the potential for eventual profitability is low due to a small patient population or to insufficient patient ability to pay.

Some policy analysts have viewed innovation prizes as substitutes for profits as a source for research funding, and have advocated a policy of 'de-linkage'. ⁵⁴ They emphasize that the awarding of innovation prizes does not impede the ability of drug firms to set high prices and obtain high prices unless some modification is made to intellectual property rights. The spirit of de-linkage is evident in arguments that citizens are 'paying twice' when they support NIH grants with their tax dollars and then pay high prices for access to the drugs derived from those grants. In this view, the NIH should use its 'march in rights' to require moderation for prices of drugs developed through governmental grants.⁵⁵ Advocates of de-linkage see prizes as the best alternative to profits as a source for research funding, of special importance in the context to efforts to enforce patent rights in global trade agreements. 56 57

The logic of innovation prizes, though not of de-linkage, has been used extensively by the FDA in structuring its regulatory processes and priorities to support R&D investments. Data requirements for market authorization add considerable delay to a product's launch, thereby reducing the return on the financial investments made in its development. Any reduction in these expenses is of considerable value to drug developers. The agency offers lighter evidence requirements and accelerated review as a prize for the development of drugs addressing therapeutic areas of high unmet need or containing novel mechanisms of action.58 The value of these regulatory prizes was expanded through legislation allowing recipient firms to sell them to other firms that had products likely to earn especially high profits. However, widespread use of these accelerated review pathways has raised concerns that the agency is sacrificing patient protections in its eagerness to offer regulatory prizes. 59

FDA also offers prizes in the form of targeted extensions of a drug's market exclusivity, the period during which recipient firms can charge prices above competitive levels. Some policy observers have proposed that firms receiving exclusivity extensions be allowed to sell them to other firms in a manner akin to the tradeable vouchers for accelerated review. Tradeable extensions of market exclusivity would be exceptionally valuable prizes, as recipients would sell them to firms whose blockbuster medications face competition from generics and biosimilars. By implication, of course, tradeable extensions of exclusivity would accentuate the problems generated by high drug pricing. ⁶⁰

Innovation prizes can be conceptualized broadly as including license contracts and product acquisitions offered to startups by established pharmaceutical firms and the internal funding allocations of research-based pharmaceutical firms. Wealthy 'angels' and venture capital partners structure their investments in startups according to the achievement of developmental milestones, in a process sometimes referred to as 'evergreen funding.' 61 The logic of prizes carries over to developmental programs managed internally by large firms. These firms fund internal projects using the cash flow from their existing portfolio and must be disciplined in deciding which initiatives to pursue and which to abandon. Research teams, typically structured around particular molecules or therapeutic indications, are subject to periodic assessment of future expected sales, and continued funding is predicated on demonstrating net present values that exceed the firm's cost of capital. Research programs that achieve specified milestones are rewarded with another budgetary allocation, while those failing to achieve their goals face de-funding.

PART 3 An Alternative Structure for Pharmaceutical Pricing



The policy framework of market exclusivity, and the high prices and profits derived from it, has caused a backlash from purchasers and patients. Alternative funding options, including research grants, tax incentives, and innovation prizes will never achieve the scale to supplant investments by industry itself. It is important to explore ways in which the structure of pricing could be modified to sustain its funding for innovation while moderating the adverse impacts.

Two-part pricing

Economic theory and the experiences of other industries support a distinct structure of prices for products that are created with high fixed but low marginal costs. ⁶² An effort by firms in those sectors to load their fixed costs onto each unit sold requires that prices far exceed marginal costs, in turn reducing consumer demand and social welfare. The textbook solution is for buyers and seller to contract for two prices, a license fee that contributes to covering the manufacturer's fixed costs and a per-unit fee that covers marginal costs. In the pharmaceutical sector, manufacturing and distribution account for only 10-20% of total costs, with the low end represented by traditional chemical products and the high end by more complex biologics. It is the loading of the remaining fixed costs onto unit prices that is responsible for the purchaser pushback.

License fees and two-part pricing do not require modification of the existing policy framework of patent exclusivity and, indeed, the value of the license depends on the maintenance of that framework. This is a political advantage over de-linkage proposals, which face heated opposition from the pharmaceutical industry. There is no reason to assume that two-part pricing would reduce the industry's ability to extract commercial benefit from its innovations and thus to continue funding its research. However, two-part pricing could offer savings to purchasers. Once their incentive to fight each additional prescription had been removed by the lowering of the drug's per-unit fee to a generic level, purchasers would have no incentive to impose prior authorization requirements on physicians and cost sharing requirements on patients. In turn, pharmaceutical firms would reduce their funding of expensive physician practice and consumer copayment support programs. The reduction in these insurer and pharmaceutical expenditures would allow purchaser

payments to fall without reducing net pharmaceutical firm revenues. The volume of drugs sold would increase after removal of access barriers, though the additional revenues to the industry would be modest because they would be priced at generic levels. The physician would face fewer administrative hurdles and the patient less cost sharing. Everyone could win.

License fees and two-part pricing already are being used in limited contexts and have been proposed for a broader set of indications where the conventional one-part pricing performs poorly.

Payment for a drug's fixed costs of development separately from its marginal costs of production lends itself particularly well to contexts where a third party is willing to cover the fixed costs on behalf of the actual users. This prevails in some low-income nations, which traditionally have only purchased generic drugs but now seek access to treatments that still have patent protection. For some infectious diseases, wealthy nations and philanthropies are willing to pay the brand value of the drug, either through a license or by topping up the payment that the recipient nations pay for each unit used. Some global pharmaceutical manufacturers are willing to donate the value of their drug's intellectual property, in effect setting a license fee at zero, and then allow the per-unit fee to be determined by competition among generic manufacturers. Gilead has developed this model for low-income nations in Africa with its Hepatitis C and HIV drugs, allowing the per-unit fee to be determined by competition among generic drug manufacturers in India.63 Pfizer has applied a variant of this model for its cancer drugs in Africa, donating the license fee but imposing a per-unit fee high enough to cover marginal costs. 64

Two-part pricing also works well for drugs where the volume of sales is expected to be very low. The most important contemporary instance is for antibiotics capable of treating bacterial strains that have developed resistance to existing treatments. New antibiotics would be used only in contexts of drug-resistance or held completely off the market until needed for a pandemic, implying very low or even zero sales. Research investments for such drugs cannot be financed from profits and, indeed, many pharmaceutical firms have abandoned antibiotics research programs despite the high public health need. Several prominent analyses have advocated a license approach, funded by taxes from donor nations or from the pharmaceutical industry itself (individual firms could choose to conduct research or pay a fee that would support research by others). ⁶⁵ The commissioner of the FDA has proposed a license fee approach for hospitals that need backup access to antibiotics in case patients develop resistance to traditional drugs. ⁶⁶

Given its theoretical appeal, why has two-part pricing not already been adopted more broadly? In part, it has. Insurers charge enrollees a copayment for each prescription filled, analogous to the per-unit fee levied as part of two-part pricing, and then pay the larger part of the drug's cost themselves, analogous to the license fee. Indeed, the viability of the specialty drug industry depends on this two-part pricing; if patients were exposed to the full price of a branded drug they would fill very few prescriptions. The challenge now facing the industry stems precisely from the erosion of two-part pricing as insurers limit their contributions through stricter coverage criteria and shift a greater part of the cost onto the patient.

Key factors in negotiating license and per-unit fees

The determination of the per-unit fee in two-part pricing models would be straightforward, since the equivalent is already to be found in the prices for generic drugs that have lost patent exclusivity. Economic theory argues that manufacturers should set the per-unit price at a level sufficient to cover, but not exceed, the marginal costs of manufacturing and distribution. Prices above marginal costs will generate purchaser pushback, as observed in the contemporary drug market, and should only be charged if the purchaser wants to create incentives for manufacturers to engage in marketing activities. Manufacturers of generic drugs do not invest in product promotion. Per-unit prices should only be set below marginal costs in contexts of significant adherence failure, as otherwise they will facilitate over-consumption and waste. The determination of the license fee in two-part pricing models is inherently more complex, though not more complex than price determination for patent-protected drugs in the contemporary market. License fees would be negotiated between the manufacturer and each payer and would vary depending on the expected volume of use, the drug's comparative clinical and cost effectiveness, and the extent of competition within the therapeutic class.

License fees would vary across payers depending on their ability to pay, whereas per-unit fees likely would be uniform (marginal costs for the manufacturer do not vary substantially depending on who is the purchaser). Purchasers representing low-income nations would negotiate lower license fees, similar to the manner by which they negotiate lower prices in the current drug market. Similarly, payers representing low-income populations within wealthy nations, such as Medicaid managed care plans in the United States, would negotiate or be statutorily eligible for lower license fees that those available to payers representing commercially insured populations. The per-unit fee charged for a drug could be the same across payers.

The total compensation to the manufacturer would be the sum of the license fees paid by each purchaser, plus revenues from per-unit fees. Each purchaser's license would be proportional to its expected volume of use, measured by demographics, epidemiology, and other criteria. In the contemporary pricing structure, each purchaser contributes to the manufacturer's total revenue in proportion to its scale, since it pays the fixed-cost mark-up on each dose purchased. Under two-part pricing, the license fee would be proportional to expected rather than actual volume. Its contribution to covering fixed costs (the license fee) would not increase each time a new patient is prescribed the drug, and so the purchaser would not face the incentive to limit volumes through prior authorization and cost sharing.

The value of access depends on the clinical and cost effectiveness of a drug compared to other available treatments. Purchasers thus would be willing to pay, and manufacturers would be certain to demand, higher license fees for drugs with strong supportive evidence of safety, efficacy, reductions in downstream costs, and other dimensions of performance. This is analogous to negotiations in the contemporary pricing context, which formally or informally incorporates the results of health technology assessments.

The license fee also will vary according to the availability of other drugs for the same clinical condition. License fees will be lower in competitive therapeutic classes because purchasers can threaten to rely exclusively on one drug and not purchase a license for competing drugs. License fees likely would be re-negotiated annually to respond to changes in competitive dynamics, such as when a new drug is launched into a class, an incumbent drug loses its patent protection, or one product proves more popular than the others among physicians or patients. License contracts between manufacturers and purchasers could extend for multiple years to support collaboration on patient education, product distribution, or other aspects of mutual interest even as the license fee itself was reconsidered annually. Multi-year contracting is common in markets where efficient production and distribution depend on long-term collaboration between buyers and sellers.

PART 4 Reforming the Funding of Research & Development



Each of the four mechanisms for funding research, including grants, tax incentives, innovation prizes, and market prices, should be reformed with the goal of sustaining investments in research while attenuating the contemporary war of all against all.

First, it is important to sustain the overall level of funding, not sacrificing health improvements in the future for budgetary savings in the present, and to rely more on sources other than industry profits. An expansion of governmental and philanthropic grants, tax incentives, and innovation prizes would reduce pressure on industry to fund research with its own revenues and thus to increase its prices. These alternative sources favor basic science and early stage development projects where uncertainty is great but the potential for major breakthroughs is large.

Second, it is important to change the structure of pricing to create the appropriate incentives. Industry's quest for research funding should not stimulate purchasers to raise impediments to utilization, burdening physicians, hurting patients, and generating costly industry countermoves. The pharmaceutical market and its regulation are so inefficient that even a modest realignment of incentives could substantially reduce transactions costs and permit more research to be funded at a lower net cost.

Research Grants

Grant funding from governmental and philanthropic sources plays an essential role in the innovation ecosystem. Longterm investments provide a non-replaceable foundation for the life sciences industry and for improvements in the health of the population. Sustaining grant funding is essential, at a minimum by ensuring that budgetary allocations for the NIH and other health-related agencies keep up with inflation. This will not be a simple task. For example, the NIH will require a budgetary augmentation of \$11.6 billion per year just to return to 2003 levels in inflation-adjusted terms.⁶⁷ The effectiveness of public funding could be enhanced by using a more diverse set of instruments and by better targeting the most innovative sectors of the ecosystem. • Direct grants to innovative firms. Most research grants are directed at universities, independent research institutes, and hospital-based organizations. These institutions have the scientific staff and organizational capabilities to conduct laboratory research and clinical trials. However, they are for the most part not directly involved in drug development, and often lack the expertise to bridge the gap between an interesting molecule and a marketable product. A greater share of research grants should be directed at pharmaceutical firms themselves, especially the startups that account for a disproportionate share of innovation. Grants targeted to early stage firms would supplement the benefit those startups already receive from research tax credits.

• **Grants as equity investments.** The grants-as-gift model should be supplemented with a grants-as-investment model in which research funding is offered in exchange for an ownership share in commercially viable research outcomes. Under the provisions of the Bayh-Dole Act of 1980, universities may commercialize research breakthroughs funded by governmental grants. This ability to leverage grants into income has contributed enormously to the vitality of the US life sciences sector. The NIH itself should expand its share of the commercial value of innovations funded by its grants. The financial return on this invested equity would replenish part of the Institutes' budget and attenuate their need for additional taxpayer support.

• Internal funding as equity investment. The NIH should commercialize the intellectual property obtained from its intramural research programs, viewing budgets for these programs in part as equity investments with an anticipated financial return. ⁶⁸ This would provide a revenue stream to the Institutes and unlock latent entrepreneurial energies in the agencies. ⁶⁹

• **Grants as subsidized loans.** Grants-as-gifts should be supplemented with grants-as-loans. Early-stage pharmaceutical startups face great hurdles in obtaining loans from commercial lenders because they have few tangible assets that could be appropriated in the case of default. Governmental and philanthropic entities should focus on this commercially risky but scientifically important set of firms,

acknowledging that the rate of return will be lower than that required by commercial lenders. Grants-as-loans can create positive incentives for recipients because the repayment obligation focuses attention on potentially profitable projects. The loan repayments also will attenuate the Institutes' need for additional taxpayer support.

• **Grants as innovation prizes.** Grants made to support research expenditures should be supplemented by grants to reward successful research outcomes, in the form of innovation prizes awarded at the time of product launch or for the achievement of developmental milestones.

Tax Incentives

There is little appetite evident in Congress to alter the structure of corporate taxes to favor research-oriented firms and industries. The 2017 tax reform reduced the orphan drug tax credit and rejected proposals for special rate reductions in research-oriented industries, preferring reductions for the entire corporate sector. Targeting increases the complexity of the tax code and creates opportunities for socially unproductive lobbying and loopholes. However, the case is strong for favoring investments in innovation as particularly worthy expenditures whose benefits to society exceed their benefits to the firms themselves. The 2017 corporate tax reform was dominated by a concern for competition among nations to attract multi-national firms and the jobs, output, and revenues they offer. When business tax reform next gains political attention, it should emphasize incentives for stimulating knowledge-based industries with high growth potential, of which the life sciences are an outstanding representative. There is no justification for the equal tax treatment of industries whose decline is inevitable and industries that are essential to a high-productivity and high-wage economy.

• **Expand research tax credits.** Research tax credits offset part of firms' expenditures on staff and materials engaged in research, reducing the need to fund those investments from past profits or by borrowing against the future. The federal research and experimental expenditure credit is a valuable support to the economy and is particularly valuable for startups that lack profits from existing products. Targeted

research credits, such as those authorized through the Orphan Drug Act, can direct those incentives at domains of greatest unmet social need. The orphan drug credits have been an important component of one of the most successful tax policy initiatives in recent decades, as evidenced by the dramatic increase in new product launches for drugs targeting small patient populations. The reduction in those credits as part of the 2017 tax reforms was unfortunate. Research tax credits for life sciences investments should be expanded and targeted at domains of high unmet need such as drugs for antibiotic resistant infections and vaccines against potentially global pandemics. The targeting should be defined narrowly and reviewed periodically; as evident in the experience of the orphan drug act, tax preferences tend to spread beyond the intended areas of greatest need. ⁷⁰

• Resist proposals for 'patent box' reductions in taxes on profits. In contrast to research tax credits, 'patent box' and other targeted reductions in the rate of tax on profits add to the complexity of the tax system without ensuring the funds reach the most innovative firms. Whereas research tax credits favor innovative startups, cuts in taxes on profits favor established firms with an aggressive policy of pricing and promotion. Patent box tax cuts inevitably generate disputes as to which profits fit the relevant criteria and whether patents are a valid measure of innovation.

Innovation Prizes

Innovation prizes constitute a promising but underused mechanism for funding R&D. The main challenge has been obtaining sufficient contributions. When research is funded from profits, contributions are enforced through limitations on access. Purchasers and patients only can access the drugs if they are willing to pay the prices demanded. There is no analogous enforcement mechanism for ensuring contributions to prize funding. As a patient, each individual benefits from the innovation regardless of whether he or she contributes, but as a taxpayer and consumer each has the incentive to hope others will bear the load. An analogous 'collective action failure' plagues efforts to convince nations to support innovation prizes addressing global health challenges. Expanding the role of innovation prizes for funding pharmaceutical research thus requires a creative expansion of the contributors and contributions.

• Expand governmental support for innovation prizes. Innovation prizes sometimes are conceptualized as a private sector alternative to governmental research grants, but taxpayer funds are essential to any expansion of prize mechanisms. As noted above, the NIH and other agencies should allocate a larger portion of their total funding as payments for defined milestones rather than merely cover research regardless of its success.

• Expand prize funding by charitable organizations and individual philanthropists. Health-related philanthropies contribute significantly to funding research. These organizations are particularly well suited to structure their support in the form of innovation prizes. They often have limited capabilities to review complex research proposals, compared to the peer-review committees organized by the NIH. Prizes contrast with grants in specifying the desired outcome of the project but leaving its conduct and methods to the potential recipients. Charitable organizations and individual philanthropists have an interest in publicizing the impact of their efforts, which is another feature of prizes that contrasts to grants and tax incentives.

• Expand prize funding from charitable events and crowdsourcing. Funding for innovation prizes need not derive solely from governments and large philanthropies, but can be raised via small donations from large numbers of people. The potential latent in broad-based prize funding is evident in charitable events such as races and contests to support research on illnesses that resonate in the population, such as breast cancer, HIV, and childhood diseases. The internet has created important new opportunities for 'crowd-sourced' funding in which appeals sponsored by celebrities or survivors are disseminated through social media. Beyond the immediate financial benefit there can be a significant cultural benefit to broad-based prize funding. The voluntary nature of fundraising initiatives can engage the enthusiasm of participants who might view tax expenditures or incentives for research as just one more instance of bureaucratic over-expansion.

The Structure of Pricing

The policy framework for supporting pharmaceutical research and development, centered on patent protection and insurance subsidies, continues to generate a rich pipeline of innovation. However, the loading of fixed costs onto the price of each prescription is leading to a breakdown of the coverage essential for drugs to be affordable to patients. It is imperative to change the structure of the prices paid by insurers to manufacturers. This requires changes in traditional one-part pricing and, more importantly over the longer term, incremental moves towards two-part pricing.

Reforms to one-part pricing

One-part pricing distorts the purchaser's and the patient's choices by loading onto each prescription a portion of the fixed costs of research and development. This is particularly undesirable in contexts where the price markup does not reflect the drug's clinical and cost effectiveness relative to alternative therapies but, rather, the inefficiencies in the market and regulatory environment. The ills of the contemporary drug pricing system have been well diagnosed, and numerous sensible remedies have been proposed.⁷¹ There is no need here to review the work that has been done, but a few key interventions deserve emphasis.

• **Removal of regulatory barriers to competition.** The high price charged for a drug may not be based on exceptional safety and efficacy, but rather may reflect the strategic exploitation of supply bottlenecks, manufacturing capacity limitations, FDA safe-use (REMS) protections, or regulatory requirements that insurers cover all competing drugs in a therapeutic class. The alignment of price with value will require the removal of regulations that limit competition.

• Promote market entry by generic and biosimilar products. The patent framework is designed to provide market exclusivity to innovative drugs for a defined period and then allow competitors to produce and market copies. The eventual loss of exclusivity transfers the value of the innovation from the producer to the consumer, who henceforth obtains the drug's clinical benefit at a fraction of the original price. For this system to work well, it is important that the

period of exclusivity be limited in practice as well as in principle. Competitive entry by generic and biosimilar products should not be impeded through excessive patent extensions, delays in FDA approval, and collusive pay-fordelay agreements between branded and generic manufacturers. 72

• Expand use of comparative clinical and cost effectiveness analysis. Many nations have incorporated comparative clinical and cost effectiveness analyses into negotiations with industry, improving the transparency, consistency, and validity of coverage and pricing decisions. In the United States, a philosophical resistance to the expansion of government's role has inhibited an analogous process, in turn leading to wide variability in insurance coverage and prior authorization criteria for the same drug.⁷³ Non-governmental organizations such as the Institute for Clinical and Economic Review (ICER), the National Comprehensive Cancer Network (NCCN), the American Society for Clinical Oncology (ASCO), and others have entered this void. Their work should be encouraged by policymakers and incorporated by purchasers.

 Reward exceptional performance with exceptional **profits.** High prices and profits that reflect breakthrough improvements in clinical performance do not represent a failure of the policy framework, but its success. Pharmaceutical firms conduct research and development under conditions of exceptional uncertainty. Many projects absorb substantial investments but fail to generate any financial return, while some newly launched innovations face immediate price competition from therapeutically similar products. For the pharmaceutical industry to sustain its research focus, some investments must compensate for the financial failures of others by generating exceptionally high returns. If these returns reflect breakthrough improvements in performance, and not a strategic exploitation of supply or regulatory bottlenecks, they should be viewed as prizes for innovation and not as a waste of social resources.

New applications of two-part pricing

No structure of pricing works best for all applications. Traditional one-part pricing works well for generic drugs where there is no need to load the fixed costs of research onto the fee for each pill or vial. It works relatively well for branded drugs that target large patient populations, because the fixed cost markup is spread over many units and does not raise the unit price too far above marginal costs. Conversely, and as evidenced in its applications to date, two-part pricing is a desirable structure where the number of units sold is very small or where a philanthropic third party is willing to cover fixed costs for low-income populations. In between these extremes lie many therapeutic classes where two-part pricing would offer advantages if applied creatively. Rather than seek a universal replacement of the status quo, it is useful to consider new contexts where the alternative pricing structure might find a sympathetic reception. Two examples will suffice.

• Combination therapy. For some cancer sub-types, optimal therapy now includes multiple specialty drugs, such as one or more targeted biologics plus a broad-spectrum stimulator of the body's own immunological defenses. Under today's one-part pricing structure, manufacturers must charge patients who need multiple drugs a price that is the sum of the prices for each drug individually. Each of these drugs already charges a price that is much higher than its marginal costs of production, because the manufacturer needs to recoup some part of its research costs. The sum of the individual prices makes the price of the combination therapy unaffordable to purchasers, who sometimes impose extreme versions of their pushback strategy. But from the perspective of the manufacturer, there is no need for the fixed cost markup to be applied to each drug and then summed for each patient. Implicitly, if not explicitly, the manufacturer would be willing to have the price of the combination therapy be calculated as the sum of the marginal costs for each of the component drugs, plus a single per-patient markup to contribute to covering fixed costs.

In this context, it would make sense for the purchaser not to license access to drugs but, rather, to a therapeutic class or

for a course of care. Physicians would retain the authority to prescribe whichever combination of drugs they felt was best for their patients. The manufacturer would charge a per-unit fee for each patient equivalent to the sum of the per-unit fees for whichever combination was prescribed. These per-patient fees would be equivalent to generic drug prices and would not be burdened by a markup. This two-part pricing model would be especially attractive when the same pharmaceutical firm provided all the drugs in the combination. Large pharmaceutical firms increasingly offer the full set of drugs needed to treat patients and could supply all the components of a combination therapy.

• Beyond the pill. The value of a drug depends not merely on its molecular structure but on the entire course of care within which it is used. This includes appropriate diagnosis and targeting, patient education and adherence, method of administration and monitoring, decision on when to switch drugs or terminate treatment, and numerous other factors. Pharmaceutical firms have developed expertise in the appropriate care for the indications treated by their products, but their financial incentive under traditional pricing models has simply been to sell more drugs. They lose money when they promote patterns of care that reduce the number of pills or vials used by the patient. Their investments in patient education, monitoring, and management sometimes are viewed by purchasers as covert attempts to stimulate more drug use. It has been hard for manufacturers to move 'beyond the pill.'

This dilemma is one familiar to the larger health care system. Physicians typically are paid on a fee-for-service basis for each visit and procedure, regardless of how it is coordinated with other components of the patient's care. Fee-for-service incentives are responsible for many of the inefficiencies and quality failures in health care, and gradually are being replaced by payment methods that cover the patient's course of care. Many of these new payment methods are similar to two-part drug pricing, involving a per-unit fee for each intervention (fee-for-service) plus a monthly or annual payment to cover the fixed costs of care monitoring, management, and improvement. In the context of two-part drug pricing, the license fee could be designed as a performance-based payment to stimulate efforts by the manufacturer to ensure appropriate use. Patient education and support today are provided by specialty pharmacies owned by pharmacy benefit management and health insurance firms. These specialty pharmacies have financial incentives to restrict the use of expensive medications that are just as strong as the incentives for pharmaceutical firms to promote use. If buyers and sellers negotiated a license for access, both could offer their expertise but neither would have the incentive to interfere with the physician's professional responsibility.

Approximations to two-part pricing

Two-part pricing offers numerous advantages over its one-part alternative but faces administrative and regulatory obstacles to implementation. Purchasers and manufacturers are experimenting with contractual structures that incorporate some of its features without requiring a complete break with the status quo. This experimentation should be extended, and its learnings incorporated into policy discussions and market contracting. Two initiatives are of special interest.

• **Budget-based pricing.** Two-part pricing reduces the amount charged for each new prescription to a level equivalent to its marginal cost of manufacturing and distribution. Low prices of this sort already are to be found in the market for generic drugs (unless they have found an anti-competitive bottleneck to exploit). The low per-unit price eliminates the incentive for purchasers to establish onerous prior authorization and cost sharing, since each prescription forestalled saves only a small sum. Not surprisingly, insurers require few, if any, utilization controls on generic drugs and, in some cases, provide positive incentives for prescription and adherence.

This feature of two-part pricing is approximated in some payment models negotiated by global purchasers that face stringent budgetary limitations. These purchasers are willing to offer manufacturers a modest return on their research investment, in the form of revenue for their branded drugs, but want to limit that contribution and not permit manufacturers to increase it through aggressive sales and marketing. Moreover, if the drug turns out to be less popular among physicians and patients than anticipated, due to the emergence of a better-performing competitor, the purchasers do not want the manufacturer to enjoy a generous license for an under-used drug.

In these contexts, purchasers and manufacturers are negotiating what might be termed 'budget-based' prices. The first step in the negotiations is to agree on a target volume of prescriptions for the covered population. The volume target would be based on assumptions about disease prevalence, physician adoption, patient adherence, extent of competition from therapeutic alternatives, and the purchaser's budgetary capabilities. Purchasers and manufacturers then negotiate a per-unit price based on the drug's comparative clinical effectiveness, which translates the volume target into an expenditure target. This per-unit price is paid for each prescription until total expenditures reach the target. For each prescription beyond that level, manufacturers are paid a lower price that covers their marginal costs but does not contain a substantial markup.

Budget-based pricing approximates two-part pricing in several ways, while deviating in others. The negotiated expenditure target approximates a license fee. In the absence of budget constraints, this volume target would cover all patients expected to benefit from the drug, and the price per patient would reflect the product's clinical and cost effectiveness. In the presence of budget constraints, however, the expenditure target will not be high enough to support both evidence-based volumes and value-based prices. Manufacturers will need to decide whether to push for a high price that brings them to the expenditure target with lower sales volumes or a lower price that reaches the expenditure target covering a greater share of the desired volume. For their part, purchasers will need to acknowledge that their budget constraint is reducing the manufacturer's incentive to promote its product for appropriate patients.

Under budget-based pricing the amount paid per prescription beyond the expenditure target approximates the per-unit fee charged under two-part pricing. However, it is not based on marginal costs nor is it determined by competition with generic entrants. To the extent it exceeds marginal costs, this second price retains but attenuates the manufacturer's incentive to promote its product beyond the negotiated volume target. Conversely, to the extent the second price falls below marginal costs, it reduces the manufacturer's incentive to promote, though as not as much as if the purchaser refused any payment for prescriptions beyond the target. At an extreme, the price paid after reaching the expenditure target could be zero, in the sense that the manufacturer agrees not to charge the payer for any prescriptions exceeding the target volume.

The analytics required to generate budget-based prices are already in use. Manufacturers must estimate prescription volumes when deciding which development projects to pursue and when establishing list prices for products that reach the market. For their part, purchasers estimate volumes and expenditures when deciding how strictly to set coverage criteria and cost sharing.

 Access-based pricing. Recent years have witnessed a proliferation of analytic frameworks that measure a drug's value in terms of its clinical benefit to patients and financial impact on budgets. These clinical and financial assessments are translated into prices in either of two ways. Purchasers in nations such as the United Kingdom use cost-effectiveness analysis and summarize a drug's benefits and risks in terms of the gain in quality adjusted life years (QALY). The ratio of the QALY for the new drug and that for the alternative is compared to the ratio of their prices to generate the 'incremental cost effectiveness ratio.' 74 If the incremental ratio exceeds the purchaser's maximum willingness to pay, the purchaser seeks price reductions or refuses to extend coverage. In contrast, purchasers in nations such as Germany focus on comparative clinical effectiveness without explicitly calculating QALYs and cost effectiveness. They summarize the benefits and risks of a new drug in terms of its major, moderate, minor, or lack of benefit compared to the most relevant alternative, and use this scale to negotiate its price.75 Purchasers in the United States traditionally have not appealed to value frameworks when negotiating prices, relying instead on the threat of coverage exclusion, utilization management, and consumer cost sharing to extract discounts and rebates. In recent years, however, some have used externally generated benchmarks as a beginning point in price negotiations. The most prominent organization conducting value assessments in the United States is the private nonprofit Institute for Clinical and Economic Review (ICER). 76 ICER publishes recommended price benchmarks using several cost-per-QALY thresholds. The ICER benchmarks often, but not always, fall below the list prices established by manufacturers. In recent years some manufacturers have expressed a willingness to consider pricing their products near ICER benchmark levels if payers were correspondingly willing to reduce prior authorization and cost sharing. Most prominent among these initiatives have been the contracts negotiated by Regeneron and Sanofi with Express Scripts, the nation's largest PBM, for specialty drugs in dermatology and cardiology. 77 78 This may be termed 'access-based' pricing.

Access-based pricing achieves some of the goals of two-part pricing but faces its own implementation challenges. Many purchasers are reluctant to acknowledge that their coverage criteria and utilization management processes are based on financial as well as clinical considerations, and many manufacturers dispute the validity of any price benchmark lower than the list price they set based on patent exclusivity. The access barriers created by prior authorization often stem less from formal criteria than from documentation demands and process inefficiencies that are difficult to monitor and remove. Cost sharing requirements often are decided by employers rather than by insurers and PBMs and hence are not available to be traded away in exchange for drug price reductions. The first step in negotiating access-based prices is for both buyers and sellers to put their current practices on the table in exchange for concessions by the other side.

Conclusion

The combination of patent protection and insurance coverage has led to a spiral of higher prices and spending that threatens the affordability of specialty drugs for society and for individual patients. Purchasers are erecting increasingly onerous access barriers and politicians are proposing evermore direct regulatory interventions. These controls on access and pricing threaten the margins available to manufacturers for funding research and product development.

Innovation is needed both in public policy and private contracting. Alternative funding mechanisms for research and development, including grants, tax credits, and innovation prizes, should be expanded and targeted at the areas of greatest scientific potential and patient need. The structure of pricing itself should expand from today's model, the source of purchaser pushback, to include thoughtfully designed alternatives. The status quo is not sustainable. There must be a better way. ¹ In 2016 total US medical and health research (not merely pharmaceutical research) was \$172 billion, of which \$116B was made by the life sciences industry, \$38B by the federal government (including \$31 billion by NIH), \$13 billion by hospitals and universities, and the remainder from foundations, (\$2.7 billion), state and local governments (\$1.7 billion), and philanthropic organizations (\$1.4 billion). Of the industry investments, \$89 billion was made by biopharmaceutical firms, with the remainder from medical device and health services firms. ResearchAmerica. US Investments in Medical and Health Research and Development, 2013-2016. https://www.researchamerica.org/sites/default/files/RA-2017_InvestmentReport.pdf

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