EDITORIAL

Lowering Cost and Increasing Access to Drugs Without Jeopardizing Innovation

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US drug costs have reached unacceptable and unsustainable levels. Evidence shows that "financial toxicity" arising from drug costs and other medical expenses is reducing financial security for many families[1] and prompting difficult choices, as patients defer or forgo therapies they cannot afford.[2] In stark contrast, comparable countries negotiate drug prices and use drugs more effectively. Recent data suggest that other high-income countries have an average life expectancy approximately 3 to 5 years longer than that of the United States, which ranks last among high-income countries and is losing ground compared with peer nations.[3] Although drug prices account for only part of these trends, they nevertheless add to disparities that dominate the trajectories of US health outcomes.

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An effective policy solution to this problem must satisfy the core requirements of reducing drug costs and increasing access to beneficial drugs, while continuing to incentivize development of new therapies. The path forward requires a sustainable, fair payment system in which drug prices reflect the value provided and reward innovations that improve outcomes. Four Viewpoints in this issue of *JAMA*[4-7] recommend different but overlapping approaches for achieving these goals.

Under the current US system, drug manufacturers estimate what the market will bear for a novel therapy. Then, if there is concern about negative publicity about drug prices, a fraction of the cost may be subtracted, at least while attention persists. Absent competition or negotiation, this fraction is determined by the company's internal moral compass and the degree of awareness in the biomedical ecosystem, which is often driven by public perception of the specific disease.

Such an approach is possible because of a societal compact that entitles innovators to exclusive sale of the drug for a limited period, ostensibly to recoup development costs. In contrast, almost all other countries assess new medical technologies to estimate value, then negotiate a price that reflects the value of that technology.[8] In essence, the United States subsidizes global drug research and development by paying high prices, but the resulting benefits are differentially realized in other high-income countries.

However, escalating initial prices of innovator drugs is only part of the problem. Often, once a drug reaches the market, the manufacturer gradually increments the price, even when the demonstrated risk-benefit profile is unchanged. Although postmarket studies sometimes show greater-than-expected benefits or impressive additional indications for use that merit an increase in price, most such increases cannot be justified based on value. More often, price hikes are driven by shortfalls in sales volume or earnings projections, and lack of transparency makes it difficult for purchasers to protest. Even when postmarket studies demonstrate less value for a drug than projected, prices seldom decline.

The generic drug system launched by the Hatch-Waxman Act (Drug Price Competition and Patent Term Restoration Act) of 1984[9] has been so successful that more than 90% of US prescriptions are now for generics.[10] Overall prices for generics have gradually decreased, but loopholes allow companies to delay the launch of generics ("pay for delay") or create legal monopolies by buying competitors or developing new indications that confer exclusivity. When a drug is critical for health, pricing tends to resemble that of new drugs, thus rewarding companies for exploiting markets and legal loopholes rather than innovative drug development.

Many of the most expensive drugs are biological molecules that are complex and difficult to reproduce compared with the small-molecule drugs that are staples of the generic industry. US laws governing biosimilars were passed several years later than comparable European Union laws and have been difficult for the industry to assimilate. This situation has enabled manufacturers of older biologics to continue charging high prices well beyond the time that a biosimilar should be available.

The current administration has made progress with straightforward maneuvers that will increase competition. Generic drugs are being evaluated quickly in record numbers, pay-to-delay loopholes are being closed, and the US Food and Drug Administration (FDA) is exerting authority to bring competitors to market quickly when an unfair legal monopoly develops. These actions should be solidified with bipartisan legislation to stop unacceptable price spikes with specific drugs. However, these tactics do not address the larger issue of pricing for innovator drugs.

The most effective ways to address pricing involve 4 categories: importation from other countries; reduction of bloated administrative and marketing activities; direct negotiations between federal payers and industry; and creation of a value-based system.

Importing drugs from other countries—a workaround born of desperation—is the least-favored long-term approach. A substantial proportion of drugs imported via the internet are either fake or only partially potent; many contain impurities, toxic substances, and adulterations.[11] An expensive infrastructure would be needed to ensure the quality of imported drugs on

large scales; furthermore, importation could exacerbate disparities as more savvy individuals and states could benefit disproportionately. Drug importation would also burden the FDA, which is shouldering a growing responsibility to protect the public with limited funds and personnel. Nevertheless, when a distorted market affects access to a specific drug so that public or individual health is at significant risk, the FDA should use its authority to support importation. Furthermore, individual importation from licensed pharmacies in some circumstances is already legal[12] and should continue. Drug pricing in other countries is not a mystery, and the use of an international price index as a metric by the current administration, as discussed by Horvath and Anderson,[4] is a positive step.

Administrative burdens in the US health care system are a major contributor to excess cost. Pharmaceutical benefits management (PBM) companies initially played a critical role in modulating drug pricing by serving as intermediaries in price negotiations. However, the mounting complexities of this system have rendered drug pricing almost wholly inscrutable, even for sophisticated professionals. List prices have escalated, and the profit taken by PBMs now exceeds the profit of insurers.[13] Pharmaceutical benefits management companies negotiate rebates from manufacturers in return for preference on payer and health system formularies—rebates that typically do not reduce out-of-pocket expenses for patients. Furthermore, clinicians and patients have limited access to prescribing options based on secret agreements, prompting reasonable suspicion that clinical benefit is not driving choices made at the corporate level without involving patients or their clinicians. The remedies proposed by Dusetzina and Bach,[5] and the Canadian focus on transparency reported by Humphries and Xie,[6] are sensible and combine more rational PBM payments with other tools such as value-based pricing.

Direct-to-consumer advertising, detailing, and excessive physician payments also drive up costs. A particularly troubling issue to health professionals is the increasingly brazen use of the internet, social media, and television for marketing[14] based on marginal or unproven benefits under the protection of current legal interpretation of First Amendment rights.

Direct negotiation between government and manufacturers is prohibited by law, under the rationale that Medicare would be too powerful and that the private sector can fulfill that function on behalf of Medicare. However, this approach works well for other countries and for the US Veterans Affairs. Notably, the Obama administration repeatedly proposed direct negotiation between the Centers for Medicare & Medicaid Services and drug companies, but the policy gained no traction in Congress, which historically has been heavily influenced by the pharmaceutical lobby and its allies. To negotiate effectively, the federal government would need access to formularies and step therapies. In addition, some newer drugs without competition would require approaches, such as forced arbitration or the setting of triggers similar to the Canadian "Cost Utility Analysis,"[6] which would engage if a company raised prices above an established threshold.

Instituting value-based payments for drugs is the most promising path toward a fair system that rewards innovation, as discussed in detail by Gurwitz and Pearson.[7] Importation, reducing administrative costs, and direct negotiation can all improve affordability for some populations, but these partial remedies would still leave many US residents without access to needed medications, while also failing to send a sufficiently clear signal for innovation.

Encouraging a vibrant innovator biopharmaceutical ecosystem requires focusing rewards on useful innovation and reducing bloated distribution systems. Furthermore, prices should be based on demonstrated risk-adjusted costs of development and actual measured value. Roughly 9 of every 10 drugs that enter clinical development fail before reaching marketing approval.[15] The cost of these failures must be factored into an understanding of the conditions needed to attract investment in new drugs. The government's exclusivity period is intended to account for this but not at unlimited price levels. Different approaches to financing may also be needed to pay for expensive new drugs such as antivirals for hepatitis C, which eliminate the enormous downstream costs of hepatic cancer and liver failure due to cirrhosis. Likewise, new biologics that target small populations can be reimbursed for improved outcomes in that population, thereby yielding incentives for better diagnostics and targeting.

The most important missing element in calculating value is an efficient way to assess risks, benefits, and effectiveness in clinical practice. The current system of drug development focuses almost exclusively on efficacy and safety in limited populations, driven by an understandable desire to approve potentially effective therapies. Determining actual effects on longevity, function, and quality of life, however, requires longer intervals, relevant direct comparisons, and broader populations. Accordingly, payers and health systems currently must guess about value, as do the health technology assessors in other countries who estimate societal cost-effectiveness based on limited available data.

The definition of value is controversial. There is general agreement that the general equation for value is the benefit as estimated by improvement in survival, functional status, and quality of life, divided by the price. The use of quality-adjusted life-years offers the attraction of being able to compare drug treatments for people with different diseases, but it also makes people uncomfortable because it reduces complex concepts into numbers that arguably are overly simplistic. However, the underlying concepts are sound, and it would be preferable to have a system in which actual measurements of benefit could supersede estimates derived from the minimal data available at time of approval for marketing.

Estimating cost can also be complex. Effective drugs can reduce costs by diminishing need for other medical services or improving the ability to work. In the case of genetic modification and targeted therapies, any cost offsets may occur at a time distant from the initiation of therapy. However, the FDA's Sentinel Initiative and National Evaluation System for Health Technology, the National Institutes of Health (NIH) Health Care Systems Research Collaboratory, and the National Patient-Centered Clinical Research Network (PCORnet), along with many other programs, are providing proof that effectiveness research can be done at much lower cost by

combining rigorous methods with data from existing digital records. The 21st Century Cures Act and the User Fee Agreements of 2016 provide a framework for a substantial upgrade of the US evidence generation system.[16,17]

Like all complex problems, the solutions lie in a combination of policies and actions that can be continuously refined. Fortunately, the crisis in drug pricing is occurring at a time when a new evidence-generation system can realistically provide actual measurement of benefits and costs. When this system is combined with closing of loopholes, selective importation to deal with isolated monopolistic pricing, reform of bloated and opaque nonscientific costs, and direct negotiation, prices can be adjusted to broaden access to therapies while continuing to stimulate innovation and funding research and development in a competitive but sustainable manner. The alternative—increasing loss of life and function, particularly among low-income families, due to financial toxicity—is intolerable and demands action.

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