Making Medicines Affordable

A National Imperative

Norman R. Augustine, Guru Madhavan, and Sharyl J. Nass, *Editors*

Committee on Ensuring Patient Access to Affordable Drug Therapies

Board on Health Care Services

Health and Medicine Division

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by grants from the American College of Physicians, Breast Cancer Research Foundation, Burroughs Wellcome Fund, California Health Care Foundation, The Commonwealth Fund, Laura and John Arnold Foundation, Milbank Memorial Fund, and the Presidents' Committee of the National Academies of Sciences, Engineering, and Medicine. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization that provided support for the project.

International Standard Book Number-13: 978-0-309-46805-3
International Standard Book Number-10: 0-309-46805-1
Digital Object Identifier: https://doi.org/10.17226/24946
Library of Congress Control Number: 2018931964

Additional copies of this publication are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2018. *Making medicines affordable: A national imperative*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24946.

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NOTE: See Appendix F, Disclosure of Conflicts of Interest.

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

Henry J. Aaron, The Brookings Institution
Troyen Brennan, CVS Health
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Gail R. Wilensky, Project HOPE

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **Harvey V. Fineberg,** Gordon and Betty Moore Foundation, and **Robert D. Reischauer,** Urban Institute. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Synopsis

Over the past several decades the biopharmaceutical sector in the United States has been very successful in developing and delivering effective drugs for improving health and fighting disease. Indeed, many medical conditions that were long deemed untreatable can now be cured or managed effectively.

This success has come at a cost, however. Spending on prescription drugs has been rising dramatically, to the point that many individuals have difficulty paying for the drugs that they or their family members need. Drug costs are a significant part of the nation's total spending on health care.

This report, *Making Medicines Affordable: A National Imperative,* from the National Academies of Sciences, Engineering, and Medicine recommends several strategies to tackle the rising costs of prescription drugs without discouraging the development of new and more effective drugs for the future.

This is a difficult challenge. There may be trade-offs between current drug affordability and new drug availability. Controlling drug costs too rigidly, for instance, could potentially reduce the expected profits of drug companies, and this could alter their decisions regarding major investments to develop new drugs.

Furthermore, the complex nature of the nation's medical system—which includes patients, clinicians, hospitals, insurance companies, drug companies, pharmacists, pharmacy benefit managers, various government agencies, advocacy organizations, and many others—makes it very difficult to predict the precise effects of any specific policy changes. This is exacerbated by the fact that there is very little publicly available information

on the costs and profitability for the drug companies and various other participants in the system.

Nonetheless, there are a number of measures that can and should be taken to improve the affordability of prescription drugs for patients in the United States.

The federal government should consolidate and apply its purchasing power to directly negotiate prices with the producers and suppliers of medicines, and strengthen formulary design and management. The government should also improve methods for assessing the value that drugs provide and ensure that incentives to develop drugs for rare diseases are not extended to widely sold drugs. In addition, increased disclosure about the financial flows and profitability among the participants in the biopharmaceutical sector should be required.

Actions to continually foster greater access to off-patent generic drugs, which are usually much less expensive than branded products, should be taken. One way this could be accomplished would be to prevent the common industry practices that delay entry of generics into the market and extend market exclusivity of branded products. Another critical step is to speed up the review processes that are required of manufacturers to produce generic drugs, to ensure healthy competition and lower costs.

Also, various actions should be taken to eliminate incentives in the system that encourage clinicians and patients to prescribe or use more expensive drugs rather than less expensive alternatives that provide comparable results. One action would be to discourage direct-to-consumer advertisements for prescription drugs and to provide more useful information to patients about the potential benefits and costs of treatments, thereby reducing inappropriate demand for higher priced drugs.

Finally, insurance plans should be modified to reduce the financial burden that patients and their families currently experience when they need costly prescription drugs, and individual cost-sharing arrangements that are based on drug prices should be calculated as a fraction of the net purchase prices of drugs rather than the list prices from manufacturers. The government should also tighten qualifications for discount programs that have drifted from their original intent to help vulnerable populations.

Ongoing monitoring will be needed, but taking these steps should bring down the cost of prescription drugs while still enabling the continuing development of new drugs.

Preface

Norman R. Augustine, Committee Chair

The amount of money Americans spend on health care today is equal to 18 percent of the nation's gross domestic product. This commitment to health care as a fraction of the United States gross domestic product has increased steadily for the past 60 years, leading to what is also the highest per capita expenditure in the world. Today, roughly half of all Americans suffer from at least one chronic disease, many of which require continuing treatment with biopharmaceuticals, the topic of this report, *Making Medicines Affordable: A National Imperative*.

The trend of increasing spending on health care, including on biopharmaceuticals, is projected to continue for the foreseeable future as the baby boomer generation ages. No other nation in the world approaches the United States' level of expenditure, yet various studies indicate that many nations have healthier populations. It is noteworthy that the better health of some nations is not a result of spending more to sustain health but instead reflects such factors as health-related choices made by their citizens (40 percent of premature deaths—i.e., before age 79—in the United States are attributed to unhealthy behaviors), and the emphasis that some governments place on public health practices that reduce the long-term costs of illnesses. According to the Organisation for Economic Co-operation and Development, the United States now ranks 25th in the world in life expectancy at birth. A recent study that ranks the quality of health care in various countries places the United States only modestly above the global average, in spite of the fact that U.S. health care expenditures exceed the entire gross domestic product of all but four other nations. On the other hand, various studies, including those conducted by the National Academies of Sciences,

Engineering, and Medicine, indicate that in the case of specific, serious illnesses, treatment outcomes tend to be more favorable in the United States than in many other developed countries.

Among the 10 nations with the largest gross domestic product, the World Bank reports that the United States spends about twice as much on health care as a fraction of gross domestic product as the average of the other nine. The nation with health care spending that most closely approaches that of the United States allocates about 7 percentage points less of its gross domestic product to that purpose. Placed in context, 7 percent of the U.S. gross domestic product would pay for the country's entire primary and secondary education system, for two of its defense budgets, or for three of its public transportation and highway budgets. While it is clearly in the interest of the public to devote significant funds to health care, such spending is not without its opportunity costs.

Annual expenditures on biopharmaceuticals in the United States now exceed a half trillion dollars and account for nearly 17 percent of the nation's personal health care bill (the occasionally quoted figure of 10 percent omits prescription drugs dispensed through hospitals and clinics). Furthermore, prescription drugs are among the fastest growing segments of health care spending—substantially exceeding over time the rate of inflation in the economy and the growth of family income. Administration, the most rapidly growing element of health care cost, accounts for more than three times the share devoted to this purpose in Great Britain. *The Economist* cites one large U.S. hospital as having more billing clerks than beds.

As the costs of hospital care, long-term care, ambulatory care, physician services, medical devices, and drugs have all escalated in recent years, insurance plans implemented benefit designs that attempt to preserve access to care yet keep health insurance premiums affordable by increasing copayments and deductibles, all of which have an impact on patient cost. Deductibles themselves have on average increased by a factor of 2.5 in the past decade. As with health care as a whole, biopharmaceuticals are critically important to the well-being of individuals and to the public at large. While few argue that the current situation is acceptable, virtually each newly proposed potential corrective measure has confronted opposition from one group or another.

An overarching moral issue remains unresolved in the United States: is access to health care—including prescription drugs—a fundamental human right? And if it is not, who is to decide, and based on what criteria, which individuals are to be denied access to the drugs and the care that they need? But if health care *is* a right, who is to pay its costs? And is this cost affordable not only to the individual but also to society as a whole, and does it represent the most appropriate allocation of the nation's resources?

Some observers point out that even widely accepted "rights" (e.g.,

freedom of speech) have limitations placed on them. And there is the additional issue of how one balances the cost of drugs to today's patients, a part of which pays for the development of new medicines, with the ability to create more capable medicines for future patients. Perhaps access to prescription drugs is not an individual right at all, but rather an obligation of society to the individual.

The complexity of these issues is noted in one study that found that the average price of an episode of treatment using anti-cancer drugs is $65,900 and results in an average survival benefit of 0.46 years (not quality-adjusted). Moreover, there are those instances when life extension far exceeds the median—a potential outcome of the utmost importance to the patient facing a major health care decision and to whom an effective drug may be priceless. Are these investments too little? About right? Too much? Answering such questions introduces considerations well beyond the realms of economics and scientific knowledge and requires entering the realms of morality, social justice, and, in many instances, politics.

The tension between the need for essential services and the ability of individuals and society to afford those services is reflected in the attention being devoted to the cost of biopharmaceuticals by the media, public, and political leaders—including both major candidates in the latest presidential election. A recent referendum in California (Proposition 61) that would have prohibited state agencies from paying more for prescription drugs than is paid by the U.S. Department of Veterans Affairs was defeated by voters in a highly contentious election. Media reports state that the pharmaceutical industry devoted approximately $110 million to a campaign for the proposition's defeat. A principal argument of opponents was that passage of the law could cause prices to increase for veterans and some other state residents. On a national scale, OpenSecrets.com reports that in 2015, the Pharmaceuticals/Health Products industry ranked second among the 18 industries it evaluated in lobbying expenditures, devoting more than 50 percent more to this purpose than the third-place industry, closely behind the industry ranked first: hospitals and health professionals.

As the public debate over the cost of biopharmaceuticals has become increasingly contentious, criticism has been aimed at the sector as a whole, including insurance companies, regulators, hospitals, pharmaceutical firms, and intermediaries such as pharmacy benefit managers. Yet, a healthy biopharmaceutical enterprise, the source of a long history of life-enhancing and lifesaving accomplishments, is important for the nation's well-being. Without the contributions of firms in this sector, supported by research funded by various agencies of the federal government, universities, private philanthropy, venture capital, and biopharmaceutical firms themselves, there would have been no vaccines for many deadly diseases, no statins,

and no cure for conditions such as hepatitis C. This is an industry that literally saves lives.

There is not enough accessible information to determine with certainty which segments of the biopharmaceutical sector are principally accountable for the rising cost of many pharmaceuticals; despite this, recent headlines suggest that the pharmaceutical manufacturers have borne the brunt of the blame. The following sampling of headlines illustrates both the intensity and the spread of the debate: "How Pharma Companies Use 'Citizen Petitions' to Keep Drug Prices High" (*The Atlantic*); "How to Stop Drug Price Gouging" (*The New York Times*); "Why Drugs Cost So Much" (*AARP Bulletin*); "Nonprofit Linked to PhRMA Rolls Out Campaign to Block Drug Imports" (*Kaiser Health News*); "The High Cost of Prescription Drugs in the United States. . . . Origins and Prospects for Reform" (*JAMA*); "Why Drugs Cost So Much" (*The New York Times*); "Defiant Generic Drug Maker Continues to Raise Prices" (*The New York Times*); "The Cost of Drugs for Rare Diseases Is Threatening the United States Health System" (*Harvard Business Review*); "Everyone Wants a Piece of the Drug Industry and It's One Reason Prices Are Rising So Fast" (*Business Insider*); "More Than 80 Percent of Patient Groups Accept Drug Industry Funds, Study Shows" (*The New York Times*); "When the Patient Is a Gold Mine: The Trouble with Rare-Disease Drugs" (*Bloomberg*); "Pushy Pharma in Overdrive" (*Business Week*); "Insulin Prices Inflict Crisis on Diabetes" (*USA Today*); and "Big Pharma Quietly Enlists Leading Professors to Justify $1,000-per-Day Drugs" (*Propublica*).

Much of the criticism directed at biopharmaceutical firms stems from the sudden, large increases that have been observed in the price of certain prescription drugs. Public concern seemingly reached a tipping point when media reports cited the unanticipated increase in the price of a two-pack of EpiPens (used to administer epinephrine, a treatment for potentially fatal allergic reactions) from $160 to more than $600. Perhaps the most egregious case during the above period involved rights to the existing, non-patent-protected drug Daraprim (used in the treatment of severe infections) with a relatively small market (making it unattractive to potential competitors). The rights to Daraprim were purchased from its developer by Turing Pharmaceuticals, which promptly raised the drug's price from $13.50 to $750 per tablet. Yet, another extreme example involved Biogen's Synraza, used to treat neuromuscular diseases, that initially had a stated price of $750,000 for the first year's dosage and $375,000 for each subsequent year. These are extraordinary examples, yet, coupled with lesser examples, they have had a sufficient impact on the health of citizens to attract sustained public attention and concern. A September 2017 survey of adult Americans' priorities for the U.S. Congress through the end of the current year found lowering prescription drug prices to be highest ranked, above raising the

minimum wage, reducing the deficit, rebuilding the nation's infrastructure, reducing taxes, or any of the other six issues considered.

A study conducted by the U.S. Government Accountability Office into the price of established generic drugs—that is, existing drugs no longer protected by patents—found that between 2010 and 2015 there were at least 315 instances when the price of generic drugs that were on the market throughout the duration of the study had sudden increases of 100 percent or greater. Of the 1,411 drugs considered in the study, a price increase of 500 percent or more was observed in 48 cases. On average, during the period covered by the study, the price of established generic drugs increased about four times the rate of inflation. However, when a basket of drugs of varying composition was considered—that is, including drugs entering or leaving the market during the period of the review—the average price declined because the drugs leaving the market during the particular period examined were more costly than those entering the market. Another study, this one by Memorial Sloan Kettering Cancer Center, found that the median monthly cost of cancer drugs at the time of U.S. Food and Drug Administration (FDA) approval increased from approximately $1,500 in 1965 to $150,000 in 2016, stated in constant 2014 dollars.

The burden of high-priced drugs often falls disproportionately on vulnerable elements of the population, in spite of government, industry, and charitable efforts to alleviate its impact. For example, the Kaiser Family Foundation reports that in 2015, about 20 percent of Americans did not fill at least one prescription due to affordability considerations, while others rationed the drugs that they did acquire. Two-thirds of personal bankruptcies in the United States have been attributed entirely or in part to the cost of medical care as a whole.

For most U.S. business sectors the pressure of competition is the dominant force in controlling prices and, to the extent that competition is present, the biopharmaceutical industry is no exception. Yet, if firms that have invested heavily to introduce new products were to be immediately confronted with competitors not having made such investments, there would be little motivation or justification for conducting research and innovating. In recognition of the importance of encouraging innovation, the U.S. Constitution provided the U.S. Congress with the authority "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." That is, in exchange for undertaking the research and development needed to introduce new products, the government can, and does, grant patents to firms and individuals and provides them with what is in effect sole-source position in the market for a specified period of time. This protection under the patent laws makes it practicable for the biopharmaceutical industry to develop new drugs. Indeed, the industry, especially its

smaller firms, devotes a higher fraction of revenues to research and development (currently about 19 percent) than other major U.S. industrial sectors.

Only about one-tenth of 1 percent of the country's gross domestic product is currently being devoted to basic biomedical research, the foundation of future preventions and treatments. Furthermore, the federal government has been significantly reducing its investment in biomedical research while at the same time industries that indirectly support the biopharmaceutical sector, responding to market pressures for short-term returns, have also been reducing their investment in research (but not development). As a result, the United States has fallen to seventh place in its overall investment in basic research as a fraction of gross domestic product. Continuation of this trend is highly likely to diminish the potential to prevent and treat diseases suffered by future patients.

Research and development is the lifeblood of the biopharmaceutical industry and its contribution to health care. It is an extremely costly, risky, and prolonged endeavor, one consequence of which is the financial cyclicality experienced by firms in the sector as major new developmental products succeed or fail and as the temporary patent protection provided those that do succeed, expires. The canonical statement about the cost of a new drug—"the first pill can cost more than $1 billion while the second costs only a dime"—captures an important truth: new drugs are exceptionally expensive to develop and failures are commonplace. Nearly 9 out of 10 new drugs entering clinical trials fail, yet the cost of the efforts to develop those drugs must be borne by someone.

When the period of patent exclusivity for a drug expires, companies other than the developer are free to introduce copies—known as generics—into the market. These products represent 89 percent of all prescriptions written and 24 percent of the total cost of all prescription drugs. When generics enter the market, experience shows that the price of the original patented product frequently drops precipitously as the developer seeks to compete with the new, lower-cost entrants—or forfeits some or all of the market. As but one example, the price of Lipitor, a widely used anticholesterol drug, dropped from $3.29 per unit to 11 cents when its patent protection expired. Historically, the greatest pricing concerns have focused on on-patent drugs; however, major price increases for generic drugs have become increasingly common as more than half of existing generics are now produced by a single supplier.

An implicit trade-off exists when setting drug prices—investments in research and development can increase the cost of *current* drugs, but failure to make investments in research and development will ultimately limit the number of new, improved drugs with which to treat *future* patients. Biopharmaceutical manufacturers often point to the need to fund research and development as the principal justification for what many see as high prices.

As has been noted, such funding is critically important, but drug prices do not map one-to-one onto a firm's investment in research and development (R&D). There are business choices to be made among numerous potential allocations of resources, including the accrual of profits, employee (usually executive) compensation, sales and marketing expenditures, dividends, lobbying, share repurchases, etc. A study published by the Institute for New Economic Thinking, reported by *The New York Times*, concluded that during a recent 10-year period drug companies in the Fortune 500 expended 11 percent more on share repurchases and dividends than on R&D. Another study concluded that manufacturers, on average, devoted more to marketing than to R&D. Thus, reductions in price can, but do not necessarily need to, result in curtailing R&D.

Reflecting, among many other considerations, the relatively high risks confronted by biopharmaceutical firms, these entities on average achieve greater net profit margins than firms in most other industrial sectors, as various studies have shown. For example, a study reported by *Forbes* found that during the period examined companies producing generics had an average 30 percent net profit margin, while major biopharmaceutical manufacturers were reported to realize an overall 25.5 percent net margin, placing them first and third, respectively, among all sectors considered in the study.

Another study, conducted at the University of Southern California's Leonard D. Schaeffer Center for Health Policy and Economics, concluded that in 2015, brand (on-patent) manufacturers averaged a 28 percent margin and generic manufacturers averaged 16 percent, placing the two segments highest and fourth highest, respectively, among the 26 industrial sectors considered. The study also pointed to the substantial costs to the consumer that it attributed to profits in the drug distribution system (i.e., not by the developer/manufacturer), that were determined to consume about one of every five dollars spent on prescription drugs.

Evidencing both the cyclical nature of the U.S. pharmaceutical industry and its financial growth over time, U.S. companies listed among the world's 15 largest pharmaceutical firms by revenue realized a 5-year rate of growth in market capitalization that exceed the rate of growth in market capitalization of the S&P 500 by more than one-fourth and a 10-year rate of growth that exceeded that of the S&P 500 by more than a factor of two.

It is particularly difficult to determine the profitability of intermediary firms in the biopharmaceutical business chain, let alone to assess the appropriateness of that profitability. Many of these entities are, for example, owned by parent firms or are privately held and make little detailed financial data publicly available.

Market forces that typically promote innovation while also providing price-controlling pressures have worked quite effectively in most U.S. indus-

trial settings, raising the question of why they seem to be far less effective in the prescription biopharmaceutical arena. The answer resides in the fact that this particular market has important features that distinguish it from most other markets.

First, before making a purchase of a prescription drug, the purchaser (patient) generally must obtain permission of a third party (nominally a registered physician) before being allowed to make the purchase. The decision as to what basic product to buy is made not by the buyer but rather by another party. Second, largely because of safety considerations, the pharmaceutical industry is particularly highly regulated. Concerns about a particular drug can take years to resolve—thereby consuming a substantial portion of the period of patent protection. (Recognizing this, patent durations have, under certain circumstances, been extended for several classes of biopharmaceuticals.) Third, in the biopharmaceutical market, the principal party directly paying the bill, in part or in its entirety, is usually not the consumer but rather an insurance firm, the government, or some other "third-party" payer such as an employer or union. Fourth, unlike most industries, biopharmaceutical firms are largely protected from foreign competitors because of safety considerations. As but one example, a recent Knowledge Ecology International study of the drug Zinbryta found that it costs at least three times more in the United States than in other high-income nations. Fifth, and most important, unlike the products of more traditional firms, pharmaceuticals can be indispensable to the purchaser—even critical to preserving life. As such, their producers bear an exceptional burden of responsibility not attributed to most businesses.

Under these circumstances the U.S. biopharmaceutical enterprise has evolved into a supremely complex amalgam of regulators, developers and manufacturers, retailers, insurers, wholesalers, physicians, employers offering benefits, and intermediaries, including organizations referred to as pharmacy benefit managers. The role of the latter is to support the overall pharmaceutical enterprise, providing such services as negotiating prices, establishing formularies (lists of drugs to be covered by insurance), and handling administrative functions. Further complicating this already rather arcane process, some smaller pharmacies have joined together to employ their own form of intermediaries that operate between themselves and the intermediary pharmacy benefit managers. In addition, some pharmacy benefit managers operate their own mail-order and retail pharmacies. Not surprisingly, the system is rife with potential conflicts of interest.

Lying at the heart of this complex, and arguably having the least influence among its participants, is the patient—the *raison d'etre* for the existence of the enterprise.

Further complicating this Gordian situation is the fact that many of the transactions among the above entities are treated as business secrets,

making it extremely difficult, if not impossible, for outsiders to "follow the money." Similarly, it is difficult, if not impossible for those outside the biopharmaceutical enterprise to ascertain with confidence the relative impact on cost to the patient of the manufacturers and the pharmacy benefit managers, although a few efforts to do so have been undertaken. The former of course bear a much greater degree of risk and demand for capital than the latter and might therefore be expected to exhibit greater net margins, but reliable data are scarce. Curiously, the pricing algorithm for some pharmacy benefit managers is based not on the services provided but rather on the value of the products that are processed.

The opacity of financial transactions in the biopharmaceutical enterprise is magnified by the practices of selectively, and usually confidentially, granting discounts, awarding rebates, and creating subsidies. When challenged regarding apparently high costs, participants commonly point to other participants as the source of the problem, as is suggested by the following sampling of recent media headlines: "Drugmakers Point Finger at Middlemen for Rising Drug Prices" (*The Wall Street Journal*); "Gilead Executive Says Pharmacy Benefit Managers Keep Prices High" (*Bloomberg*); "Drug Lobbyists Battle Cry Over Prices: 'Blame the Others'" (*The New York Times*); "In the Debate Over Rising Drug Prices, Both Drugmakers and PBMs Claim Innocence" (*Biotech and Pharmaceuticals*).

Various practices, some initiated by the government and some simply tolerated by the government, have magnified the challenges confronted by those who would seek to reduce the cost of biopharmaceuticals while not undermining innovation. Such practices include precluding key government entities from negotiating the prices of the pharmaceuticals for which they pay; extending patent-protected periods when minor changes are made to a drug's design or even to its packaging (a practice known as "evergreening"); permitting developers to deny potential generic competitors access to the supplies of patented drugs they need to establish "equivalence" (a necessary requirement of the FDA); permitting large backlogs of drug approval requests to accumulate; permitting terms of transactions—for which the government pays 80 percent of the cost (above a specified threshold in the case of Medicare Part D)—to be held in secrecy; and tolerating a particularly dubious practice wherein firms pay potential generic competitors to defer entry of their products into the market ("pay-for-delay" settlements). In one recent example of such creativity, Allergan, a manufacturer of an established drug that was threatened by a patent challenge, transferred the rights to the drug, in exchange for an upfront payment and royalties, to a Native American Mohawk Tribe, presumably to escape jurisdiction of the conventional patent resolution process.

It should be noted that the FDA is taking action to ameliorate some of these problems that reside within its purview. Nonetheless, the complexity

of the biopharmaceutical system makes it rife for exploitation. A number of states, responding to inaction at the federal level, are now legislating their own cures, the potential result of which will likely be a collection of inconsistent, conflicting, and overlapping laws and regulations.

Further compromising competitiveness, three distributors now control 85 percent, and three pharmacy benefit managers possess a 73 percent share of the pharmaceuticals market. With regard to on-patent drugs, the patent holder (usually the developer/manufacturer) has a de facto 100 percent market share.

A seemingly relevant quotation attributed to various sources states, "Every system is perfectly designed to get the result it gets."

Within this complex, technologically sophisticated, often non-transparent environment, manufacturers set the list price for the drugs they produce. These firms themselves confront a compound dilemma. First, they are part of the nation's free enterprise system and must therefore compete for talent and money in the same human resources and capital and debt markets as any other publicly held entity. Furthermore, because of the time it takes to generate sufficient evidence to obtain safety and efficacy approval for a new drug from regulators, companies are generally left with a limited number of years of protection remaining before the patent protection of a specific drug expires and a generic competitor unburdened by R&D and other related costs can enter the market. (This is somewhat less of a concern in the case of producers of biologics because of the extended period of market protection that has been granted to their products in recognition of the especially prolonged development and approval periods associated with such products.) Prices must therefore be set sufficiently high during this relatively narrow window of protection to compensate for much of the one-time costs incurred in developing a drug, as well as to provide a competitive profit as demanded by the company's shareholders. When Kymriah, Novartis's new drug treatment for leukemia entered the market priced at $475,000, *STAT* reported, "The $475,000 price tag is much less than Wall Street expected and might disappoint some investors who hoped for a premium on such a complex drug." And as noted, products newly entering the market must bear an allocation of the very substantial costs associated with products that fail to reach the market. Of primary importance, and as also previously noted, it cannot be disregarded that biopharmaceutical firms bear the heavy responsibility of providing a product that can be indispensable to the well-being of individuals and to the public at large.

The task of creating suitable pricing algorithms has not surprisingly proven to be relatively intractable, particularly given the number of parties that can affect the price of a drug to the consumer. Four general approaches for solving this conundrum have gained particular attention.

The first of these is most commonly used in other product areas, that is, "what the market will bear." Critics have argued that in the case of biopharmaceuticals (at least in situations bereft of competition) moral considerations make this an untenable strategy because of the critical public need that such products and their producers serve. A second approach, pricing biopharmaceutical products at a level that generates profits commensurate with the returns from alternative investment opportunities that demand comparable commitments of capital and acceptance of risk, suffers from being a form of price-control that effectively places a limit on the incentive to create new products. A third alternative, used to some extent in other developed countries (which generally also use single-payer systems), is referred to as "value-based pricing," that is, pricing based on cost-effectiveness considerations. While the latter approach is extremely attractive conceptually, "value" can be difficult to determine in the case of biopharmaceuticals. For example, what is the "value" of 1 year of human life, even if quality-adjusted? Additionally, cost-effectiveness calculations, even if of perfect fidelity, suffer from the fact that various parties may embrace very different criteria for decision making based on those calculations. For example, a government may seek the most cost-effective solution, an insurer may desire the least costly solution, and a patient may simply want the most effective solution. A number of countries have used versions of value-based pricing in insurance benefits design and formulary definition with reasonably wide acceptance, but not without some concern over the credibility of the value analyses and the potential denial of certain drugs to some patients. Finally, a fourth option is for government to set a price, or de facto price (e.g., by establishing a maximum reimbursement), by which producers must abide. In so doing, the benefits of a competitive, incentivized free market are largely forfeited.

Despite the challenges in implementing value-based pricing, it has attracted an increasing number of adherents. In what is among the simpler versions of value-based pricing—based on future (discounted) cost avoidances—many practical complications still arise, some because the original investor is rarely the same party as the eventual beneficiary of the costs that are avoided. A related approach is to establish a price based on the apparent superior effectiveness of a new drug as compared with that of existing treatments. This, however, can once again lead to inconclusive debates over the value of a human life in economic terms and, in cases when more than one disease or more than one treatment is involved, as happens with some regularity, how the benefit is to be allocated among the various treatments. Nonetheless, where direct comparisons can in fact be made between the efficacies of two drugs there can be significant opportunities to generate cost savings. For example, a recent article in *JAMA Internal Medicine* cites research on Progestin that indicates no statistically significant dif-

ference in efficacy between a branded prepackaged drug and a compounded version of the same drug having identical active ingredients, yet the former costs $11,000 per full treatment and the latter $200.

Several of the models addressed above, or derivatives thereof, could be adopted by, or imposed on, the U.S. biopharmaceutical enterprise. However, each of these would represent a substantial departure from the structure that actually exists today and which over the years has generally served patients well. These alternative models include the government setting prices (as with public utility industries in the United States); or setting limits on reimbursement (the latter being more common in the pharmaceutical sectors of other developed countries); or having the government pay for R&D but retain the rights to the resulting products (as is fairly common in the U.S. defense sector). Many developed nations have implemented single-payer systems (i.e., the government pays), in part because of their apparent simplicity, while other developed nations have adopted a hybrid form of this model wherein the private sector provides basic coverage that is backed by a government-funded safety net.

This report seeks to address the market failures that currently permeate the biopharmaceutical sector, including the lack of competition due to distortions in the application of the patent protection process; concentration throughout the supply chain; limitations on foreign competition; the imbalance between the negotiating power of suppliers and purchasers; the opacity of prices; the lack of information on product efficacy; the separation among decision makers, payers, producers, and consumers; and the convoluted structure of the supply chain.

The considered view expressed in *Making Medicines Affordable* is that in the case of the United States, changes made within the current system, even though those changes will be demanding, are likely to better serve the nation. Simply stated, bitter pills are sometimes necessary for providers as well as for consumers.

There are few observers who argue that the status quo is acceptable. Should the package of corrective measures offered herein, or comparable ones offered elsewhere, be determined, for one reason or another, to be ineffectual, the remaining realistic choices would be either the status quo or a system embracing substantially increased government sponsorship and control. In the latter instance, plausible choices include various combinations of single-payer (government) insurance accompanied by government price regulation, in one form or another.

The overarching conclusion driving the recommendations presented in *Making Medicines Affordable* is that consumer access to effective and affordable medicines is an imperative for public health, social equity, and economic development and that this imperative is not being adequately

served by the biopharmaceutical enterprise as it functions today. Simply stated, the current system is not sustainable.

While none of the committee members who contributed to the preparation of this report would likely agree with every word it contains, each of the recommendations offered enjoys the support of a substantial majority of the members and some enjoy unanimous support. In those instances where disagreement among the members could not be adequately resolved, dissenting views and commentaries have been provided as footnotes and in Appendixes A and B. The lack of unanimity among the committee members on certain issues largely reflects the considerable effort that was devoted to including individuals possessing diverse expertise and experience in the committee. It also reflects the reality surrounding the complex topic of balancing the affordability and the availability of prescription medicines.

In the end, drugs that are not affordable are of little value and drugs that do not exist are of no value.

Contents

Summary

Thanks to remarkable advances in modern health care attributable to science, engineering, and medicine, it is now possible to cure or manage illnesses that were long deemed untreatable. At the same time, however, the United States is facing the vexing challenge of a seemingly uncontrolled rise in the cost of health care. Total medical expenditures are rapidly approaching 20 percent of the gross domestic product and are crowding out other priorities of national importance. The use of increasingly expensive prescription drugs is a significant part of this problem, making the cost of biopharmaceuticals a serious national concern with broad political implications. Especially with the highly visible and very large price increases for prescription drugs that have occurred in recent years, finding a way to make prescription medicines—and health care at large—more affordable for everyone has become a socioeconomic imperative.

Availability relates to the existence of certain types of drugs in the market place, and is alone not sufficient to control costs. *Affordability*, however, is a complex function of factors, including not just the prices of the drugs themselves, but also the details of an individual's insurance coverage and the number of medical conditions that an individual or family confronts. Therefore, any solution to the affordability issue will require considering all of these factors together. The current high and increasing costs of prescription drugs—coupled with the broader trends in overall health care costs—is unsustainable to society as a whole.

A COMPLEX SYSTEM OF SYSTEMS

The biopharmaceutical sector[1] of the United States has a market structure that is more complex than any other sector in health care—and perhaps more complex than any other sector in the entire economy. Conventional markets involve relatively straightforward transactions with products and cash flows that can be readily traced. Producers make or import products which are then generally distributed to wholesalers who resell them to retailers who make final sales to consumers who in turn pay the bills.

Prescription drug markets are far more complex, beginning with the concept of a "prescription." Both federal and state laws regulate consumer access to certain classes of drugs, requiring the approval of a clinician before the drug can be sold to the patient. Furthermore, a prescription drug may only be purchased under the supervision of a government-licensed pharmacist. While some drugs can be acquired "over the counter," or without a prescription (which is how most other consumer goods are bought), the purchase of any medicine is considered to be potentially harmful and may warrant the approval of a clinician.

The U.S. government stringently regulates which prescription drugs are available for sale. Before a drug is approved for use, it must undergo an extensive review by the U.S. Food and Drug Administration (FDA) for safety and efficacy. If approved, its subsequent use is monitored in order to identify any adverse effects that were not detected in the original approval process. Both new branded drugs and their generic competitors (drugs usually made by companies other than the original patent holder after the patent has expired) are subjected to the FDA's approval process.

This complexity is compounded by the structure of the health insurance market, which is more complicated for prescription drugs than for other aspects of health care. Medicines are sold by retail pharmacies or by mail-order providers who purchase the drugs from wholesalers, who in turn purchase them from manufacturers, much as in a regular consumer market. But in the case of prescription drugs, health insurance plans intervene to help pay for the drugs, and there are additional layers of financial intermediaries. The most prominent of these intermediaries are the pharmacy benefit managers (PBMs), who interact with prescription drug insurers—and sometimes directly with employers offering health insurance plans—to negotiate prices both with manufacturers and with retail pharmacies. Adding further to the complexity, drug manufacturers very commonly offer price rebates to PBMs, but no meaningful information exists to determine the size of those

[1] The term "biopharmaceutical sector" used in this report encompasses a wide range of participants from researchers and physicians to industrial producers, from public and private payers to intermediaries such as pharmacy benefit managers, and from health care organizations and care providers who can prescribe medications to patient advocacy organizations.

rebates, what portion of the rebates eventually results in lower prices for patients, or the portion that the PBMs retain as profit.

Adding still another layer of complexity to the system, biopharmaceutical companies advertise their products directly to consumers via television, the Web, and other media. In some cases, the companies also offer patients copay coupons to offset the cost sharing of payments required by most prescription drug insurance plans. This commonly occurs when a branded (and relatively high priced) drug is placed in a high cost-sharing tier by insurance plans and a lower-cost (commonly generic) alternative drug is placed in a low cost-sharing tier by those same plans. The net effect of this cost-sharing model is to steer the consumer to choose the more expensive drug, with the additional cost being incurred by the insurer (thus raising premiums).

The resulting complexity of the system makes it difficult to understand the contributions of the various factors that affect drug costs, a difficulty only magnified by the fact that there is very little publicly available information concerning the financial transactions among the various participants in the biopharmaceutical supply chain. The sort of meaningful data required for developing a clear understanding of even the most basic issues, such as the distribution of funds among participants in the production chain (manufacturers, wholesalers, and retailers) and the financing chain (manufacturers, PBMs, insurance plans, and retailers), simply do not exist or are not accessible. This lack of transparency frequently makes it impossible to pinpoint the root causes of increasing drug prices. Thus, the various participants in these processes can plausibly deny responsibility and blame others for price increases. Moreover, some of the participants in the supply chain vigorously assert that making these transactions transparent would harm consumers by further increasing costs, although the validity of this claim largely depends on the specific information that might be disclosed and to whom it is disclosed.

In sum, the biopharmaceutical sector is fraught with discordant viewpoints, divergent priorities, and conflicts of interest that can impede the provision of quality health care, especially to socioeconomically disadvantaged populations. Beyond all this complexity and uncertainty, with the vast and ever-increasing amount of material available on the Web, television, and other sources, patients frequently find themselves confronted with information regarding treatment options that may contradict the information they receive from their clinicians, even in the case of very specific health conditions. Other factors, including a patient's personal financial circumstances and insurance coverage, compound the difficulties that clinicians, patients, and their families face when attempting to make sound health care decisions, often involving prescription drugs.

Against this background, policy makers—and the people they represent—face a crucial question: How can the desirable goals of making

medicines affordable and new products available best be balanced in a world where the market mechanisms that usually moderate product prices have been blunted or even eliminated? To answer this complex question, the National Academies of Sciences, Engineering, and Medicine undertook a study with the task shown in Box S-1.

The overarching conclusion of this resulting report, *Making Medicines Affordable: A National Imperative*, is that **consumer access to effective and affordable medicines is an imperative for public health, social equity, and economic development; however, this imperative is not being adequately served by the biopharmaceutical sector today.** This conclusion is supported by the report's **32 findings** on a variety of issues relating to the affordability of medicines, including the vital need to broaden the current understanding of the biopharmaceutical supply chain, the financial interactions among its participants, and the often contradictory and confusing nature of the information that is available.

BOX S-1 Scope of the Study

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will examine patient access to affordable and effective therapies, with emphasis on drug pricing, inflation in the cost of drugs, and insurance design. The committee will examine:

- Structural factors influencing drug pricing: for example, patents (regulated monopolies), the role of health insurance, and information asymmetries between patients and providers.
- Policy factors, such as drug reimbursement and cost-sharing policies (such as copays and coinsurance), Medicare and Medicaid reimbursement policies, and state laws prohibiting restrictions on drug prescribing.
- Drug access programs, such as the 340B program and copay assistance programs.
- The emerging role of comparative effectiveness assessments in payment policies.
- Changing finances of medical practice with regard to drug costs and reimbursement.
- Measures to prevent drug shortages and foster continued innovation in drug development.

The committee will issue a report with findings and recommendations for policy actions that could address drug price trends, improve patient access to affordable and effective treatments, and encourage innovations that address significant needs in health care.

The findings presented in this report are based in part on analyses of the effects of the entry of generics into the market, the bargaining power dynamics between the government and its suppliers in the biopharmaceutical supply chain, and the way in which current insurance benefit designs affect the affordability of medicines for patients. Other findings in this report relate to the effects of drug marketing practices, the implications of inefficiencies in price relief programs for vulnerable populations, the various challenges associated with the development of innovative drugs for rare diseases, and the ongoing debate surrounding "value" frameworks for drug pricing.

PROPOSED STRATEGIES TO IMPROVE THE AFFORDABILITY OF MEDICINES

To approach the proper balance between affordability and future availability of medicines in the interest of public health, this report offers a set of eight specific recommendations, with interlinked actions for their implementation.[2] Many of the recommended actions can be implemented by the relevant federal agencies with existing legislative authority; some, however, will require new legislation. In a few cases it is unclear whether existing authority suffices. The recommendations in this report are therefore made with the presumption that in cases where new legislative authority is required, the U.S. Congress will create that authority. A summary of the recommendations follows, with the relevant actors and other details for those actions specified in Chapter 4.

Recommendation A: Accelerate the market entry and use of safe and effective generics as well as biosimilars, and foster competition to ensure the continued affordability and availability of these products.

Specific implementation actions are:

- Vigorously deter manufacturers from paying other producers for the delayed entry of generics and biosimilars into the market.
- Expand the enforcement of policies that preclude mergers and acquisitions among companies possessing significant competing generics and biosimilars—either by preventing the mergers or acquisitions or by requiring the divestiture of potentially competing drug products to independent entities.

[2] Dissenting and minority views concerning these recommendations are presented in Chapter 4 and Appendixes A and B.

- Identify specific means to reduce "evergreening" of drug exclusivity via new patents or extensions on existing drugs.
- Seek reciprocal drug approval arrangements for generics and biosimilars between the regulatory agencies of the United States and the European Union, and such countries as Australia, Canada, Japan, and New Zealand.
- Reduce barriers to generic market entry and promote the expeditious market entry of additional domestic and international providers of generics and biosimilars, particularly including those not marketed by the original patent holder.
- Develop policies to restrict the use of "dispense as written" practice by prescribers that may unnecessarily impede the use of generics and biosimilars.

Recommendation B: Consolidate and apply governmental purchasing power, strengthen formulary design, and improve drug valuation methods.

Specific implementation actions are:

- Allow federal negotiation of drug prices, including on behalf of state agencies that wish to be represented.
- Test and further refine methods for determining the "value" of drugs and identify approaches to support value-based payments, formulary design, and price negotiation.
- Expand flexibility in formulary design to allow the selective exclusion of drugs, such as when less costly drugs provide similar clinical benefit.
- Amend the Medicaid Drug Rebate Program to allow for exclusion of certain drugs from coverage under the rebate provisions.
- Expand demonstration projects that test alternative payment models for prescription drugs and assess the impact of such models on health care outcomes and costs.

Recommendation C: Assure greater transparency of financial flows and profit margins in the biopharmaceutical supply chain.

Specific implementation actions are:

- Require biopharmaceutical companies and insurance plans to disclose net prices received and paid, including all discounts and rebates, at a National Drug Code level on a quarterly basis. Obtain, curate, and publicly report this collected information. Conduct

analyses of these data and inform relevant congressional committees, and examine these data to identify and act on any anticompetitive practices in the market.
- Require biopharmaceutical companies to submit an annual public report stating list prices; rebates and discounts to payers, including changes thereto; and the average net price of each drug sold in the United States. All net drug price increases that exceed the growth in the consumer price index for the previous year should be reported to the relevant congressional committees.
- Expand the disclosure requirements on all sources of income by organizations in the biopharmaceutical sector that are exempt from income tax under the Internal Revenue Code.

Recommendation D: Promote the adoption of industry codes of conduct, and discourage direct-to-consumer advertising of prescription drugs as well as direct financial incentives for patients.

Specific implementation actions are:

- Terminate the tax deductibility of direct-to-consumer advertising expenses.
- Adopt industry codes of conduct that reduce or eliminate direct-to-consumer advertising of prescription drugs and support efforts to enhance public awareness of disease prevention and management.
- Prohibit patient coupon programs, in which pharmaceutical companies give payments or discounts to consumers who fill prescriptions for the company's drug, except in cases where no competing drug is available in the market.

Recommendation E: Modify insurance benefits designs to mitigate prescription drug cost burdens for patients.

Specific implementation actions include:

- Establish limits on the total annual out-of-pocket costs paid by enrollees in Medicare Part D plans that cover prescription drugs by removing the cost-sharing requirement for patients who reach the catastrophic coverage limit.
- Modify the designs of plans offered through Medicare Part D and governmental health insurance exchanges to limit patients' out-of-pocket payments for drugs when there is clear evidence that treatment adherence for a particular indication can reduce the total cost of care.

- When patient cost-sharing is calculated as a fraction of drug prices in insurance policies through Medicare Part D and governmental health insurance exchanges, this calculation should be based on net prices, not list prices. All state and private prescription drug plans should be encouraged to follow this approach.
- Specifically include the costs and clinical effectiveness of prescription drugs and available treatment alternatives when determining patient cost-sharing rates. This evaluation should address, where feasible, the total costs of care rather than simply the costs of the drugs themselves.

Recommendation F: Eliminate misapplication of funds and inefficiencies in federal discount programs that are intended to aid vulnerable populations.

Specific implementation action is:

- Increase oversight and regulation of the 340B program to assure that participation by covered entities, contract pharmacies, and drug manufacturers is consistent with the intent of the original legislation. Oversight should include systematic collection and assessment of data from qualified medical providers and participating drug manufacturers regarding the volume of drug purchases eligible for 340B discounts, revenues generated from 340B program participation, and safety-net services funded by these revenues.

Recommendation G: Ensure that financial incentives for the prevention and treatment of rare diseases are not extended to widely sold drugs.

Specific implementation actions are:

- Promote agreements that enable concessions on launch price, annual price changes, or assistance in satisfying important public health goals.
- Ensure that drugs with orphan designation receive program benefits under the act only for the target rare disease, not for ancillary non-orphan indications.
- Eliminate unnecessary sub-classifications of disease categories that create artificial eligibility for orphan drug status, and limit eligibility to only one orphan condition per drug.
- Limit the market exclusivity awarded to orphan drugs to one 7-year extension.

Recommendation H: Increase available information and implement reimbursement incentives to more closely align prescribing practices of clinicians with treatment value.

Specific implementation actions are:

- Establish payment policies for drugs administered by clinicians in medical practices and hospitals that do not differentiate for the site of care (site neutral payment).
- Ensure that clinicians have readily accessible and routinely updated information regarding drug cost and efficacy to support sound prescribing decisions at the point of care. This information should include the relative clinical benefits of alternative treatment regimens and the relative financial costs of treatment settings to both patients and payers.
- Eliminate the practice of reimbursing clinicians and standalone and hospital-based clinics on the basis of list prices for drugs covered under the Medicare medical benefit. Replace the current reimbursement model with fixed fees supporting clinical care and the costs of storing and administering these drugs.
- Substantially tighten restrictions on pharmaceutical detailing visits, the acceptance and use of free drug samples, special payments, and other inducements paid by biopharmaceutical companies to clinicians, medical practices, and hospitals.

STEPS TOWARD AN IMPROVED BIOPHARMACEUTICAL SECTOR

Economic incentives created by laws that protect intellectual property have served the United States and other countries well in terms of increasing the availability of prescription drugs. However, for a number of reasons, including the widespread adoption of health insurance that covers prescription drugs, in the United States the normal market forces that would be expected to control prices on these drugs have been dissipated.

Most other developed countries have patent-based economic systems similar to the one used in the United States. These systems are generally interrelated through international treaties and in many cases appear to provide prescription drugs at lower costs than in the United States. A primary difference is that many other nations have regulatory systems that do not exist in the United States to control, directly or indirectly, the cost of prescription medications. As a consequence, people living in the United States often pay substantially more for prescription drugs than people in other high-income nations.

The actions recommended for implementation in this report—even if wholly adopted—would likely be insufficient to bring the cost and availability of drugs to the point apparently sought by much of the public. A number of additional alternatives remain, none of which are, at this point, presented as recommendations in this report because of the significant disruption they could evoke in the biopharmaceutical sector. These options range from taxation on excess profits and federal appropriation of intellectual property to the further centralization of government price negotiation or price control, and implementing pricing models similar to those used in public utilities or defense.

While legitimate arguments can be made that the package of actions recommended in this report could themselves produce unintended changes in some parts of the biopharmaceutical sector, the alternative is to preserve and propagate the status quo—which, along with the benefits it has offered, would continue to produce damaging consequences on the health and welfare of the public. Simply stated, the biopharmaceutical sector needs repair.

Some attributes that an ideal biopharmaceutical system would possess include focusing on prevention as well as treatments and cures; stimulating robust research and development on drugs that enable fundamental improvements to human health; rapidly adapting to new discoveries; adopting technologies, systems, and practices that improve health care; providing effective drugs that are affordable to all patients, including the disadvantaged; being affordable to society as a whole; sustaining itself financially over time; and ultimately, improving the health of the nation.

Unfortunately, no known biopharmaceutical system possesses all these attributes; some attributes might even be mutually exclusive. The recommendations of this report are therefore oriented toward reducing the cost of prescription drugs while still enabling the continuing development of new drugs—always keeping in mind that the foremost responsibility of the biopharmaceutical sector is to serve the patient.

1

The Affordability Conundrum

"Every system is perfectly designed to get the result it gets." Credited to various individuals, this quote is descriptive of the U.S. health care system and, specifically, the biopharmaceutical sector.[1] The subject of many commentaries—often political, occasionally technical, and frequently humanitarian—the U.S. health care "system" is antithetical to the very concept of a system, with its components pursuing differing and often contradictory goals. The system's participants—from patients to clinicians and health plans to product manufacturers, as well as various intermediaries such as pharmacy benefit managers—constitute and interact within a complex enterprise that is projected to consume 20 percent of the nation's gross domestic product by 2025 (Keehan et al., 2017).

The high cost of health care is—and has been for some time—a burden on individual patients, their families, and society as a whole. People with chronic health conditions are particularly vulnerable because their illnesses or the treatments for their illnesses impede their ability to work, with some patients losing employment altogether. Such individuals frequently incur significant financial debt and deplete the assets they need to pay for treatment, some to the extent that they must resort to bankruptcy. Cancer patients especially face severe financial risks—or "financial toxicity" (NCI, 2017)—and have a materially higher rate of personal bankruptcy than

[1] The term "biopharmaceutical sector" used in this report encompasses a wide range of participants from researchers to physicians to industrial producers, from public and private payers to intermediaries such as pharmacy benefit managers, and from health care organizations and care providers who prescribe medications to patient advocacy organizations.

those who have not been diagnosed with cancer (Ramsey et al., 2013). One important factor in this economic reality is the nation's highly complex system of creating, manufacturing, and supplying prescription drugs—products that are critical to improving health, saving lives, and enhancing public welfare.

The past half-century has seen a steady rise in the expenses associated with prescription drugs and other key elements of the health care system. To illustrate the growing importance of prescription drugs as a driver of medical spending, Figure 1-1 displays compound annual growth rates in inflation-adjusted, per capita spending for various segments of the health care system. The graph shows two relevant periods: 1960 to 1980 and 1981 to 2015. The year 1980 creates a convenient separation both for hospital and clinician payments as well as for biopharmaceutical products. While spending relating to hospital and clinician payments fell because of Medicare reforms, the growth pattern for prescription drugs followed an entirely different path as influenced by three legislative changes: the Bayh–Dole Act of 1980, the Orphan Drug Act of 1983, and the Hatch–Waxman Act of 1984. Since the early 1980s, spending on drugs has increased at

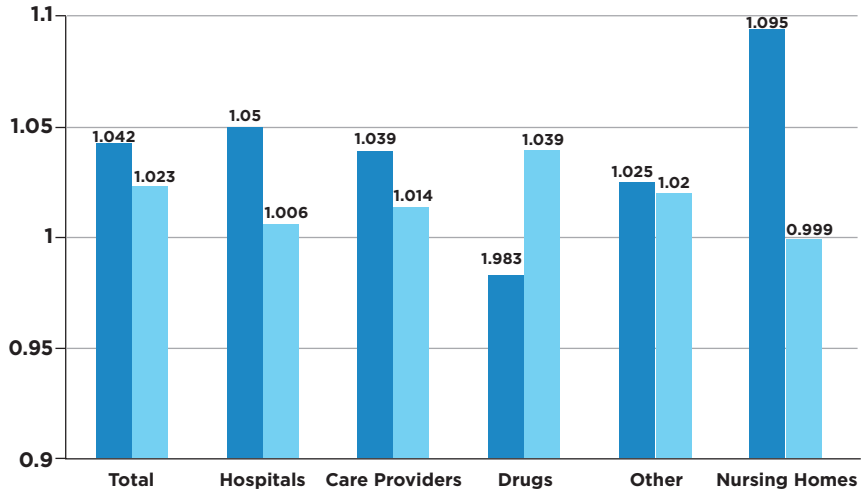

FIGURE 1-1 Proportional change in real per capita spending by sector before (dark blue bars) and after (light blue bars) 1980. Retail expenditures on "drugs" grew slightly more rapidly than other components of the health care spending. "Drugs" corresponds to retail sales, excluding drugs dispensed in hospitals, nursing homes, and clinician offices. "Other" spending includes the proliferation of private surgical and imaging centers as well as urgent care facilities, none of which would in general be classified either as hospital or clinician.
SOURCE: Data from Phelps, 2018, Table 1.8.

nearly 4 percent annually, even after adjusting for general inflation and population growth.

THE MICROCOSM OF PRESCRIPTION MEDICINES

Prescription drug expenditures in the United States are currently about 17 percent of the overall cost of personal health care services (Kesselheim et al., 2016) (see Box 1-1 for additional discussion). Referred to by some as "priceless goods," prescription medicines are becoming steadily more expensive and have become both a regular topic in the popular press and a major sociopolitical concern (KFF, 2017a). However, it is difficult to determine exactly what corrective measures should be introduced because both the biopharmaceutical sector, which is responsible for developing and delivering medicines to the public, and the policies that govern this sector are exceptionally complex and non-transparent—more so than nearly any other sector of the health care system or, indeed, any other sector of the entire economy.

Prescription drug policies at both the federal and the state level are the result of extensive technocratic decision making. However, individual patients and their families relate to the biopharmaceutical sector in a very direct manner, responding to such issues as access, cost, and efficacy on a very personal level. More than half of all people in the United States routinely use prescription drugs, and 15 percent of the population regularly takes five or more drugs (Kantor et al., 2015). For example, a woman in the initial stage of treatment for one type of breast cancer may take cytotoxic chemotherapy drugs and a monoclonal antibody (a specialty drug) along with anti-nausea drugs and perhaps an antidepressant.

Specialty drugs[2] are among the most expensive of all drugs, and in recent years their prices have grown at a double-digit rate (Hartman et al., 2015). This sharp increase in prices is due in part to the introduction of expensive new drugs (such as those for hepatitis C, multiple sclerosis, and cancer) and in part to rapid price hikes for existing specialty drugs (QuintilesIMS, 2016). For illustration, a recent analysis showed that a

[2] "Specialty drug" is a general term for medications that feature one or more of the following characteristics: highly expensive, complex molecularly (often derived from living cells), non-standard administration process such as via injection or infusion, limited availability or having a specialized distribution network, or indicated for a rare or complex syndrome. Historically, drugs in the specialty category have included biologic agents that require special handling and ongoing monitoring and that are administered by injection or infusion. The Centers for Medicare & Medicaid Services considers any drug that exceeds a cost threshold of $670 per month to be a specialty drug, and this applies only to Medicare Part D but not Medicaid. There is no uniform definition of a specialty drug, and different pharmacy benefit managers have different collections of drugs that make up their specialty lists.

BOX 1-1 How Big Is the Share of Prescription Drugs in the U.S. Health Care Spending?

The share of health care costs in the United States attributable to biopharmaceutical products is a contentious topic, with the numbers currently ranging from 10.2 percent to 16.7 percent.

In the calculation of total costs, two parameters affect the numerator: retail sales (directly to patients) and institutional sales (to hospitals, clinicians, nursing homes, infusion centers, home health agencies, and clinics). For 2015, based on data from the report of the Office of Assistant Secretary for Planning and Evaluation for the U.S. Department of Health and Human Services (ASPE, 2016),[a] retail pharmaceutical product sales accounted for $328 billion (71.9 percent of total). Institutional pharmaceutical product sales and total pharmaceutical product sales were $128 billion (28.1 percent of total) and $457 billion, respectively.

Similarly, two numbers affect the denominator: personal medical expenditures and other medical expenditures. The latter includes expenditures on construction and equipment, research, and administration of both public and private health insurance plans. Personal medical expenditures include payment for all health care services and products (such as medications, durable medical equipment, and supplies) directly used by patients. For 2015 (ASPE, 2016), personal medical expenditures totaled to $2,729 billion (85.1 percent of total), other medical expenditures were $477 billion (14.9 percent of total), leading to total medical expenditures of $3,206 billion.

Ratios can be calculated from the numbers above in four possible ways:

1. Retail sales to total medical expenditures is 10.2 percent.
2. Retail sales to personal medical expenditures is 12.0 percent.
3. Total pharmaceutical sales to total medical expenditures is 14.3 percent.
4. Total pharmaceutical sales to personal medical expenditures is 16.7 percent.

The ASPE report identifies 16.7 percent as the most relevant calculation for assessing trends in prescription drug spending, and also notes that: "Expenditures on prescription drugs are rising and are projected to continue to rise faster than overall health spending, thereby increasing this sector's share of health care spending."

The 16.7 percent number is used in this report because it is the most relevant to patients.

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[a] The ASPE report states that, "The most widely used estimates of prescription drug spending in the United States come from the National Health Expenditure Accounts (NHEA). The NHEA estimates include only retail prescription drug spending (drug spending at outlets that directly serve patients); non-retail prescription drug spending (spending by medical providers for drugs they provide directly to patients) is classified under the spending category corresponding to the provider purchasing the drugs, such as hospital spending or physician services spending. Thus, most estimates of prescription drug spending in the United States omit the non-retail portion of drug spending and present an incomplete picture of the total cost associated with prescription drugs" (ASPE, 2016, p. 2).

Total medical expenditures are from the Centers for Medicare & Medicaid Services National Medical Expenditure data.

branded injectable synthetic progestin used to lower the risk of preterm birth costs more than 50 times that of the identical generic formulation, consuming on a national level more than $1.4 billion per year compared to the $27.5 million costs associated with the generic option (Fried et al., 2017). Although specialty drugs accounted for about 2 percent of prescriptions dispensed in 2016, they represented more than one-third of total prescription drug spending (Express Scripts, 2017; QuintilesIMS, 2017).

The general public considers lowering the cost of prescription drugs as one of its highest health care priorities. In 2017, 61 percent of the respondents in a poll assigned the issue a top priority (KFF, 2017a), with another survey ranking it first among domestic issues requiring priority action from the U.S. Congress (Politico, 2017). Although the vast majority of the public believes that prescription drugs have improved the lives of people in the United States, most also have an unfavorable view of pharmaceutical companies and believe that they make excessive profits (KFF, 2017b). Not surprisingly, patients who take multiple prescriptions as well as low-income and uninsured patients are most likely to report having difficulty affording prescription medications (KFF, 2017b). Reflecting this public sentiment, in the past 2 years, state legislators have proposed a multitude of bills focusing on unfair drug pricing and price transparency. Several of these bills have passed into law.

Efforts to reform the market for prescription drugs in the United States have often become entangled in larger policy debates about overall health care financing and delivery. Health care in the United States is financed by a variety of payers, including federal and state government insurance programs, private employers, unions, and households (CMS, 2015). Individual payers, such as insurers and health plans, negotiate prices—often unique—for the prescription drugs they cover. These negotiations are generally promulgated through intermediaries such as pharmacy benefit managers (PBMs). Individuals without prescription drug plans self-pay and are unable to take advantage of the lower prices that can be negotiated by large insurers or PBMs (Danzon, 2014). Accordingly, the uninsured often depend on financial assistance programs from pharmaceutical companies or others. The size and structure of the U.S. health care system and the sheer number of participants and roles in the biopharmaceutical sector complicate the manner in which drugs are valued and costs are determined.

THE REAL PRICE OF A "PRICELESS GOOD"

Determining the "value" of a drug and what constitutes "fair" pricing is a contentious and confounding topic. Various stakeholders have different concepts of the value of a drug and what a fair price for it would be. Within this dynamic, participants in the biopharmaceutical sector can each assert

that their ultimate goal is to make safe and effective medicines and provide "value" to patients. However, an inherent conflict exists between the desire of patients (and society) for affordable drugs and the expectations of—as well as legal obligations to—corporate shareholders and other investors in biopharmaceutical companies for a competitive return on investment.[3] In short, patients emphasize value in terms of their direct personal benefit rather than in business or economic terms (Buzaglo et al., 2016).

Presently, different patients pay different prices for identical drugs, with individual prices depending mainly on the specifics of their health insurance plans, which generally include cost-sharing features such as copays, deductibles, and coinsurance. In severe financial circumstances, patients' health care expenses also adversely affect other members of their families. Consider, for example, an individual with rheumatoid arthritis who has an annual income of $55,000 (near the national median), a spouse, and two dependents. Assume that the individual's monthly payroll contribution to purchase health insurance is $400 ($4,800 yearly) and that the deductible is $3,500, coinsurance is 20 percent, and the annual out-of-pocket maximum under the individual's insurance policy is $7,000. The yearly cost of that person's medications may well reach $30,000 if the rheumatoid arthritis is treated with an expensive specialty drug; thus, that individual will need to pay $11,800 ($4,800 for the insurance plus $7,000 for the maximum out-of-pocket expenses) each year for health-related expenses. The individual would then need to cover the rest of the family expenses with the remainder of his or her income, after taxes. This is a reality that many patients face when medical expenses consume much of their gross income. For those who are uninsured, the situation is far bleaker.

Drug manufacturers often attribute the high cost of medications to the complexity of the technology and of the testing required of new products, the high failure rates associated with drugs under development, and national and international regulations intended to ensure that medicines are safe and effective (Rosenblatt, 2017; Rosenblatt and Termeer, 2017). Drug candidates must first be discovered and then tested, with each step requiring a series of intricate experiments. If the initial tests are promising, the drug candidate is then put through a series of clinical trials to determine its safety and efficacy. Gaining approval from the U.S. Food and Drug Administration (FDA) requires large, complex, multicenter—and often multinational—trials that are carried out by a network of clinical investigators, statisticians, consultants, and other professionals, all of which is very expensive.

Despite the generally recognized expense of developing drugs, many individuals believe that drug companies and intermediaries in the supply

[3] Some members of the committee disagree with this statement. Please see Appendix B for a minority perspective.

chain are exploiting the complexity of the system by charging high prices for drugs without transparency and without justification. These views are common even for drugs that have moved into the generic market (Bach, 2015).

To understand this concern among the public, consider, again as just one example, the case of the leukemia drug imatinib (Gleevec). Upon its U.S. release in 2001, it cost $4,540 per month of treatment. In 2016, after 15 years on the market, it cost $8,500 per month in the United States, but cost $4,500 and $3,300 per month in Germany and France, respectively (Bach, 2016). This increasing cost over time is not unique to Gleevec; cancer drug prices, for example, have on average quadrupled in the United States over the past 20 years (Bach, 2017; Conti et al., 2015; Dusetzina, 2016). In the case of Gleevec, this price increase occurred despite the presence of two factors that would normally bring prices down. First, because leukemia patients are living longer due to the drug's effectiveness and because new indications for the drug have been approved (Bennette et al., 2016), the population treated with the drug has expanded, which has increased sales volume of the drug. Second, other drugs that target the same abnormal protein have entered the market. For most types of non-medical products, such a combination would result in more options and lower costs and prices.

Most other cancer drugs are considered to be less effective than Gleevec in extending the lives of cancer patients, yet when new cancer drugs enter the market, their prices are similarly high (Dusetzina and Keating, 2015). A lack of competition, combined with state and federal regulations specifying that insurers must include cancer drugs in their formularies (Bach, 2009), provides sellers with considerable pricing flexibility. These factors—and others—tend to drive the already high prices of drugs in the United States even higher, but it is not clear exactly how large a role each factor plays or how the various factors interact. One powerful force, however, is the extensive and increasing health insurance coverage for prescription drugs that blunts—and in the case of full coverage, eliminates—normal consumer-related market forces that might otherwise control prices.

A SYSTEM OF CONFLICTING SYSTEMS

The current structure of the biopharmaceutical sector often gives rise to conflicting interests and positions. The principal conflict is between two desirable objectives: (1) making drugs affordable from the standpoint of patients and society, and (2) making new drugs available from research and development efforts. *Affordability* refers to how easy or feasible an individual (or, more broadly, society) finds it to pay for a drug. It is a function of drug prices, insurance coverage, a family's financial circumstances, and, sometimes, the purpose of the drug. To some, for example, $200 might be

an unreasonable amount to pay for a migraine prescription, but it might not be too much to pay for a drug that extends a person's life. *Availability* refers to the presence or absence of particular types of drugs in the marketplace. As described above, drugs become available only after a long process of discovery, development, approval, manufacturing, and marketing, and might be unavailable because they have not been discovered and developed or because of a failure in the supply system.

Policy interventions can and often do advance one of these two objectives at the expense of the other. As a simple example, it has frequently been proposed that restrictions should be imposed on the launch prices of medicines in order to make them more affordable. However, such price controls could erode incentives and make drug companies less likely to make the investments necessary to pursue the research and development that leads to future therapies (Maitland, 2002; Scherer, 2000).

An alternative to price control is formulary control. For example, the setting of copayment tiers by PBMs and insurance plans can be an effective tool to influence patients' choices among competing treatment options. It can also influence the prices manufacturers offer for their products in order to gain access to a more favorable tier. But providing greater insurance coverage for individuals, without other mitigating changes can increase both the quantities of the medications consumed and their prices (Newhouse, 1988). This in turn would drive total insurance expenditures further upward.

Most policy changes introduced to address these and other issues have been, at best, incremental and have often been subject to substantial compromise among the entities possessing market power and political influence. These issues are not entirely unique to the United States; however, a major challenge in the United States is that the market is exceptionally large and highly fragmented. Efforts to consolidate this market are likely to create substantial backlash from the diverse groups that benefit from the current market arrangement.

MARKET FORCES

One approach to the resolving conflict between biopharmaceutical affordability and availability is to let the "free market" determine the best course forward. For most consumer goods, free market maximizes consumer choice and makes decisions based on the economic "votes" of people participating in a particular market. In the United States, market forces are generally considered to be the most economically efficient way of determining what goods are provided and at what price—and also the fairest way of determining how limited resources should be allocated (Elegido, 2015; Friedman, 2009). However, relying entirely on free market

solutions in the case of prescription drugs is complicated because describing the biopharmaceutical supply chain in the United States as largely driven by *competitive* market forces would be substantially misleading.

The dynamics of the biopharmaceutical supply chain reflect the actions of profit-seeking enterprises operating within an extremely complex array of privileges and constraints set by the government. The nature and significance of these government interventions—which include the funding of research, the granting of market exclusivity, the enforcement of strict product requirements and standards, and acting as the ultimate purchaser for large segments of the population—mean that the market is distorted in many ways. Simply stated, the typical presumption that market forces will work—and work best—does not hold well for the biopharmaceutical sector. The nature of these market forces is powerfully shaped by government and other interventions, and is also contingent on specific diseases and their overall impact. In contrast with the market for most household goods, in which consumers are the primary decision makers, consumers wield relatively modest influence over decisions related to medicines. Instead, prescribers largely determine which drugs are to be purchased and in what quantity, and patient cost-sharing arrangements specified by prescription drug insurance plans influence whether patients obtain the medicines prescribed.

Another unique characteristic of the biopharmaceutical supply chain relates to the number of intermediaries. One approach frequently posed as a solution to make current drugs affordable while not affecting future drug development is to reduce the value extracted by the biopharmaceutical intermediaries in the supply chain. The profits generated by PBMs, wholesalers, and retail pharmacies, coupled with insurer's profits and the margins on reimbursement for drugs administered in the hospital or outpatient setting, ultimately affect the patients and their ability to pay for therapies, and do not increase the incentives to develop new drugs.

This is not to say that intermediaries play no useful function. Managing drug plans, wholesale logistics, and retail dispensing are among the essential functions performed by intermediaries in the biopharmaceutical supply chain. Another benefit intermediaries offer is to negotiate lower prices for their clients, including insurers and self-insured employers who can potentially turn those savings into lower insurance premiums or cost sharing for their enrolees. The question is whether market forces in the biopharmaceutical sector work effectively enough to ensure true competition and prevent excessive profits that otherwise might have been passed on to patients. The answer to this question is hotly contested, with participants in the biopharmaceutical supply chain typically pointing at each other, while claiming that their own activities deliver substantive benefits to patients.

Another form of market failure relates to externalities, which occur

when an economic activity (such as the purchase or sale of a product) has costs or benefits for others not directly involved in the transaction. Many choices about drug treatments carry societal externalities, both positive and negative. The use of effective vaccines and drugs for infectious diseases, for example, has benefits that are widely diffused across society, as people who might otherwise have been exposed to the disease are protected by others' use of the pharmaceuticals (Boulier et al., 2007). Yet, vaccinated patients and their insurers are generally asked to bear the entire cost of the preventive action. Conversely, a person who chooses not to receive vaccines or drug therapies may cause negative externalities, including reduced herd immunity and greater spread of the disease as well as the associated costs to society when resources need to be devoted to subsequent medical interventions that could have been avoided. In certain cases, a treatment can eliminate substantial non-drug medical expenses later in life (e.g., the use of a hepatitis B vaccine), and the financial and emotional benefits of treatments are thus realized by both individuals and society as a whole.

SOCIAL JUSTICE

Market failures aside, another reason to question the wisdom of allowing the market to determine the optimal balance between affordability and availability of medications is the potential consequences of this approach for vulnerable populations. Because the organization of the market requires, or allows, high prices to be charged for many drugs, individuals with serious health needs may be unable to afford effective medications and will therefore fail to enjoy the health gains and higher quality of life that would otherwise have been possible. In some cases, the outcomes include death. As was true with HIV/AIDS in Africa, millions of people died despite the development of effective antiretroviral drugs because they were not affordable. Only the advent of generic antiretroviral combination therapy that cost $100 (versus $12,000 for branded combination medicines) allowed millions of Africans to gain access to lifesaving medicines. A similar situation exists today for patients around the world with hepatitis C, who cannot afford treatment because generic medicines will not be available for many years to come (Kamal-Yanni, 2015).

There is a degree of public consensus in the United States that allowing individuals to suffer or die because they cannot afford health care is morally wrong (Lynch and Gollust, 2010). However, there are deep disagreements about the extent to which the government should or can intervene to ensure that patients get the care they need. Overall, there is little agreement in the United States concerning the extent to which patients are ethically entitled to health care.

One view is that justice requires providing individuals with access to a

universal health insurance benefit that includes effective medications. There are several arguments made in support of this claim. One argument is that health insurance is important because access to health care eliminates needless suffering, which is a morally important end in and of itself. Another line of reasoning is that providing access to health care that includes effective medicines is important to advancing other fundamental goals of social justice. For example, health care helps advance equality of opportunity—the ability of people to fully develop their innate talents and skills regardless of their financial status (Daniels, 2007; Rawls, 1971).

Access to health care and equality of opportunity are causally linked because of the role that such access plays in preventing disease or disability that would otherwise affect an individual's ability to pursue socially meaningful goals. Having access to health care helps an individual maintain his or her health-related functioning (e.g., the ability to hold a job, earn a living, pursue activities of self-care, and maintain one's role in the family and society). On the other hand, maintaining these functions makes it possible for individuals to pursue a broad range of opportunities that society may offer them. For example, access to bronchodilator medication can control the symptoms of chronic asthma, enabling people with that condition to pursue occupations that would otherwise be closed to them.

This linkage between access to health care and equality of opportunity is a major argument for certain policies, such as those that provide government subsidies to increase the affordability of health care. However, there is no clear guidance or even agreement as to how society should prioritize which prescription drugs should be covered and to what extent subsidies should be provided. There are disagreements, for example, about the extent to which payers should balance subsidies to purchase drugs against tools to manage overall spending on drugs, such as formulary restrictions or cost sharing for patients.

Further complicating matters, policies that are optimal for some patients may not benefit other patients (e.g., the small numbers of people with rare diseases often require the most costly medicines). Some even question the extent to which society should be responsible for diseases that are attributable to behaviors of choice. In light of such issues, insurance plans need explicit and transparent processes for setting priorities, yet there is little national agreement as to what those processes should be.

THE ROLE AND RESPONSIBILITY OF FIRMS

Beyond the sorts of moral considerations that are applicable to all firms, some ethicists believe that biopharmaceutical companies have a special obligation to ensure that their products are accessible to patients who need them—even if doing so reduces profitability and returns to share-

holders (De George, 2005). But even among those who hold this view, there is widespread disagreement about the nature and extent of this obligation. No widely agreed-upon approach has emerged to prescribe the ethical obligations of pharmaceutical companies to patients or to assist management in making decisions involving such obligations. This has been a longstanding challenge, and it exists for certain other types of for-profit providers of health care goods and services as well (Vagelos, 1991).

Patients who depend on unique lifesaving drugs are especially vulnerable. If they cannot survive or maintain a tolerable quality of life without drug therapy, they arguably have no meaningful choice but to pay whatever price is demanded. Some commentators argue that this creates an ethical obligation on the part of the seller to not extract excessive profits—or perhaps in some instances even to suffer losses—in providing drugs to those who cannot refuse the seller's offer (Valdman, 2009). However, others argue that although this morally distressing situation may generate an obligation on the part of society—or, more specifically, on the part of government—to ensure that the patient has access to the drug, it does not create such an obligation for the drug's producer (De George, 2005; Maitland, 2002).

As for-profit entities, biopharmaceutical firms must compete for capital and talent in the same marketplace as other for-profit firms in other sectors of the economy, and they must therefore offer competitive returns to investors and rewarding careers to employees. Yet, unlike providers of most consumer goods and services, they are at times delivering lifesaving products to highly vulnerable individuals. Indeed, drug companies appear to see themselves as more than just another business. Their mission and vision statements often announce the intention to bring transformative therapies to patients around the world. Box 1-2 explores the potential of new business models—beyond traditional profit maximization—in the biopharmaceutical sector.

Because of the dual identity of biopharmaceutical companies as both for-profit manufacturers of goods and providers of medical products that significantly contribute to the public good, there is today no agreed-upon approach for applying ethical standards to their operations. The ordinary principles of business ethics (focusing, for example, on honesty and adherence to commitments) seem to not go far enough in defining drug companies' obligations to their patients and shareholders. Alternative frameworks, such as principles of medical ethics, demand an absolute fidelity to patients' interests. But at this point there is no agreement on what ethical obligations to patients, if any, spring from the distinctive and very important role of biopharmaceutical companies. Nor is there broad understanding of the impact "an absolute fidelity to patients' interests" might have on a firm's viability—and on its contribution to future patients.

A considerable controversy also exists regarding what constitutes a fair

BOX 1-2 Alternative Business Models

In the biopharmaceutical sector "innovation" tends to be thought of mostly in terms of research and development. And certainly research and development is a crucial part of the sector and has made possible many important drug therapies. But other sorts of creative approaches are important as well, and they are often overlooked. For example, the underlying business and distribution models that deliver new technologies to the public are rarely acknowledged. Almost all companies advancing new health technologies in the United States—and in most developed and transition economies—do so with traditional for-profit models. The expectation is that in exchange for assuming a certain amount of risk, shareholders and other investors will get reasonable returns on any of a company's successes.

One of the primary reasons to augment the traditional business model is to significantly increase affordability and availability for underserved populations. Numerous nonprofit business models have been tested and deployed effectively in the realm of global health (IOM, 2009), including, for example, a nonprofit pharmaceutical company that developed a cure for visceral leishmaniasis, that later also developed artemisinin for malaria in partnership with a for-profit pharmaceutical company and a nonprofit public health organization (Hale et al., 2005; Reuters, 2014).

Traditional for-profit corporations are often hesitant to broadly increase access to new medicines to underserved populations because of some concerns that doing so may lead to a significant loss of profits and that shareholders will not be adequately or even fairly served. However, there are many opportunities to experiment with various hybrid for-profit and nonprofit business models, social benefit corporations, and product development partnerships that are intended to improve health and health care. These efforts could specifically inform the creation and evaluation of new entities for drug research, development, and distribution.

return on investment in biopharmaceutical research and development. One particular conception of the principle of fairness relies on the notion of just rewards for effort expended and risk incurred. Because biopharmaceutical companies incur substantial risk and invest considerable time, money, and effort in the development of new products, the argument goes, fairness in pricing implies that they should be able to reap the returns of their investments (De George, 2005). The argument is bolstered by the fact that pricing its products very affordably could even drive a drug company out of business. Those who apply this particular framework in discussions about drug pricing are likely to be resistant to suggestions about restricting prices or intellectual property rights in the biopharmaceutical sector.

The idea that investments in research and development must be fairly rewarded is closely related to another general concern for biopharmaceu-

tical companies: leaders of public companies have a fiduciary obligation to maximize shareholder value while operating within the law. Similarly, leaders of smaller companies that rely on venture capital to finance their research and development feel obliged to fulfill their promise to deliver highly competitive returns to their investors. Corporate leaders, then, may not feel at liberty to price prescription drugs in a way that maximizes affordability to consumers.

The principle of near-absolute fidelity to shareholders is itself controversial, especially when profits are derived from non-market circumstances. In at least some cases, drug companies may be able to take advantage of market failures caused by aspects of the regulatory process. As one example, the backlog of applications for generic drugs at the FDA has at times resulted in situations in which one generic firm may be the sole manufacturer of a lifesaving drug. On occasion, firms appear to have taken advantage of this situation by increasing the price of the drug beyond what would be justified based on the cost of developing and producing the drug. In this situation, the company is exploiting a weakness in the regulatory process to enrich itself at the expense of patients. Some argue that it is unjust for businesses to enrich themselves from such market dysfunctions (Heath, 2014).

Persuasive arguments have been made that corporate executives are not, in reality, obliged to maximize profits. They may instead pursue long-run shareholder value by sacrificing some short-run profit in the pursuit of the public interest, although most legal advisors suggest that doing so is not without risk to the firms and their managements (Elhauge, 2005). Some have advanced the proposition that executives may sacrifice shareholder interests under some (usually unspecified) conditions if by doing so they can alleviate human misery (Dunfee, 2006; Hsieh, 2009). Indeed, some corporate leaders have urged keeping price increases consistent with general inflation (Vagelos, 1991) and encouraged product donations—as was seen in the case of Merck's donation of medications for eradicating river blindness—in the interest of public health (Mackey et al., 2014; Vagelos and Galambos, 2004).

Whichever of these arguments, if any, one accepts, the basic tension between affordability and availability remains: there are inevitably trade-offs between maximizing affordability in the short term and rewarding investment in order to promote the development of the greatest number of effective therapies in the long term. Some believe that drug companies will be more likely to develop new therapies if they perceive that the market will reward them for their research and development (Taurel, 2005). To some commentators, this justifies allowing markets to set higher prices even for the most essential medications (Maitland, 2002).

Humans have a natural tendency to prefer short-term benefits to "identified lives" as opposed to more distant benefits that "some people" in the

future may enjoy (Cohen et al., 2015; Frederick et al., 2002). Indeed, the public conversation about drug prices has been galvanized by publicity surrounding highly sympathetic cases in which particular patients cannot afford particular drugs.

Ultimately, however, the tension between taking steps to help patients and continuing to foster additional research and development for public health and future patients is fundamental and must be explicitly confronted if a defensible pricing policy is to be established in the United States. This will not be easily done.

GLOBAL TRADE-OFFS

The issue of drug affordability has in recent years become highly politicized, with frequent references to the fact that drugs, often developed in the United States, are priced lower in many other parts of the world. On a per capita basis, the United States indeed spends more than any other country on prescription drugs, more than twice than what the United Kingdom spends (Kanavos et al., 2013) (see Figure 1-2). Something of a crisis atmosphere has been created by congressional and media attention to the issue,

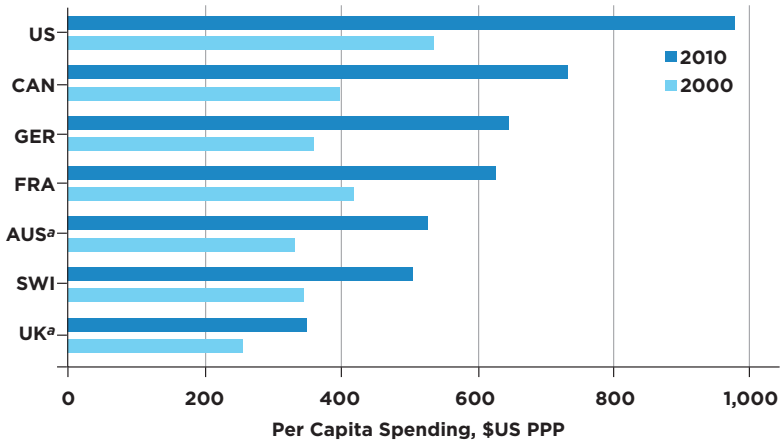

FIGURE 1-2 Total pharmaceutical spending per capita (depicted in U.S. dollars using purchasing power parity, PPP, as reference) in seven countries (2000 and 2010) with the United States showing the highest increases in comparison with other major countries. NOTES: "Expenditures are in 2000 U.S. dollars, purchasing power parity (PPP). OECD data on total pharmaceutical spending (spending for both brand-name and generic drugs) per capita generally do not include the cost of pharmaceuticals consumed in an inpatient setting. [a] Because of lack of data for 2010 from Australia and for 2009 and 2010 for the United Kingdom, 2010 expenditures for those countries are from 2009 and 2008, respectively" (Kanavos et al., 2013). AUS = Australia; CAN = Canada; FRA = France; GER = Germany; SWI = Switzerland; UK = United Kingdom; US = United States. SOURCE: Kanavos et al., 2013, Exhibit 1. Data from World Bank and Organisation for Economic Co-operation and Development.

much of which has focused on alleged "price gouging" by some biopharmaceutical companies. Under these conditions, public demands for quick actions are at odds with the otherwise deliberative policy-making processes.

Furthermore, there may be trade-offs between improving the affordability of drugs domestically and maintaining their affordability to patients in other countries. In many cases, if not in most, the prices of branded prescription drugs abroad are lower than they are in the United States, even though the drugs significantly rely on research funded by the tax dollars of the United States.[4] Pharmaceutical manufacturers argue that the potential for higher profits creates incentives for continued research and development, which can ultimately benefit people in all nations. Thus, decisions about drug prices in the United States could potentially affect drug availability and pricing in other countries, particularly those with developing economies.

The counterargument is focused on whether people in the rest of the world, particularly in high-income countries, also have any obligations to boost their research, development, and investments that lead to global health benefits. The higher prices paid by people in the United States typically benefit people in the rest of the world who are paying relatively less for their drugs. In a sense, people in these other countries may be taking advantage of the benefits of high drug prices in the United States without having to pay those high prices themselves. Most other developed countries have explicit price controls or bargaining mechanisms in place for prescription drugs, some of which use cost-effectiveness metrics. In the United States, currently there are no centralized price controls, and payers do not explicitly deny access to treatments on the basis of costs, thus enabling biopharmaceutical companies to set higher prices than in other countries. To the extent that the higher profits the companies accrue can lead to more research and development, paying higher prices for drugs in the United States could confer benefit to the people of other countries. Moreover, if purchasers in other advanced economies paid more for their drugs, there might be a benefit to the patients in the United States through more research and development, but it would likely have no direct impact on the prices paid in the United States because manufacturers could still price their products based on what the various markets will bear.

These arguments also raise a question about global justice: what obligations, if any, do the United States and other advanced economies have to patients in the less developed countries of the world? Some theories of global justice posit that members of wealthier states have moral obligations

[4] The United States commonly pays less for generic drugs than many other countries, an outcome thought to be due to greater emphasis on competition in the generic market than observed in other countries. This topic is discussed further in Chapter 3.

to consider the welfare of individuals in poorer states in their internal decision making (Beitz, 2005), but other observers have questioned the extent to which such duties can exist (Nagel, 2005). If such obligations do exist, what sacrifices would be reasonable to expect from the United States and other developed countries in order to keep drugs affordable to the rest of the world?

INSURANCE COVERAGE

The basic concept behind health insurance is that the financial risk borne by individual patients can be ameliorated by spreading the risk across large populations. This reduces the cost of treatments to some individuals, but at a cost of increasing the financial burden on others. The presence of insurance can affect people's behavior in many ways. For example, with a lower effective price, people will generally seek more and more expensive treatments than they might without insurance (Cutler and Zeckhauser, 2000). The extent to which this occurs is measured by the "elasticity of demand"—the degree to which consumers will purchase more or less of something as the price goes down or up—which appears in the prescription drug market in two distinct ways: decisions concerning whether to seek prescriptions (and care) from clinicians and choices among different prescription drug options.

In the United States, as of 2016, about 50 percent of individuals gained health insurance coverage through their employers and about 14 percent through Medicare, which is available to those older than age 65 and those who are disabled, among others. More people are covered under Medicaid and the Children's Health Insurance Program than under Medicare (19 percent).[5] Others are covered through public programs including the U.S. Department of Veterans Affairs, military service benefits, individual insurance contracts (supported in recent years by the Patient Protection and Affordable Care Act's [ACA's] health insurance exchanges) and prison systems.

Because people over the age of 65 use considerably more medications than younger people, Medicare has a substantially larger role in drug expenditures than suggested by the proportion of the population enrolled. The Medicare Modernization Act created the Part D drug benefit, which started in 2006, and was later modified in the ACA. The original Medicare structure included Part A to cover hospital services and Part B to cover clinician services and some other medical costs. Prescription drug expenses are covered under these parts if they are directly purchased and administered by the hospital or the clinician. Many Medicare enrollees also purchase private

[5] Estimates from the Kaiser Family Foundation are based on the U.S. Census Bureau's Current Population Surveys (Annual Social and Economic Supplements).

"Medigap" insurance that pays for copayments and deductibles in Parts A and B and previously also often covered prescription drug expenses. With the advent of Medicare Part D, the Medigap plans ceased to cover prescription drug costs. Medicare Part D specifically covers outpatient prescriptions. The Part D benefit is voluntary and is purchased through commercial insurance providers approved by the federal government.

The Medicaid prescription drug benefit is an optional outpatient drug benefit that all states provide. Until 2006, Medicaid provided the benefit to enrollees dually eligible for Medicaid and Medicare. However, with the passage of the Medicare Modernization Act, Medicaid ceased to provide outpatient prescription drugs to this population, which in 2013, totaled 10 million. Due to certain changes resulting from the ACA, states have increasingly been providing the benefit through managed care, an approach focused on controlling health care costs, use, and quality. Even though cost sharing is minimal for the drug benefit in Medicaid, the high cost of prescription drugs is an important issue in Medicaid, because states must fit Medicaid expenditures into their state budget.

The financial risk associated with an individual's cost of prescription drugs has increased in recent years because of the significant increases that have occurred in drug prices and in their usage. As knowledge of the complexity of human biology has increased, researchers have uncovered more and more pathways through which to treat and prevent illnesses using complex and costly biopharmaceutical products. This growing capability has also played a major role in the steady increase in the amount being spent on prescription drugs and related insurance.

For many medical conditions multiple treatment options exist, often involving choices among different types of drugs. In some cases the choices involve alternatives between using prescription drugs and other forms of medical intervention. The latter might include, for example, psychotherapy in lieu of psychoactive drugs (although the two are often used in parallel) to treat depression or other mental illnesses. Similarly, surgical alternatives and prescription drugs sometimes compete or complement one another. This commonly occurs with cardiovascular disease, where many prescription drugs (the most common class being statins) can reduce the incidence of coronary artery blockage. Without the use of such drugs, clogged coronary arteries regularly result in the need for surgical intervention or inserting stents to ensure adequate blood flow.

Pursuing this example further, among the drugs that might reduce cardiovascular risk, some statins are now available as generic products at far lower cost than their branded counterparts. Thus, clinicians and patients often confront an array of choices when deciding among various treatment options. For patients with health insurance, the cost-sharing provisions of their health plan can influence these decisions. For example, nearly

all prescription drug insurance plans create multiple tiers of drugs, with increasingly higher consumer out-of-pocket costs for the higher-tier drugs. This "tier pricing" is widely viewed as a means of steering patients to lower-cost alternatives—commonly, generics. Overlaying this is the complexity of health insurance plans in the United States, which makes it difficult for patients to become familiar with the specifics of their plan, including its cost-sharing provisions.

THE STUDY CONTEXT

Given the sheer complexity of the subject—and its high stakes—it is clear that much greater clarity is needed to guide the biopharmaceutical sector that serves the nation's (and to some extent the world's) health and economy. It is in this context that the National Academies of Sciences, Engineering, and Medicine conducted this study at the request of multiple sponsors.[6]

An ad hoc committee[7] composed of individuals with diverse professional and personal backgrounds (biographical information is provided in Appendix E) examined the structural, policy, economic, and ethical factors that influence the cost of prescription medicines. The study was focused on developing and issuing findings and recommendations for policy actions that address the fundamental tension between affordability and availability of medicines (as noted in Box S-1).

The committee held five multi-day meetings, three of which included sessions open to the public, with the other two having closed deliberations. Numerous subgroup discussions within the committee were conducted via teleconference and email exchanges. Various individuals who presented information and engaged in discussions with the committee during the public sessions are listed in Appendix D. Additionally, various stakeholders offered comments during the public sessions. Over the course of the study, letters and position statements from individuals and organizations were received, each of which was carefully considered. Several thousand pages of publicly available documents pertaining to the issue were also reviewed.

Finally, a note on how analysis was conducted for this report. There were numerous instances where the materials used by the committee cited a direct connection to—or financial support from—participants in the biopharmaceutical sector. The same was true of many persons making

[6] The study sponsors were the American College of Physicians, Breast Cancer Research Foundation, Burroughs Wellcome Fund, California Health Care Foundation, The Commonwealth Fund, Laura and John Arnold Foundation, Milbank Memorial Fund, and the Presidents' Committee of the National Academies of Sciences, Engineering, and Medicine.

[7] The committee originally contained 18 members. One member died during the course of this study; another member resigned for personal reasons.

presentations in the public stakeholder sessions. In each instance, the committee resolved conflicting and contradicting information to the best of its ability, with the understanding that the presentations and publications it accessed may have reflected the particular points of view of the authors or presenters or their organizations. No materials were discarded from consideration based purely on financial or other connections that their authors may have had with participants in the biopharmaceutical sector or other interested parties; however, this circumstance was considered in interpreting such materials.

2

Complexity in Action

The market for prescription drugs in the United States is unlike most other markets for consumer products. In fact, it is unlike even other health care markets—which themselves differ from conventional markets. In conventional markets, consumers can search for available alternatives with access to information, including discounts, reviews, and ratings. Such information enables purchasers to make informed trade-offs relating to price and quality. In the case of biopharmaceutical products, such comparative information is technical and complex, and generally inaccessible. Moreover, clinicians generally do not have information about cost-sharing details and the general financial situation of their patients. As a result, the traditional process where consumers directly search for products has to a considerable degree been replaced by insurance companies that assess benefits and costs of drugs and steer patients' choices using insurance plan design.

In contrast, the safety, efficacy, production, and distribution of prescription drugs—although not their pricing—are all highly regulated in the United States. Such regulations are intended to balance a variety of considerations, including, in particular, the needs to protect the public and to reward the risky endeavor of investing in research and development. In protecting the public, regulations are intended to ensure that drugs are both safe and effective. The severity and impact of disease need to be balanced with the possible side effects of treatment, and also with the harms that may arise from the lack of availability of those drugs. For example, lack of access to treatments for infectious diseases due to cost not only result in death of an individual, but can also lead to infection and death of others.

Regulations naturally influence the pricing of drug therapies, which are ultimately paid for by patients, their families, and society as a whole, whether through direct payments, insurance premiums, or taxes.

The processes for ensuring that various, sometimes conflicting goals are reasonably satisfied add both to the financial costs of developing drugs and to the risks and consequences of product failure. Arguably, the best interests of patients should be paramount. To begin exploring how one might approach these potential trade-offs, this chapter describes the highly complex biopharmaceutical supply chain, from drug discovery through development, distribution, financing, and the end use by patients.

RESEARCH TO RESULTS AND RETURNS

Biomedical Research

Basic biomedical research, which is usually conducted in universities and specialized research organizations, is usually the first step in a long sequence of activities that ultimately produces safe, effective, and approved drugs. Much of this research is not intended to result in directly marketable biopharmaceutical products, but rather to gain a mechanistic understanding of health, disease, and fundamental science. Historically, though, a certain amount of basic research has led to opportunities to develop new medications, at which point the applied research and development efforts commonly shift from the university or research institute setting to corporations, the latter of which bring the skills and resources necessary to develop, produce, and market prescription drugs. Almost all of these corporations operate on a for-profit basis and depend on the free market for the capital that makes them viable as developers and manufacturers of the drugs sought by patients. Researchers involved in basic research are often poorly positioned to develop their findings into a commercially viable product.

The passage through the transition from discovery to development—often termed the "valley of death"—has been (and can be further) facilitated by "incubators," organizations that help bridge the valley between discovery and application. Such technology development facilities and related clinical trial networks have been established in many forms by research universities, private corporations, state governments, and others (IOM, 2010, 2012). These joint arrangements have served an important role in making many drugs available for the benefit of patients.

Inventions emerging from research funded by the government can be patented by the university or organization performing the research. The technology covered by the patent can then be further advanced by the patent owner or licensed to others for industrial development. This situation was created by the Bayh–Dole Act, which assigned property

rights for federally sponsored research to the inventors and their institutions rather than to the government funder (e.g., the National Institutes of Health), as had previously been the case (NRC, 2011). This major shift in how property rights were assigned led to a significant expansion in drug discovery and development within universities and other research institutions. The U.S. biopharmaceutical industry is structured as it is today in part because of the Bayh–Dole Act and the response of universities and researchers to that act (Gabriel, 2014). The annual number of patents filed and licensed from government-sponsored research is estimated to have increased by almost a factor of 10 since the passage of the Bayh–Dole Act, thereby adding billions of dollars to the U.S. gross domestic product (*The Economist*, 2002; Schacht, 2009). The act motivated collaboration between academia and industry, that in turn has helped enhance the transition of products from the laboratory to the public and resulted in better treatment options for patients.

Translational research and clinical development can be conducted in companies both large and small. Many "spin-off" entities have been created by universities to move basic science into more advanced stages of product development. These entities commonly receive investments from venture capital firms or individuals who gain partial ownership of the products of the entity in exchange for their infusion of capital. This investment process is fraught with risk to both the discoverer and the investor. Each step of the biopharmaceutical research and development process has a high failure rate even before a drug gets to the point where it is ready for regulatory review. As a result, the returns on investment for successful drug products may appear to be abnormally high, since the average expected return, from the manufacturer's point of view, must also compensate for many failures. Financial markets reward those who invest in riskier ventures by providing them with higher-than-average returns. More risk leads to a higher average reward for success, thereby encouraging investments that might not otherwise occur.

Legal Exclusivity

Patent law gives an inventor exclusive right for a period of time to the use of an invention as an incentive to invent. In exchange for the legal period of exclusive use[1] of the invention, patent holders must provide sufficient information in the patent (which is a public document) to allow others to use the invention once the period of exclusivity has ended. During

[1] The term "legal monopoly" and related variants—including "regulated monopolies" as noted in this study's statement of task— have also been used by some to refer to the exclusive market protection feature bestowed by U.S. patents.

the exclusivity period, patent holders have the right to prevent others from using or bringing to market products covered by the invention without the patent holder's permission. Patents, like other forms of property, can be sold, leased, or licensed on terms mutually agreeable to the parties. Because biopharmaceutical product markets are international in scope, inventors often seek patent protection in many countries, the patent laws of which are generally coordinated through the World Intellectual Property Organization based on the Patent Law Treaty adopted in 2000. In the United States, the Leahy–Smith America Invents Act brought U.S. patent law into general alignment with these international standards.

In biopharmaceutical products, a single item often involves many patents, ranging from the chemical entity itself to the forms of delivery and sometimes even the packaging. Thus, a situation can arise where multiple patent holders mutually claim infringement by others. In such cases, agreements among the various patent holders may be necessary to bring the product to market in its final form. Patent holders are generally responsible for enforcing the exclusive use of their patent through civil court action against alleged infringement. Under 35 U.S.C. Section 284, a patent owner can claim "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty."[2] The standard 25-year exclusivity period—resulting from the Hatch–Waxman Act—begins when the patent is granted, but marketing of the drug in the United States requires approval from the U.S. Food and Drug Administration (FDA). This process can take from 1 year to more than a decade depending on the drug, shortening the effective time during which the patent has economic value.

A natural tension arises in regulatory policy between safety and efficacy versus incentives for product development. One could imagine a hypothetical world wherein no FDA safety and efficacy rules existed, but only the patent exclusivity period existed. This would increase the incentives to invest in product development but could greatly reduce the safety and efficacy of drugs appearing on the market. At the other extreme, one could imagine a world with the FDA processes in place as is the case today, but shorter (or no) legal exclusivity created by patent rights. This would likely lead to less investment and a lower rate of drug discovery and development than is achieved with the current system.

[2] An alternative to a patent for an inventor is to protect the invention as a "trade secret," in which case the legal protections of patent law are not provided, but the period of exclusive use is also not limited by law. The trade secret path is not normally available to the biopharmaceutical industry because of the disclosures that the FDA requires in order for a product to be licensed for sales.

Testing and Regulation

Once drugs have been developed, they must pass a rigorous regulatory review conducted by the FDA in the United States before they can be marketed—and, if they are to be sold abroad, after review by the corresponding agencies in other countries. To gain market approval, drugs must demonstrate both safety and efficacy. The very nature of this approval process demands considerable time and money and, once again, poses the risk of failure at every step of drug development. The first step in the regulatory review process involves animal testing to determine whether the drug indeed affects the intended target and to gather basic safety information concerning toxicity. Assuming that the results are satisfactory, the manufacturer will next file an investigational new drug (IND) application with the FDA, setting the formal review process in motion. For the subsequent human testing, the FDA seeks to ensure that adequate consent and human subject protection procedures are in place (Arrowsmith and Miller, 2013; FDA, 2006). Only a very small subset of new discoveries (1 out of 1,000 to 2,000 candidates) reaches the stage of IND application (AACR, 2011).[3]

Phase I (initial human) trials—which typically involves 20 to 80 healthy human volunteer subjects—seek to characterize drug concentrations in blood and plasma and how the drug is metabolized and to detect the most common side effects (FDA, 2016). However, in the case of severe conditions such as cancer, phase I trials may be conducted in patients with end-stage disease who have exhausted all standard therapies.

Phase II trials commonly involve several hundred human subjects and pursue several goals. First, they assess whether the drug has the potential to be effective against the target disease by testing them in patients with the disease in question, randomizing between the treatment and a placebo drug or the standard of care, or both. Researchers carrying out these trials continue to monitor side effects and safety issues. A phase II trial also seeks to determine the optimal dosing regimen (total amount, spread over a specific number of doses) and perhaps the duration of the required treatment. Approximately 70 percent of phase II trials are unsuccessful and the drug candidates are abandoned, either because the drug was no more effective than the placebo or because additional safety concerns arose during testing on the expanded number of subjects (FDA, 2017a).

[3] One approach to for reducing prices is reducing the IND failure rate. In recent years, there have been a number of efforts to do so through such steps as making otherwise proprietary clinical data, especially on failed drug candidates, publicly available to all researchers. This report acknowledges that reducing IND failure rate is critical in the drug development process; however, this topic could not be considered in detail amid the competing demands of other topics presented in the study scope. Furthermore, the committee lacked the necessary expertise on this topic.

Phase III trials further expand the number of patients involved in the testing—commonly into the thousands—and continue to assess the safety and efficacy of the drug against either a placebo or the existing standard of care, depending on the status of current therapeutic options. If no current therapies exist, these studies will use placebo controls. If an existing therapy has been shown to have clinical benefit, the ethics of human subject testing normally precludes withholding that therapy. In this case the randomization compares the new drug against the existing treatment (the standard of care). Phase III studies are crucial for regulatory review, and sample sizes are predetermined to ensure that a sufficient statistical base exists to support a final FDA regulatory approval decision. About half of all the drugs that reach phase III do not proceed to market (Arrowsmith, 2011), and judging by historical trends, only about 5 to 10 percent of IND applications ever gain FDA approval (Van Norman, 2016).

The safety of human subjects is of extreme importance in these studies. Clinical trials in the United States have an independent body of experts (including clinicians and statisticians) to monitor safety by regularly reviewing interim data for the treatment being assessed and for control groups in order to spot any differences that may exist between them in either safety or efficacy. Most such trials are "double-blind"; that is, neither the researcher nor patient is aware of which specific treatment is being provided to a specific patient. Pre-specified measures are used to determine efficacy, and a review is conducted to assess the rates of adverse events, including mortality. The monitoring committees have the authority to recommend that a randomized trial be stopped at any time if major safety concerns appear or if the evidence of efficacy is so strong that there is an ethical imperative to place the therapy into general use as quickly as possible.

Upon successful completion of a phase III trial, the next step is for the sponsor of the drug to file a new drug application (NDA), submitting the results from the clinical trial to the FDA. The manufacturer also submits proposed labeling information (highly detailed data on safety, efficacy, and dosage, and the indication for which it will be approved) intended for use by clinicians. The FDA will inspect the facilities where the drug will be produced in order to assess safety and manufacturing quality standards. If everything is acceptable, the FDA will approve marketing of the new drug for the specified indication. Patients can then gain access to the new drug by prescription from a qualified professional.

Once a drug is available to consumers, it enters the phase IV safety review, known as post-market surveillance. The sponsor, typically the drug manufacturer, must submit periodic safety reports to the FDA. These data play a major role in ensuring continued drug safety, sometimes revealing adverse effects that occur too rarely to have been detected even in the large phase III trials. Per the Prescription Drug User Fee Act, all these costs are

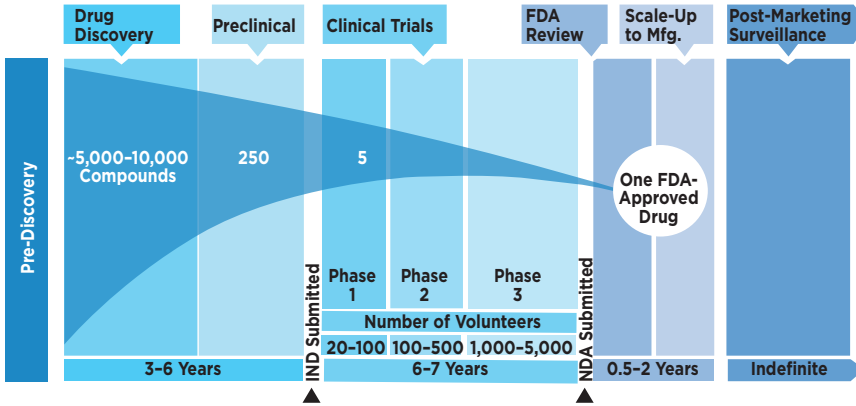

FIGURE 2-1 A typical timeline for drug discovery and development.
NOTE: FDA = U.S. Food and Drug Administration.
SOURCE: Adapted from AACR, 2011.

borne by the sponsoring organization, including the cost of the FDA review process itself. The timeline for the entire process varies, but historical data indicate that it can take as long as 15 years (FDA, 2015; Ng, 2015) (see Figure 2-1). It generally takes less time to approve generics because of the data previously generated for the comparable branded drugs and also less time for those products that meet the criteria of the Orphan Drug Act.

Competitive Market Strategies Following Product Launch

"Evergreening" of Exclusivity

While evergreening is not a formal concept within patent law, it is a commonly used term that refers to various techniques for extending the legal exclusivity granted by the patent (Dwivedi et al., 2010). The practices include patenting the method of administration, patenting a minor reformulation with no therapeutic advantages, and even patenting the metabolites produced in the body after the drug is ingested (Kesselheim et al., 2006). As an example, one biopharmaceutical company filed for a patent to administer its drug after crushing it and spreading it on applesauce (Kesselheim and Mello, 2006).

Evergreening—with various versions referred to as "product hopping," "product switching," or "line-extension"—is frequently used when high-revenue branded drugs (i.e., "blockbusters") reach the end of their patent life (Carrier and Shadowen, 2016; Jones et al., 2016). Under ordinary circumstances, once a branded drug reaches the end of its patent term, the

manufacturers of generic drugs are provided an opportunity to enter the market. The manufacturers of the branded drug can stall a generic competitor from entering the market by filing patents that cover not only the active ingredient, but also secondary features of the drug such as methods of formulation. A recent analysis of all drugs on the market between 2005 and 2015 found that at least 74 percent of new patents for drugs were for existing drugs. This addition of new patents and associated exclusivities was especially pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, almost 80 percent had their patent protection extended at least once, with nearly 50 percent extending patient protection more than once (Feldman and Wang, 2017).

While these patents are generally considered weaker and less novel than the original patent, they can allow the branded company to allege that the competitor will infringe these additional patents. Litigation by generic firms against branded manufacturers can help to counteract evergreening, as one analysis found that weaker patents are more likely to draw challenges from generic manufacturers (Hemphill and Sampat, 2012). Another recent analysis found that, particularly in recent years, branded firms have been less likely to win cases involving challenges to peripheral features of drugs than those involving challenges to active ingredients (Grabowski et al., 2017). However, the cost of litigation can be a deterrent to generic manufacturers, and litigation (even when ultimately unsuccessful) can be an important mechanism for extending the market exclusivity of the branded drug (Rumore, 2009).

Evergreening also sometimes refers to the creation of so-called "me too" drugs, in which minor modifications are made by manufacturers to the active ingredients in an existing pharmaceutical product. These new molecules may offer little or no additional clinical benefit compared with the existing molecules, but can nevertheless provide a substantial new stream of revenue to the branded manufacturer. From industry's perspective, evergreening has been considered a legitimate business strategy to increase revenue. What critics may see as the exploitation of loopholes may well be seen by corporations as legitimate "product lifecycle management" and therefore an approach to maximize shareholder value.[4]

[4] Policy developments such as the Medicare Modernization Act (MMA) have prevented companies from filing a series of patents staggered to protect specific features of biopharmaceutical products such as isomers and metabolites—patents that could otherwise result in a longer period during which manufacturers could sue for patent protection in the event they are challenged by a generic entrant. Under the Hatch–Waxman Act, a manufacturer is granted a 30-month stay during the resolution of such a challenge, during which the generic manufacturer cannot sell its product. Some observers have called for the FDA to tighten the criteria for approving minor modifications of existing drugs. For example, rather than making noninferiority the standard for approving new applications, the FDA could in some cases (such

Delaying the Entry of Generic Products

"Pay-for-delay" reverse settlements between manufactures of branded drugs and prospective generic entrants have emerged because of the incentives for generic entry created under the Hatch–Waxman Act. Specifically, the act grants 180 days of generic market exclusivity to the first generic firm to successfully demonstrate either that a patent is not legitimate or that the generic product does not infringe the existing patent. This provision—known as "Paragraph IV"—often concerns challenges to peripheral aspects of a patented medication design. For example, the patent on the active ingredient in omeprazole (Prilosec) expired in 2001, but patents on the coating of the pill and other properties were in effect until 2007 (Kesselheim et al., 2011). In response to Paragraph IV challenges, manufacturers can countersue the generic entrant, and can delay the generic application for 30 months.

Given the uncertainty of litigation and the likelihood that a patent holder will lose its protection on a relatively weak patent, it is often mutually advantageous to the generic firm and the firm owning the patent to enter into a pay-for-delay agreement. Specifically, the firms can settle on a payment to cover the 180-day period that exceeds the amount the generic manufacturer might have earned if it were participating in the market but less than what the firm with the patent would have lost due to generic entry. Pay-for-delay keeps prices higher than they would be if a generic competitor were able to enter the market immediately.

One analysis of the economic impact of pay-for-delay settlements in response to Paragraph IV challenges found that settlements tend to

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as when a generic drug is already available) require new drug applications to demonstrate superiority over existing drugs (Gagne and Choudhry, 2011).

Under recent legislative proposals, reformulations of existing drugs can attain an additional 2 years of protection from generic competition if they are shown to (as quoted from H.R.1353: PATIENT Act):

- "promote greater patient adherence to an approved treatment regime relative to the previously approved formulation or design of the drug;
- reduce the public-health risks associated with the drug relative to the previously approved formulation or design of the drug;
- reduce the manner or extent of side effects or adverse events associated with the previously approved formulation or design of the drug;
- provide systemic benefits to the health care system relative to the previously approved formulation or design of the drug; or
- provide other patient benefits that are comparable to the benefits described above."

Such provisions highlight the challenges of effectively regulating the instances when product modifications might offer real benefits to patients, but any such benefits have to be weighed against the impact of delaying the entry of low-cost generics.

inflate prices and reduce the quantity of prescriptions for several years after the settlement—long after the protected 180-day period. For each settlement, the authors estimated a loss of $835 million in consumer benefits over 5 years. Conversely, the study found that eliminating settlements would tend to increase consumer welfare and have a minimal effect on the investment in research and development and the entry of new drugs into the market (Helland and Seabury, 2016). Pay-for-delay settlements have received substantial regulatory scrutiny, especially in those cases when they may violate antitrust law.[5]

Another approach by branded manufacturers uses the Risk Evaluation and Mitigation Strategies (REMS) process to delay generic entry. The FDA requires REMS as a safety strategy to manage known or potential risks (FDA, 2017b), but the Federal Trade Commission (FTC) has expressed concern about "the possibility that procedures intended to ensure the safe distribution of certain prescription drugs may be exploited by brand drug companies to thwart generic competition" (FTC, 2014a, p. 1). A recent study estimates that this could lead to about $5.4 billion in unnecessary spending on branded drugs annually (Brill, 2014). This analysis also highlighted that REMS and associated programs could also be used to impede the market entry of biosimilars.

THE MARKET STRUCTURE

The complexity and interdependence within the biopharmaceutical supply chain makes it extremely difficult to understand the motivation and behavior of its various participants, even under the best of circumstances. Nonetheless, any analysis of the availability and affordability of prescription drugs needs to take into account the frequently and extensively altered incentives, trade-offs, and constraints imposed on these markets, and the ultimate impact they have on individual patients.

[5] In recent years the Federal Trade Commission has pursued antitrust cases against a number of pay-for-delay settlements. In the 2013 case *Federal Trade Commission v. Actavis*, the U.S. Supreme Court held that reverse payment settlements should receive antitrust scrutiny, but it did not conclude that such agreements should be presumed to be illegal; instead the court advised that they need to be evaluated on a case-by-case basis (Boumil and Curfman, 2013). After the *Actavis* case, lower courts have grappled with how to determine if specific cases meet the threshold for antitrust violations. Courts have searched for evidence of settlement amounts (either monetary or in-kind) that suggest an improper payoff intended to have an anticompetitive effect (Perkins Coie LLP, 2016).

A "Conventional" Market

To understand the complexity of the pharmaceutical market, it is useful to first consider the characteristics of more conventional markets, such as those for automobiles, food, and consumer electronics. Each of these products involves the transformation of raw materials into final tested products. As shown in Figure 2-2, goods flow from manufacturers to consumers, and money flows from consumers back to manufacturers. Consumers collectively pay $\$X_1$ to retailers, who in turn pay $\$X_2$ to wholesalers, who in turn pay $\$X_3$ to manufacturers. The gross margin for retailers, $\$X_1 - \$X_2$, must cover the costs of conducting business and provide profits for their investors. Similarly, wholesalers retain $\$X_2 - \$X_3$ to cover their costs of operation and profits. Manufacturers receive $\$X_3$, which pays such costs as those associated with compensating its workforce, product development and manufacturing, and a return to investors. In larger firms, these "investors" are typically shareholders in corporations, bondholders, or lenders. In order of legal priority, investors (particularly, shareholders) have the last claim on assets. These residual claimants bear the greatest financial risk and in a typical financial market, demand the greatest returns on their investments.

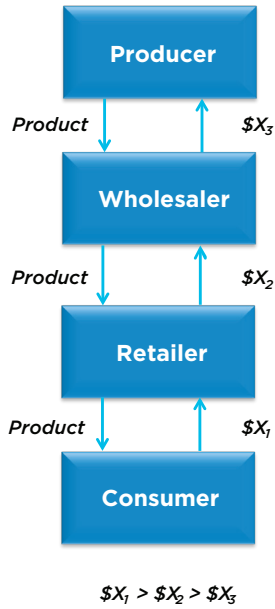


FIGURE 2-2 A typical market in a free enterprise economy, showing the flow of products and revenues across the participants.

A Simplified Standard Health Care Market Model

The U.S. health care market differs from the above standard business model in a unique way: in health care, a third party—a health insurer—intervenes in the flow of goods and services, in the flow of money, and sometimes in the choices of products available to individual consumers. People desire health insurance not only because health care is critical and intrinsically expensive, but also because the need for health care services is often highly unpredictable. This creates a significant financial risk to both individuals and to society as a whole. This risk appears in many ways, perhaps most notably in the fact that 5 percent of patients account for half of all health care spending, and the top 1 percent account for one-fifth of all medical spending. Conversely, the half with the least health care spending accounts for just 3.1 percent of medical spending (Cohen and Yu, 2012).

These data highlight how unevenly the financial burden of health care is spread and thus why it is important to have some sort of insurance against this risk—just as homeowners purchase home insurance, auto insurance, disability insurance, and life insurance in response to financial risks in those areas. However, unlike the case with these other forms of insurance, the behavior of consumers can be affected quite strongly by the simple fact that they have health insurance. Specifically, because health insurance subsidizes the cost of medical care, its presence increases the use of health care because people become less sensitive to its price (Newhouse, 1993). Simply put, if consumers pay less than they would otherwise (because of insurance) to visit a clinician or undergo a procedure or buy prescription drugs, they become more likely to do those things.

Figure 2-3 illustrates how these considerations alter the flow of services.[6] Individuals, often through their employer, purchase or are provided with health insurance policies for themselves and their families, usually paying part of the annual premium (see Box 2-1 for a note on the role of employers in the control of drug prices). Then, when obtaining services such as clinician care, dental care, hospital care, or emergency room visits, or when buying products, the individual or associated party provides a copayment to the health care provider, as specified in the contract between the insurance plan and the patient. The insurance plan then pays a separate amount to the clinician or the hospital as specified in their contracts. For people without health insurance, clinicians maintain set list prices that they collect directly from the consumer (who, at this point, can appropriately be called

[6] Because most health care transactions involve personal services rather than physical goods, Figure 2-3 does not include a wholesale level of the supply chain, but in some cases (e.g., durable medical goods such as wheelchairs, walking aids, or oxygen supplies) a wholesale level would appear in the medical transactions as well. This has been omitted in Figure 2-3 for simplicity.

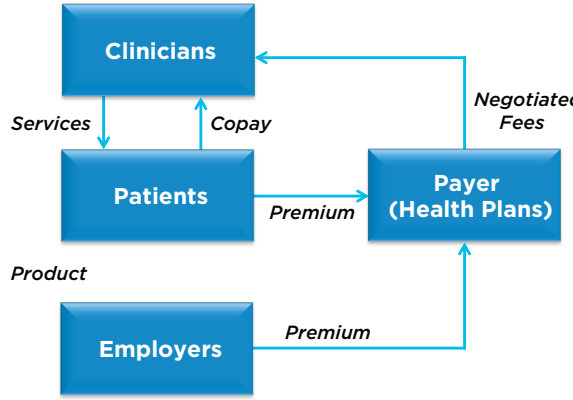


FIGURE 2-3 A simplified health care market with third-party health insurance.
NOTES: This figure also omits two other forms of intermediaries that consolidate bargaining power. Retail pharmacies use pharmacy services administration organizations to negotiate with pharmacy benefit managers and they also use group purchasing organizations to negotiate with wholesalers.

the "patient") or waive a part or all of such charges as charitable contributions or bad debt. However, the great majority of transactions take place not directly between the patient and provider but with the health plan as an intermediary.

For people ages 65 and over and younger adults with permanent disabilities covered by Medicare, low-income people enrolled in state Medicaid programs, or individuals in special federal programs devoted to military service members and veterans, the relevant governmental programs become the health insurance plan, and taxpayers substitute for employers as payers for some of the cost of health insurance.

A Simplified Biopharmaceutical Market

Figure 2-4 illustrates the structure of a very simplified market for biopharmaceuticals that includes many of the basic players, including patients, clinicians, drug manufacturers, health plans, and pharmacy benefit managers (PBMs). There are several distinctive characteristics of this market that are worth noting. First, individuals cannot simply choose to buy medications, but rather require a prescription from a clinician. Without such a prescription, pharmacists are not permitted to dispense prescription drugs.[7]

[7] The same "permission" is required for some types of medical care (most obviously hospitalization), where patients cannot "admit themselves" into a hospital for (say) a surgical procedure or medical treatment.

BOX 2-1 The Role of Employers in Containing Prescription Drug Costs

Most large employers offer health insurance to their employees, but those who self-insure may have the most at stake in terms of financial risks. The Kaiser/Health Research & Educational Trust 2017 Employer Health Benefits Survey found that, in 2017, 60 percent of covered workers are in a self-funded plan (KFF and Health Research & Educational Trust, 2017). Furthermore, the Employee Benefits Research Institute reported that, in 2015, nearly 40 percent of firms self-insured at least one health plan that they offered, compared to 26.5 percent in 1999 (EBRI, 2016). As one might expect, the attractiveness of self-insured plans varies with firm size. Over 80 percent of firms with 500 or more employees self-insure at least one plan, compared with about 25 to 30 percent for mid-sized firms (100–499 employees) and less than 15 percent for smaller firms (under 100 employees). The proportion of employees in self-insured plans also breaks down by firm size. While 81 percent of covered employees at firms with 1,000–4,999 employees are in self-insured plans, that percentage drops to 47 percent at firms in the 200–999 employee category and only 23 percent at smaller firms (KFF and Health Research & Educational Trust, 2017). Similarly, of those companies with self-insured plans, 70 percent have more than 1,000 employees and 80 percent have at least 500 employees (BLS, 2016).

Self-insured employers have the most direct link between their health care costs and their company profits and thus, logically, the greatest interest in controlling those costs. In the world of prescription drug insurance (about which no specific data exist regarding self-insurance rates), many of these employers will contract directly with pharmacy benefit managers to manage their pharmaceutical drug insurance because they believe that there is an economic benefit in doing so.

The "manufacturer" in Figure 2-4 includes producers of branded and generic products. PBMs serve as intermediaries between both health insurance plans and retail pharmacies and the manufacturers of prescription drugs. A full portrayal of the market for biopharmaceutical products would also show the regulatory intervention of the FDA and the U.S. Patent and Trademark Office (USPTO). These additional elements are omitted from Figure 2-3 in order to focus on the product and financial flows within the prescription drug market.

As indicated in Figure 2-4, there are multiple pathways between the drug manufacturer and the patient. Before the creation of prescription drug insurance, the sole pathway operated much as displayed in Figure 2-2: drug manufacturers sold to wholesale distributors who sold to retail pharmacies who sold to patients possessing a proper prescription. This remains the primary pathway for patients without drug insurance today.

For those with drug insurance, alternative pathways exist. In one case, the PBMs (and major pharmacy chains) operate mail-order services, selling

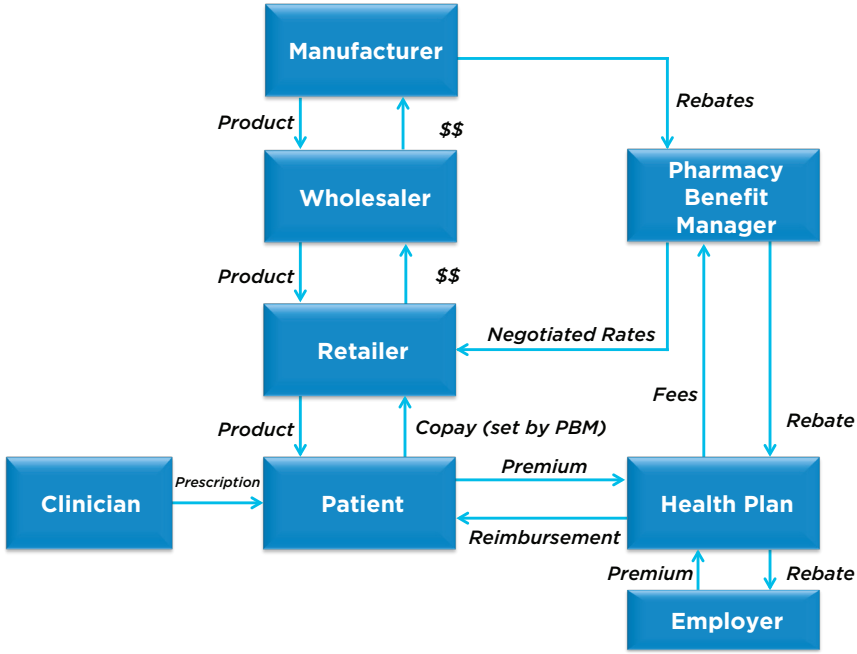


FIGURE 2-4 A simplified biopharmaceutical products market including health insurance and pharmacy benefit managers.

medicines directly to patients (with the usual requirement of a prescription from a clinician) and collecting copayments from the patients and payments through insurers. The other option for such patients is to go directly to a retail pharmacy and offer the copayment specified in the insurance plan. In this latter pathway, the retail pharmacy has previously purchased the drug from a wholesale distributor, and the PBM compensates the retail pharmacy (per the contract between the PBM and the pharmacy) for the cost of the drug plus a processing fee.

A More Complete Portrayal of the Biopharmaceutical Market

Figure 2-5 is a more descriptive illustration of today's biopharmaceutical enterprise, with several additional participants beyond what is shown in Figure 2-4, but still omits elements of the distribution mechanism for certain drugs used to treat specific patient populations. In particular, many drugs are purchased by hospitals and dispensed or administered to patients cared for in the inpatient hospital and outpatient clinic setting.

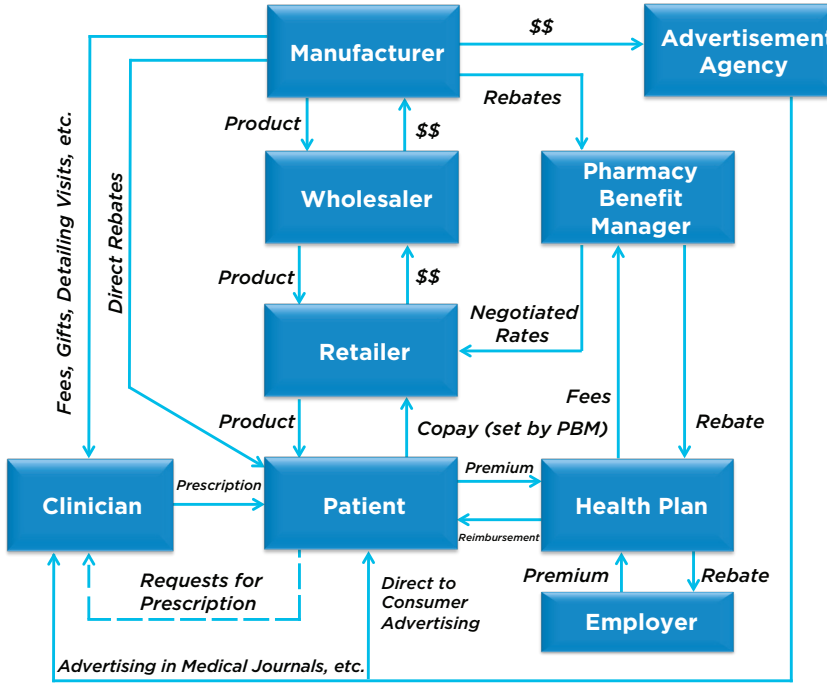


FIGURE 2-5 A broader representation of the current private-sector retail market for prescription drugs. The structure of the market would vary in the cases of federally supported plans. Drug supplies to clinicians for direct administration to patients and through Medicaid occur in different pathways and are not shown here.

Drugs dispensed to patients in the hospital or infused or injected during an inpatient hospital stay are purchased by hospitals through wholesalers and distributors and are covered under Part A of Medicare, and inpatient benefits provided by state Medicaid programs and commercial insurers covering the non-Medicare eligible population. Use of these drugs by Medicare beneficiaries is largely covered through payments to hospitals under prospective bundled reimbursement arrangements. In 2013, Medicare spent $112 billion on payments for drugs and pharmacy services (MedPAC, 2016); 16 percent of this total (approximately $18 billion) was for drugs billed under Part A.

Standalone and hospital-based clinics purchase drugs from wholesalers and distributors and dispense or administer these drugs to patients as part of outpatient care. These drugs are covered under Part B of Medicare, and outpatient medical benefits provided by state Medicaid programs and commercial insurers covering the non-Medicare eligible population. In

2013, 15 percent of total Medicare spending on prescription drugs was for those covered under Part B (approximately $17 billion) (MedPAC, 2016). In contrast, 57 percent of total Medicare spending on prescription drugs in 2013 was on outpatient prescription drugs covered under Part D (both standalone drug plans and Medicare Advantage drug plans) (approximately $63 billion).

Drugs covered under outpatient medical insurance benefits have an unusual payment structure: clinicians, outpatient clinics, and hospital-based clinics purchase these drugs at their wholesale acquisition cost and then bill insurers and patients for their use and are paid a reimbursement price. This system is commonly called "buy and bill." Since 2006, standalone and hospital-based clinics that administer drugs in the outpatient setting covered under Medicare Part B have been reimbursed at the average sales price of the drug plus 6 percent plus an administration fee. Commercial insurers set reimbursement rates for these drugs using average sales price, average wholesale price, or another metric, and also reimburse for administration fees.

Figure 2-5 also displays several interlinked communication channels involving pharmaceutical manufactures, clinicians, and patients. While some health care markets (and most non–health care markets) employ direct advertising to consumers, this form of marketing has several distinct features when applied to prescription drugs. Pharmaceutical companies collectively spend billions of dollars annually to "inform" and influence the choices of clinicians and patients. They do this with direct visits to clinicians (referred to as "detailing"), presentations and booths at professional medical meetings, by providing free samples to clinicians, and advertising in medical journals, and also directly providing copay coupons to patients.

BARGAINING POWER AND FORMULARY MANAGEMENT

In any market a buyer's bargaining power is usually determined by two factors: their ability to walk away from the deal, completely or in part, and the volume of goods they are purchasing. For buyers to be able to negotiate on price, they must have credible alternatives other than purchasing from the seller (OECD, 2009). If a purchaser is always going to buy the product whatever the price, the seller can charge what price they like.

In the biopharmaceutical sector, buyers often appear to be in a weak position, with little alternative but to purchase the drug whatever the price. The drug manufacturers have a strong bargaining position, because their products are protected from competition by patents, and payers are understandably reluctant to deny patients the drugs they need. Even when payers do have credible alternatives, the fragmented nature of the U.S. health care system weakens their bargaining position.

Health care payers typically seek to gain bargaining power in drug pricing negotiations through tier-placement and through formulary design (GAO, 2007). A formulary describes which drugs a health care payer will cover for which disease indications, and at what cost. Formularies can be "open" or "closed." An "open" formulary ostensibly covers all drugs, but typically includes mechanisms to constrain usage of drugs the payer considers too expensive, such as tiering, with higher tiers requiring greater patient cost sharing, prior authorization, or more tightly defined permissible indications. A "closed" formulary allows for drugs the payers deems very expensive or otherwise undesirable to be excluded from coverage. Formularies are used to steer patients and prescribing clinicians toward generic substitutes, biosimilars, drugs with similar therapeutic efficacy for the same disease, or other therapeutic options.

Formularies contribute to payers' bargaining power by enabling them to restrict the volume of prescriptions in response to higher prices. Placing a drug on a higher tier triggers higher copayment from patients and therefore discourages the use of the high-priced drugs. Narrowing the indications for which a drug can be used also constrains the potential volume. Excluding the drug entirely from coverage is the most powerful lever, one most readily employed when alternatives exist to treat the same condition. For example, in 2014, Express Scripts, a PBM that covers 25 million people, negotiated a significant discount from AbbVie on its new hepatitis C drug (Viekira Pak), by making it the exclusive option in its formulary, while excluding both competitor drugs Harvoni and Sovaldi (Pollack, 2014; Wilensky, 2016a).

All of these levers work by restricting access to the drug in some way or other: if they did not, they would not contribute to the payer's bargaining power. This points to the importance of another crucial aspect of formulary design: the basis on which these restrictions are imposed. In some contexts, such as in the United Kingdom, the British National Formulary is determined through an assessment informed by the National Institute of Clinical Evaluation. In the United States, in part due to a lack of broad agreement on how to define and assess "value," many different approaches are used in formulary design, and transparency about decision making may be lacking (Frank and Zeckhauser, 2017).

Some other countries operate formulary systems that provide much greater ability to restrict or exclude drugs from coverage than is the case in the United States. The health systems in the United Kingdom and Australia, for example, explicitly apply cost-effectiveness and related criteria to determine whether drugs will be included in the formulary. Total exclusion from coverage is relatively rare. What happens more frequently is that approval for the most expensive drugs is only given for a tightly defined set of indications. Even if a drug is excluded from the formulary, this does not generally prohibit patients from purchasing the drug, but removes it from the realm

of insured products and services. However, the exclusion of drugs from a national formulary can generate significant controversy, since there are almost always some patients who would benefit from inclusion and who protest its removal.

By contrast, in the United States, the Centers for Medicare & Medicaid Services (CMS) makes coverage determinations for Medicare enrollees based on the language of the original legislation that created the program: that the treatment be "necessary and reasonable." Historically, CMS and its predecessor organizations have relied on approval by the FDA for those determinations, and have not used cost as a component of coverage determinations (Neumann et al., 2005, 2008). In other areas of health care, most notably the Prospective Payment System for hospitalization in Part A and the Resource-Based Relative Value System in Part B, Medicare sets prices administratively, using a combination of historical costs and efficiencies that have been deemed achievable. The Congressional Budget Office (CBO) has not expressed confidence in this strategy as a way to produce savings on drug costs (CBO, 2014; Wilensky, 2016b), but to date, there is no CBO estimate on the effect of allowing the U.S. Department of Health and Human Services (HHS) to negotiate both drug prices and formulary placement (Shih et al., 2016). Individual states in the United States also encounter various challenges, each specific to them, in curbing prescription drug costs, with related implications on their formulary structure, a topic explored in Box 2-2.

Formulary designs in the United States typically put greater reliance on tiering than explicit exclusion, with drugs that are allocated to the higher tiers requiring higher cost sharing by patients. The logic is that higher cost sharing will simultaneously make patients more reluctant to use such drugs and, by imposing some of the costs on the individual patient, reduce the burden on the overall insurance pool and thus, control consumer premiums. However, tiering with high cost sharing can also have downsides, since it can lead to reduced adherence or the discontinuation of medications because of high out-of-pocket costs to consumers.[8] Such designs may also discourage consumers with high drug expenditures from enrolling in health plans (Happe et al., 2014; Huskamp and Keating, 2005), which could further adversely affect health outcomes. But without such formulary controls within pharmacy benefit plans, insurance premiums would rise, potentially also leading to lower enrollment and similar undesired health consequences. The tiered price mechanism can be used by insurers to negotiate better prices for branded drugs (Duggan and Scott Morton, 2010).

If insurance plans do not have some cost-control mechanisms in place, increased coverage leads both to higher utilization (Newhouse et al., 1993)

[8] This topic is further discussed in the insurance design section of Chapter 3.

BOX 2-2 Role of State Governments

State governments have been challenged by high and increasing prices of drugs that have implications for their potential bargaining power and formulary design. Between 2013 and 2014, total Medicaid prescription drug expenditures grew from $37.1 billion to $42.3 billion, a 24.6 percent increase and the highest rate of growth since 1986. Growth slowed to 13.6 percent in 2015. This surge in expenditures is in part related to several new high-cost specialty drugs to treat serious conditions that commonly afflict state Medicaid beneficiaries (Martin et al., 2016).

States provide access to a broad range of health and non-health services for low-income individuals and families, often to meet federal requirements (Stuard et al., 2016). The per capita cost for Medicaid beneficiaries is about $2,000 more than the per capita cost in the commercial insurance market because Medicaid enrollees often have complex, expensive health needs (CMS, 2015). Patients and clinicians want to have access to new therapies through state Medicaid programs, but these programs operate under fixed budgets that require legislative approval and are subject to state constitutional limits that often include a balanced budget requirement. In some cases, states have been faced with class-action lawsuits over access to therapies (Ollove, 2016). Unlike commercial insurers and Medicare, state Medicaid programs have very few options to shift costs to Medicaid enrollees through premium or cost-sharing requirements, which are largely prohibited by federal law. Furthermore, except for very limited exceptions, the Medicaid Drug Rebate Program requires coverage of all products made by manufacturers that enter into federal rebate agreements. As a result of these requirements, Medicaid essentially has an open formulary. Some states develop criteria for determining which patients should have access to expensive medications (e.g., based on severity of the condition). This is discussed in Chapter 3.

and higher costs from providers who have any ability to set their own price. But when cost controls such as tiered prices and prior authorization enter, the net effects are theoretically ambiguous. The introduction of Part D in Medicare provided a way to estimate the net effects. One analysis tracked the prices of the most commonly prescribed branded (non-generic) drugs in Part D upon its introduction, and concluded that, on net, the extended coverage and strengthened bargaining power of the buyers (collectively, through the insurance plans) caused a reduction in many prescription drug prices (Duggan and Scott-Morton, 2010). Specifically, the analysis noted that "Part D plans have succeeded in negotiating lower price increases for Part D enrollees—approximately 20 percent lower than they otherwise would have been."

Balancing national affordability (which translates into premium costs to consumers or to the taxpayer) and individual affordability (as reflected in copayment costs for specific drugs) is the complex task facing those designing drug insurance plans and associated formularies. But it seems

clear that from a payer's perspective, effective bargaining cannot take place without the ability either to exclude drugs from a formulary or place them in unfavorably high tiers. Formulary management and effective bargaining go hand in hand.

In sum, significant price negotiating power entails a payer being able to refuse a deal, and a formulary that allows coverage restriction, whether through exclusion, tightening permissible indications, or tiering. The placement of drugs in a formulary needs to be based on some logic. Ideally, this would be an assessment of cost and value to both patients and society.

In addition to formulary design, the other major determinant of a buyer's bargaining power is their scale: buying more product translates into greater bargaining power. In the world of prescription drug insurance, a commonly used measure of scale would be "covered lives." However, this is a far from perfect measure of drug purchasing scale, because the rate of using prescription drugs varies enormously by age, among other factors. People older than age 65 spend approximately three times the amount per year on prescription drugs as adults younger than age 65, a point not captured by the "covered lives" metric.

In the United States, private payers are relatively fragmented. Currently, the largest private health insurance company (United HealthCare) has 14.1 percent of the total U.S. population, the second largest (Aetna) has 10.1 percent, and the top eight firms together have less than half of the U.S. population insured (AISHealth, 2016). Compared with other industrial sectors, this would be considered a relatively "low" level of concentration among buyers, meaning even the largest firms would have relatively weak bargaining power.

This fragmentation of purchasing power is a primary reason for the emergence of the PBMs, a form of market intermediary that appears almost unique to the United States. The PBMs negotiate prices and manage formularies on behalf of payers, whether private insurers or self-insured large employers, exploiting the fact that PBMs have achieved far greater scale and thus have greater purchasing power. Recent estimates show that the top three PBMs cover 85 percent of the individuals with prescription drug insurance (Sood et al., 2017). Increased concentration among PBMs undoubtedly enables them to have greater purchasing power versus manufacturers. However, it also enables them to have greater market power versus payers. While some PBMs act as agents for payers, receiving a fee for their services, in many case PBMs act as principals, retaining a share of the discount they have negotiated from the manufacturer. In a sense, the market concentration of PBMs can be seen as a double-edged sword from the patient and the payer perspective: it enhances the ability of the PBMs to extract bigger discounts from the manufacturer, and also the ability to pass on less of these discounts to the patients than would be the case if they

were less concentrated. These dynamics are obscured by the lack of clear information in the public domain, and the increasing integration between PBMs and insurance companies and retail pharmacies.[9]

Besides the private health insurance markets, the U.S. federal and state governments collectively provide health insurance coverage for a significant portion of the population, including Medicare (55 million), Medicaid (74 million), U.S. Department of Veterans Affairs hospitals and clinics (8.9 million), TRICARE for active duty and retired military and their families (4.7 million), and prisoners (2.2 million). Yet, the buying power for these different organizations is highly diffuse. Even within Medicare's 55 million enrollees, bargaining power is highly dispersed because HHS is prohibited by statue[10] from negotiating drug prices. Here again the PBMs play a central role. For virtually all of those enrolled in Part D insurance for prescription drugs dispensed through retail channels, price negotiations are delegated to the PBMs. However, for the six protected classes of drugs in Part D, for which inclusion on formularies is mandatory, PBMs may not achieve discounts because there is no real lever for negotiation. Part D retail drugs represent approximately 60 percent of the total cost of prescription drugs dispensed under Medicare. The remainder is covered under Medicare Parts A and B through sales directly to hospitals, clinics, infusion centers, and providers' offices. These non-retail drugs—which may well constitute more than half of all prescription drug spending—come through channels that have relatively weak bargaining power, and generally lie outside the domain of PBMs, entities with the strongest bargaining power currently.

Enabling HHS to negotiate drug prices for all Medicare enrollees would increase bargaining power versus drug manufacturers if HHS also had effective formulary control. The legislative "non-interference" clause of the MMA prohibited CMS from negotiating or administratively setting prescription drug prices and instead advanced private market competition as the means of setting prices (Channick, 2006). However, in every other sphere, whether in purchasing big items like defense equipment or for infrastructure and transportation projects, or in buying more routine items like utilities, uniforms, or stationery, the government uses its scale in price negotiations to the benefit of taxpayers. Furthermore, characterizing this approach as being tantamount to price control or regulation is misleading, and the effect of not allowing HHS to negotiate prices is to tilt the balance of bargaining power further in favor of drug manufacturers.

[9] In October 2017, CVS, the pharmacy chain, proposed to acquire Aetna, one of the largest health insurers in the country (Mattioli et al., 2017). Aetna had previously sought a merger with Humana, another large health insurer, a move that was abandoned after a federal judicial ruling against the proposed merger (Tracer, 2017).

[10] Section 1860D-11(i) of the the Social Security Act. 42 U.S.C. § 1395w-111(i).

There are many questions regarding scope and mechanism that would need to be addressed before HHS could undertake negotiation if given the authority by the U.S. Congress to do so. For example, HHS would have to determine which drugs would be subject to negotiations, what would be negotiated (i.e., price, formulary placement), and how to implement negotiated prices in Part D plans (Shih et al., 2016). A pricing model to guide decisions would need to be defined, including how various types of evidence and other considerations would inform conclusions on drug value and price. Factors such as evidence of clinical benefit and the impact of drug pricing on future research and development would likely play a role (Shih et al., 2016). A recently proposed payment framework for negotiation focuses on drugs that are "high cost (e.g., $1,000 per month), incur high levels of Part D program spending (more than $500 million), and have few close substitutes" (Frank and Zeckhauser, 2017, p. 11). The goal of this framework is to develop a negotiated payment system that would simultaneously enable profits for manufacturers and improve health outcomes for patients. This proposal also uses quality-adjusted life-years as a key metric to assess the "value" of drugs, the subject of the following section.

While one cannot readily estimate the extent of available purchasing power that a consolidated federal agency might have, it would almost certainly exceed the largest power currently available in the private sector (85 million covered lives). If one takes the 55 million covered lives in Medicare and uses the multiplier of three times the average per-person spending that leads to 165 million effective "covered lives." Adding other federal and state agencies would further increase the strength of bargaining power available to the government, should that power be granted through legislative authorization.

Price negotiations in biopharmaceutical markets exhibit a number of factors that differentiate them from other kinds of markets: most notably the price-setting power arising from government-granted exclusivity and the political challenges buyers face in limiting access to prescription drugs, some of which are deemed as "lifesaving." These factors are exacerbated in the United States by the way formularies are designed, the relative fragmentation of private payers, and the diffusion of governmental purchasing power, not least through the legal restriction on CMS negotiating prices.

THE "VALUE" OF DRUGS

One common proposal to moderate the cost of prescription medicines has been to adopt the so-called "value-based pricing" for drugs, although the meaning of the term "value" varies widely among the participants in the biopharmaceutical sector. A fundamental challenge facing those who would apply value-based pricing is how to determine whether a drug intervention

is in fact of "value," especially when sufficient evidence is lacking. It is not even straightforward to determine what "evidence" means (IOM, 2011, 2015a; Mayo-Wilson et al., 2015, 2017; NRC, 1985, 1989; Page et al., 2012; Stewart and Parmar, 1993).

Syntheses of clinical trial evidence are known to be biased in some cases, and thus may introduce additional distortion referred to as "meta-bias" (Goodman and Dickersin, 2011). Moreover, the trial and meta-analysis outcomes that are studied and reported frequently do not overlap, so the results are of little use or benefit to patients (Juthani et al., 2017; Saldanha et al., 2017). Conclusions from these studies may be more relevant to clinicians than to patients and consumers. However, the challenges of developing and identifying reliable evidence are becoming increasingly well understood, and some remedies have been proposed (IOM, 2011; NRC, 1985, 1989). At the very least, data need to be collected in a way that provides reliable evidence that can be used to inform what "value" means. In concept, if value is characterized properly and agreed upon, a value-based approach may lead to more efficient resource allocation and improved patient outcomes (Garber and Phelps, 1997; Sorenson et al., 2017). Applying such an approach could also eliminate "indication creep," the expansion of the use of drugs and interventions that are less likely to benefit the populations.

In the United States, value assessments have been frequently conducted in the realm of oncology by evaluating changes in life expectancy and costs over time (Howard et al., 2010; Lakdawalla et al., 2010; Lichtenberg, 2009; Woodward et al., 2007). Table 2-1 describes the factors considered in various value frameworks. Despite its application in many areas and other Organisation for Economic Co-operation and Development countries (WHO, 2015), expanding the use of value assessments into the practice of actual pharmaceutical pricing and payment in the United States presents a number of challenges. The first is that, as noted earlier, there is ongoing debate about the best methods to assess value (Rubin, 2016).

Value assessments often involve cost-effectiveness analysis, in which the ratio of the added health gains from a medical intervention to the added costs of treatment is calculated, and a pre-established cutoff value is used to determine which interventions are worthy of support (Frakt, 2016; Neumann et al., 2016). The use of a quality-adjusted life-year as the health outcome measure in cost-effectiveness analyses has gained wide acceptance in many countries and is used in coverage and reimbursement decisions. The National Institute for Health and Care Excellence in the United Kingdom, for example, uses cost-effectiveness to provide advice about which drugs and treatments should be made available in its National Health Service (Sussex et al., 2013). A recent statement from the American College of Cardiology and the American Heart Association also concluded

that "it is important to consider both the cost-effectiveness and total cost of burden of performance measures before selection" (Anderson et al., 2014). However, simply using cost-effectiveness as the outcome measure leaves out other factors such as public perceptions of a disease, political interests, social justice, and other practical considerations, that need to be taken into account when making important societal decisions (Phelps and Madhavan, 2017; Phelps et al., 2017), and many frameworks do take those elements into consideration as well (Rawlins et al., 2010).

Another value-based approach would be to assess comparative effectiveness. In its simplest terms, comparative effectiveness analysis compares the therapeutic benefits of different interventions. In some randomized controlled drug trials, the comparison is a placebo treatment with no known therapeutic effects. However, even "placebo effects" can be significant, attesting to the powerful effect of the human mind on physiologic functioning. The effects may be larger when study participants are told that the drug being tested on them is very expensive (Lewitt and Kim, 2015). More importantly, despite the widespread application of cost-effectiveness criteria to coverage decisions in insurance programs in other countries (Sussex et al., 2013), federal law in the United States sharply limits the extent to which comparative effectiveness research findings can be used as the basis for coverage decisions in the Medicare program (Rosenbaum and Thorpe, 2010). Commercial insurers, however, do not face this legal restriction.

Effectiveness can, of course, have multiple dimensions. For drugs that affect life expectancy (as in the case of cancer, heart disease, strokes, and some neurological diseases), survival time is a key measure of effectiveness. But these drugs have many other relevant dimensions of effectiveness as well. Treatments (as with many chemotherapy options) often have significant adverse side effects. Some drugs may enhance the quality of life even if they do not extend it, or may even improve the quality of life for caregivers (e.g., in the case of dementia patients). Most drug therapies are effective for some patients but not for others. Side effects are also variable, affecting some patients and not others. This inconsistency in individual responses may be due to variability in disease presentation and progression, co-morbidities, differences in the patients' biological makeup and drug dynamics in their body, and adherence to the medication regimen. The fundamental issue is "incremental effectiveness"—the additional benefit brought about in comparison to alternatives. Some newer drugs have limited incremental effectiveness compared with older drugs (including generics), but nevertheless do improve patient conditions at least to some extent.

The growing thirst for methods to measure "value" has led to the emergence of a number of proposed measures for specific disease conditions, including models for assessing the value of therapeutic options for cancer and heart diseases, as well as taxonomies to assess the strengths and

TABLE 2-1
Examples of Value Frameworks

Organization	Factors Considered	Description
American College of Cardiology–American Heart Association (ACC–AHA)	Clinical benefit versus risks Magnitude of net benefit Precision of estimate based on quality of evidence Value (cost-effectiveness)	Magnitude of treatment effect ranges from class I ("benefit [greatly exceeds] risk," "procedure or treatment is useful or effective") to class III ("no benefit or harm," "procedure or treatment is not useful or effective and may be harmful"). Precision of treatment effect ranges from level A ("data derived from multiple randomized trials or meta-analyses") to level C ("only consensus opinion of experts, case studies, or standard of care"). Value corresponds to cost-effectiveness thresholds (high: less than $50,000 per QALY; intermediate: $50,000 to $100,000 per QALY; low: more than $150,000 per QALY). The framework lists the clinical benefit and value designations without combining them.
American Society of Clinical Oncology (ASCO)	Clinical benefit Overall survival Progression-free survival Response rate Toxicity Bonus factors Palliation Time off all treatment Cost per month	A therapy can be awarded up to 130 points. Clinical benefit (≤80 points) reflects end point and magnitude of benefit, with preference given to evidence on overall survival if available. Toxicity (±20 points) reflects the rate of grade 3 to 5 toxic effects with treatment relative to standard of care. Bonus point score reflects palliation (10 points if therapy improves symptoms) and increased time off all treatment (≤20 points). The framework does not combine each drug's point score and cost.
Institute for Clinical and Economic Review (ICER)	Incremental cost-effectiveness plus care value components Comparative clinical effectiveness Other benefits and disadvantages Contextual considerations Budget impact	Cost-effectiveness ratio must not exceed a threshold ranging from $100,000 to $150,000 per QALY. Selection of final threshold is based on (a) comparative clinical effectiveness, reflecting "judgments of the health benefit magnitude" and "strength of a body of evidence"; (b) other benefits and disadvantages, including such outcomes as factors influencing adherence or return to work; and (c) contextual considerations, including "ethical, legal, or other issues" (e.g., high burden of illness, availability of alternative treatments). Budget impact is acceptable if a drug's introduction is compatible with an annual health care budget increase of GDP growth plus 1 percent. ICER reverse-engineers a "value-based price benchmark" that independently satisfies both the cost-effectiveness and budget-impact criteria.

Memorial Sloan Kettering Cancer Center (DrugAbacus)	Efficacy (survival) Toxicity Novelty Research and development cost Rarity Population health burden	Framework assigns values to each domain. Efficacy is assessed as improvement in overall survival, if available. Efficacy score also reflects evidence quality. Toxicity is a drug's impact on probability of severe side effects and treatment discontinuation. Novelty is scored as 1 (novel mechanism of action), 0.5 ("known target but different mechanism of targeting"), or 0 ("next-in-class"). Research and development cost corresponds to the "number of human subjects enrolled in the approval trials for the first indication." Rarity is the 2015 projected disease incidence. Population health burden is the annual years of life lost to the targeted disease in the United States. Fair price is the product of the scores, each of which is scaled by a user-adjusted weight.
National Comprehensive Cancer Network (NCCN)	Efficacy Safety Evidence quality Evidence consistency Affordability	Each area is scored on a scale of 1 to 5, with 1 indicating least favorable and 5 most favorable. The framework presents the scores separately. There is no explicit synthesis. Stakeholders judge acceptability on the basis of their overall impression of the listed factors.
European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)	Toxicity Quality of life Overall survival Progression-free survival Long-term survival	The framework assesses the clinical benefit for cancer drugs using a structured approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a cancer therapy. It is developed only for solid tumors. Clinical benefits are measured on the basis of oncology-specific thresholds for overall and progression-free survival outcomes. Scores are awarded by virtue of improvements in the variables under investigation in a comparative trial or cohort study. The ESMO score ranges from 1 (worst) to 5 (best).

NOTE: GDP = gross domestic product; QALY = quality-adjusted life-year.

SOURCE: Adapted from Neumann and Cohen, 2015.

limitations of different value frameworks (Mandelblatt et al., 2017). One approach would be to conduct post-launch surveys of therapeutic effectiveness and then adjust payments in proportion to actual (versus forecasted) success rates (Barlas, 2016). In its most extreme form, this approach would pay only for cures. Such an approach was used experimentally by the U.K. National Health Service, but no conclusions could be made about whether it was actually effective or workable in practice (Garber and McClellan, 2007). In the United States, a similar approach is being tested by Novartis, the manufacturer of a very expensive new cell-based immunotherapy for cancer, in which payment for the therapy will only be made when pediatric and young adult patients with acute lymphoblastic leukemia respond to the treatment by the end of the first month of therapy (Novartis, 2017).

Ultimately, the lack of a broad consensus on the definition of "value" is a hurdle to advancing a uniform approach to value-based purchasing. Nonetheless, health insurers are beginning to apply various approaches to foster use of treatment regimens that they consider a better value. For example, the Institute for Clinical and Economic Review is funded by nonprofit foundations to undertake value assessments within the U.S. setting, and also has membership support from pharmaceutical companies, PBMs, and insurers (ICER, 2017). PBMs use those value assessments in negotiations with manufacturers. In addition, some insurers have been experimenting with value-based insurance design, in which patient cost sharing is aligned with the value of treatments (Gibson et al., 2015; Lee et al., 2013). Some use value assessment to assign the position of drugs in formularies.

Insurers have also been defining preferred treatment pathways and incentivizing clinicians to follow them (DeMartino and Larsen, 2012; Gesme and Wiseman, 2011; Zon et al., 2016). However, one criticism of this approach is a lack of transparency on how treatment regimens are selected for pathways (IOM, 2015b). A recently announced collaboration between Optum and Merck also aims to promote a value-based form of contracting referred to as "outcomes-based risk-sharing agreements" (UnitedHealth Group, 2017). Manufacturers have also relied on value statements to justify launch prices for new drugs (McKinsey & Company, 2013).

In sum, the use of value assessments of products is not an alternative to "market forces" but they could potentially be used as tools to enhance market performance. Markets in general can work better when participants are well informed about the relative value of the goods they are trading.

OPACITY IN THE SUPPLY CHAIN

As the public concern and frustration over increasing drug prices escalate, it has become clear that information needed to directly establish the sources of these increases is lacking. Prescription drug manufacturers

blame the PBMs and insurers, saying that their price discounts are not wholly passed on to consumers (Walker, 2016). Manufacturers also say that since their rebates are commonly calculated as a fraction of the list price, reducing the manufacturer's list prices would cause the PBMs to terminate the existing contracts because a lower list price would mean a lower discount to the PBMs (Vandervelde and Blalock, 2017). The PBMs blame both the drug manufacturers for raising prices and the insurers for not passing discounted prices on to consumers (Hopkins and Tracer, 2017).

Drug manufacturers have the ability to use a portion of their sales revenue to stimulate demand by creating incentives for various participants in the biopharmaceutical supply chain and beyond. The primary incentives they use are discounts and rebates, each of which can take a number of different forms (Eickelberg, 2015). Between 2010 and 2014, the average rebates from drug manufacturers to insurers increased by 10 percentage points, from 18 percent to 28 percent of list price, for branded drugs (QuintilesIMS, 2016), and they continue to climb.

List prices grew 9.8 percent in 2016, modestly less than the 10.8 percent increase in 2015. The resulting increases in drug prices added $8.7 billion to 2016 net income for the 28 companies analyzed in a Credit Suisse report. Rebates in 2016 were up by almost 2 percentage points from the average of 35.7 percent in 2015 (Credit Suisse, 2017), and were estimated to be around $130 billion (Goldberg, 2017). Average rebates have also risen over time in the Medicare Part D program, from 8.6 percent in 2006 to nearly 20 percent a decade later (CMS, 2016). Rebates to PBMs can actually increase out-of-pocket spending for patients who pay a percentage of their drug's list price and those paying deductibles, as the discounts are rarely passed through to the patient at the point of sale (CMS, 2017; Dusetzina et al., 2017). The effects of such pricing strategies have been demonstrated to drive up out-of-pocket spending for patients on Medicare Part D even when net prices received by manufacturers are virtually the same (Dusetzina et al., 2017). For specialty drugs nearly all plans require enrollees to pay a percentage of their drug's price (Dusetzina and Keating, 2015; Jung et al., 2016; Polinski et al., 2009; Yazdany et al., 2015). Recognizing the role of rebates for increasing spending by beneficiaries and the federal government, in 2016 the Medicare Payment Advisory Commission outlined recommendations for restructuring Medicare Part D to provide incentives to sponsors to improve cost protections and reduce catastrophic spending. Specifically, they would require higher cost sharing from Part D plan sponsors and eliminate patient out-of-pocket contributions in the catastrophic phase of coverage (currently set at 5 percent of drug costs with no lifetime or annual out-of-pocket maximum). They would also require manufacturer payments in the coverage gap to stop counting toward patient out-of-pocket spending (MedPAC, 2016).

The interaction between rebates and list prices can be complicated. For example, market price negotiations based on a drug's list price can even induce drug manufacturers to further increase their drug prices (Hopkins and Tracer, 2017). Furthermore, some private insurance companies have begun to operate their own PBMs (Kirchhoff, 2015), and retail pharmacies have been merging with PBMs to provide integrated health services. These consolidations can produce conflicts of interests regarding decisions about the inclusion of drugs on a PBM's formulary (Cook et al., 2000).

In this complex supply chain many opportunities exist to enhance various participants' revenue and profits—often at the expense of patients. The only sources of data available to understand this system come from the participants, who release data and statements that conflict with each other and justify their positions. The relevant data needed to conclusively analyze this system do not exist at present, and, indeed, some of the participants (most notably the PBMs) argue that revealing their transactions would actually increase the drug prices paid by patients.

Arguments for and Against Transparency

The biopharmaceutical sector is rife with divergent, strongly held views regarding the concept of transparency.[11] As noted earlier, various participants in the prescription drugs pricing debate offer divergent statements about who is responsible for high and steadily rising drug prices, but with little to no relevant data to support their claims. In addition, some urge greater transparency in the biopharmaceutical sector, while others assert that transparency would harm competition and thus negatively affect consumers. Proposals vary widely concerning what information should be reported, to whom, and whether this information should be linked to price control measures. No empirical studies demonstrate that transparency in the biopharmaceutical supply chain will cause harm to patients. However, the debate, including in public testimonies, continues about whether transparency would weaken the market and pose harm to patients (Balto, 2014, 2015, 2017; Shepherd, 2014).

Opponents of transparency cite a series of letters from the Federal Trade Commission (FTC) (FTC, 2004, 2006, 2009, 2011, 2014) to state officials regarding policies on the disclosure of financial transactions among

[11] Public debates over transparency continue to be intense and unresolved, with numerous price transparency bills proposed at both the state and federal level. Recent legislation proposed in both chambers of the U.S. Congress would expand transparency by requiring PBMs to provide information for public posting on how much they rebate various drugs. Such price information could decrease the likelihood of excessive profiteering, particularly among PBMs—an industry mainly controlled by three firms. Several states have also introduced bills concerning drug price transparency. Much of this legislation is aimed at drug manufacturers.

the participants in the biopharmaceutical supply chain. For example, in a 2014 letter to the advisory council of the Employee Retirement Income Security Act, the FTC noted that "mandatory disclosure requirements may hinder the ability of plans to negotiate an efficient level of disclosure with PBMs" and that such disclosures, if they reveal discounts negotiated with PBMs, "may result in less aggressive pricing by, or even collusion among, pharmaceutical manufacturers" (FTC, 2014b). These concerns relate to state-by-state information and hence are more likely to reveal confidential contract information than data aggregated to the national level.

Proponents argue that lack of transparency negatively affects patients and enables the largest PBMs to engage in anticompetitive behavior, including securing kickbacks from drug manufacturers in exchange for exclusivity arrangements that may keep lower-priced drugs off the market (Balto, 2014). There is no way to test these claims in a controlled experiment. However, transparency has improved the functioning of markets in other sectors of the economy (see Box 2-3), and the potential gains from improved transparency in the biopharmaceutical sector appear to outweigh the potential risks emerging from increased transparency. The primary questions pertain to what level of information is needed and who would have access to the information. For example, the information would not need to be used directly by consumers to lead to improvements in market functioning. It could be used by other participants in the distribution chain for biopharmaceutical products, by specialists who study market behavior, and by regulators to control these markets.

One way to improve transparency in the pharmaceutical supply chain would be to require manufacturers to disclose detailed information on a drug-by-drug basis for their gross and net prices (the difference reflecting discounts given within the supply chain and discounts given directly to patients). Information about the prices paid at the end-stage of distribution in retail pharmacies or their mail-order counterparts and by hospitals, clinics, nursing homes, and other relevant organizations that purchase and directly administer drugs to patients would also need to be gathered in parallel. Logically, the difference between what the manufacturers report and what the final distributors (e.g., retail pharmacies, hospitals, doctor offices) report has been retained in the intermediary system either as costs or profits.

These data may provide clarity about the interactions—specifically the flow of funds and products—among the intermediaries of the biopharmaceutical supply chain, or they may point toward necessary regulation for additional data gathering from each participant in the biopharmaceutical supply chain. This proposed approach would involve a sequential process of first gathering information at the two ends of the supply chain—manufacturers at one end and consumer payments at the other—with the

BOX 2-3 Transparency Lessons from Other Sectors

The mandatory disclosure of information (with regulatory intent) has become an important component of policies across the economy (Fung et al., 2007). In 1976, the U.S. Congress passed the Government in the Sunshine Act, which affects the operations of the U.S. Congress, federal commissions, and other legally constituted governmental groups. The stated purpose of the act was to ensure that the public is informed about the impact that regulatory staff, officials, and other participants in the process have on decision making. In 2010 the Physician Payments Sunshine Act was enacted by the U.S. Congress as part of the Patient Protection and Affordable Care Act to increase the transparency of financial relationships among clinicians, teaching hospitals, and the manufacturers of drugs, medical devices, and biologics (Pham-Kanter, 2014).

Practices from other fields, such as finance, hospitality, occupational safety, and transportation, suggest that transparency does offer certain benefits to the public. For example, federal and state legislators applied transparency policies to improve the health and safety of foods through the passage of the Nutrition Labeling and Education Act of 1990. This act provides the U.S. Food and Drug Administration with specific authority to require nutrition labeling of most foods regulated by the agency and to require that all nutrient content claims and health claims be consistent with agency regulations. The U.S. Congress has also mandated transparency policies in the workplace through the Occupational Safety and Health Act.

Another area where transparency policies have been applied is auto safety and fuel economy ratings, through the implementation of Corporate Average Fuel Economy (CAFE) standards. The CAFE standards set the average new vehicle fleet fuel economy, as weighted by sales that a manufacturer must achieve. The disclosure policies and the regulatory mechanism supporting them have led to lower energy consumption as auto makers complied with the fuel economy standards for cars and light trucks. The enactment of the Home Mortgage Disclosure Act is another application of transparency policies. The act requires financial institutions to maintain and disclose to the public specific information about mortgages. Still another example of transparency policy is the Securities Exchange Act, which regulates exchanges, brokers, and over-the-counter markets and provides for monitoring the required financial disclosures.

Transparency policies that are targeted—that is, require specific information to be disclosed in a standardized format to achieve a clear public policy purpose—have been found to be generally effective, as opposed to broad right-to-know disclosures (Fung et al., 2007). Targeted policies that have been reported as having worked particularly well include those related to mortgage lending disclosures and corporate financial disclosures (Fung et al., 2007). However, it is important to note that most disclosure laws do not directly affect decisions regarding the pricing of individual products or individual transactions.

understanding that more refined data may be needed later to completely understand how the biopharmaceutical supply chain operates. Experience from other sectors would suggest that transparency on supply chain costs tends to reduce these intermediary costs (see Box 2-3).

Profitability Across the Supply Chain

Another argument in favor of transparency is based in the importance of understanding the profitability of the participants in the biopharmaceutical supply chain. Such an understanding would, at minimum, help bring clarity into how the biopharmaceutical supply chain affects prescription drug prices in the United States compared with those in other nations. Of greatest importance in this question is how profitable the manufacturers of branded and generic drugs are, because their profitability is commonly seen as a source of funds for investing in new research and development to bring new lifesaving and life-enhancing products to the market.

To address this question, four key sources of information were reviewed. The first was a 2015 projection in *Forbes* showing the top 10 most profitable industries for 2016 (Chen, 2015). The listing showed generic pharmaceutical companies as the most profitable sector (with 30 percent margin), while major pharmaceutical companies appeared fourth on the list (25.5 percent margin) and biotechnology companies were sixth on the list (24.6 percent margin). Other industries on the list included investment managers (29.1 percent margin), tobacco (27.2 percent margin), Internet and software services (25 percent margin), and various banks (between 22 and 24 percent margin).

The second source was a recent study published by the University of Southern California that assessed the profit margins for various industries (Sood et al., 2017). This study found branded pharmaceuticals to be the industry with the greatest profit margins (28 percent) and generic pharmaceuticals to be fourth (26 percent), with tobacco and alcoholic beverages in between. The reported rate at which profit has been growing in the pharmaceutical sector significantly outpaced the rates of all other reported sectors of the U.S. economy (see Figure 2-6).

Third, corporate bond ratings on major pharmaceutical companies from the Morningstar bond rating agency were reviewed for insights into the financial health of companies. While some of these companies in the biopharmaceutical sector did not have bond ratings (some companies do not issue corporate bonds), of those with a rating provided by Morningstar, which accounted for 86 percent of the market capitalization considered, the bond ratings were all A– or higher, with one AAA rating (Johnson & Johnson), the highest rating given by Morningstar. The lowest bond rating among pharmaceutical companies (three firms representing 4.5 percent of the total market capitalization) was BBB–.[12] For the sake of comparison, the bond ratings of some familiar corporations in other sectors of the

[12] AAA = extremely low default risk; AA = very low default risk; A = low default risk; BBB = moderate default risk; BB = above average default risk; B = high default risk.

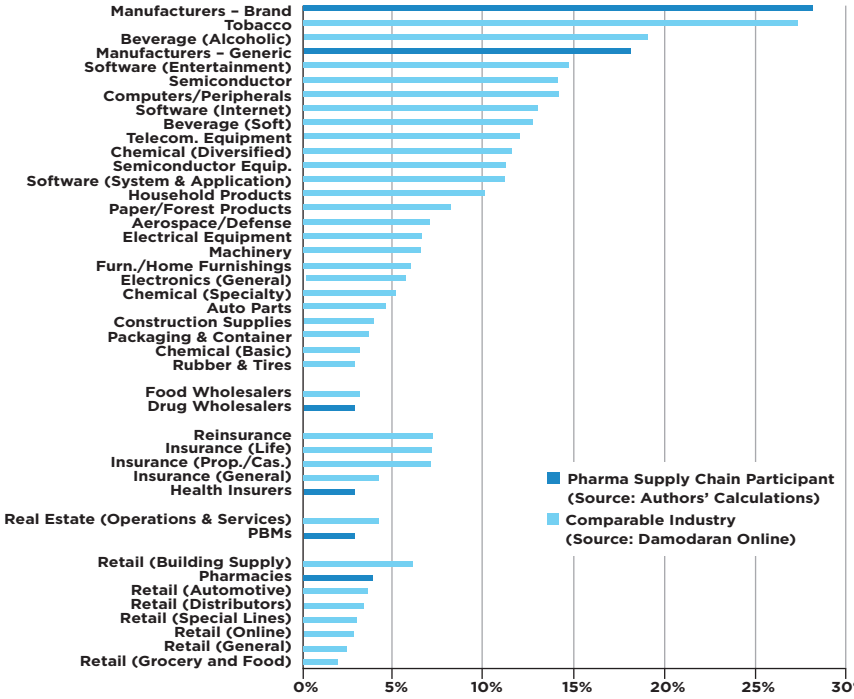


FIGURE 2-6 Average sector net margins for companies in the biopharmaceutical sector and comparable industries.
SOURCE: Sood et al., 2017, Figure 4.

U.S. economy were Microsoft: AAA; Exxon: AA+; Google: AA; Apple Computers, Chevron, Intel: AA–; Home Depot, IBM: A+; Amazon, Shell Oil (Royal Dutch), Starbucks, U.S. Steel: A; McDonalds: A–; Southwest Airlines: BBB+; Ford Motors, General Motors, Hewlett Packard, Verizon: BBB; T-Mobile, United/Continental Airlines: BB; and Sprint: B.

However, a concern about the future profitability of biopharmaceutical companies emerges from a recent analysis from Deloitte LLP (2016), which reported a steadily declining return on investment (ROI) for research and development in the biopharmaceutical sector. According to that report, the ROI fell steadily from 10.1 percent in 2010 to a low of 3.7 percent in 2016. The analysis focused on the performance of 12 large-cap companies (i.e., companies with a large market capitalization) since 2010. A group of mid-cap companies that were also newer companies had a higher average ROI, but their return also showed a decline—from a prior peak of 17.7

percent to 9.9 percent in 2016. The Deloitte report's summary statement stated, "Costs per asset have stabilized for the original biopharma cohort, but forecast peak sales per asset continue to decline" (p. 2).

Share of Costs and Profits Within the Biopharmaceutical Supply Chain

This section presents available assessments of share of costs and profits in the biopharmaceutical supply chain. However, these assessments used different methodologies and data that differ in scope; thus, they are not directly comparable.

One recent analysis of profitability across the biopharmaceutical drug supply chain illustrates the difficulties in working with currently available data for U.S. firms (Sood et al., 2017). The U.S. analysis, reported in a white paper, used financial information that is publicly available through the Securities and Exchange Commission (SEC) for firms that are publicly traded on stock markets—a subset of the entire market that selectively eliminates both privately held firms and smaller firms. The omission of smaller firms may be more important at the front-end research and development stage of the market than further along the supply chain, but the omission is relevant to some extent at all levels of production and distribution. The approach used for this white paper also excluded nonprofit organizations. A further complication arises because some of the intermediaries in the supply chain operate in more than one segment of the supply chain, for example, both as a PBM and an insurer, as a PBM and a retail pharmacy, or other similar combinations.

While public reports generally separate these different lines of business into different areas of profit, the choice of exactly where to report profits remains somewhat arbitrary on the part of the reporting entity. For example, if a $1 million rebate is received from a drug manufacturer by a PBM, that rebate could be retained at the PBM level (where it would increase the reported PBM profit margin), or it could be passed along to an affiliated insurer or retail pharmacy. The same $1 million would have different effects on profit margins depending on the underlying level of economic activity, and it would appear smallest on a percentage of revenues if it were reported as being accrued by the largest of the component businesses.

With these considerations in mind—and emphasizing that the committee does not view these data as conclusive—the analysis does shed light on the profitability of various elements of the biopharmaceutical supply chain. The key result is presented in Figure 2-7, which shows that $41 out of every $100 spent on prescription drugs is retained in the supply chain, including wholesalers, retailers, PBMs, and insurance companies (Sood et al., 2017). This would suggest that the intermediaries in the U.S. bio-

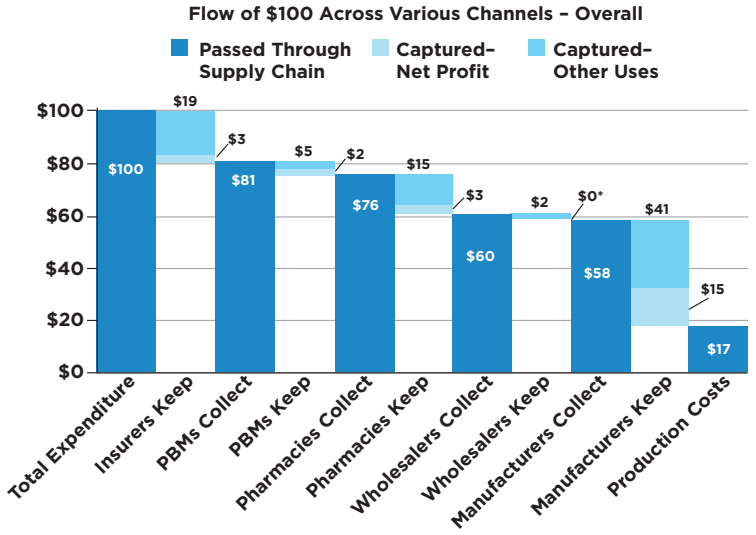


FIGURE 2-7 Flow of a hypothetical $100 expenditure on prescription drugs covered under private insurance through the U.S. biopharmaceutical supply chain.
*Wholesaler net profit is $0.32.
SOURCE: Sood et al., 2017, Figure 2.

pharmaceutical supply chain consume a greater fraction of total costs than is apparently the norm in other nations.[13] As noted above, the distribution-related costs in six comparator countries averaged 32.7 percent of end-user price based on a simple average and 28 percent based on a population-weighted average (QuintilesIMS, 2014). The Sood analysis also estimated gross and net margins for each sector, segmented by branded drug, generic drug, and the total market, and found the following: net margins resulted: 28.1 percent for branded drug manufacturers, 18.2 percent for generic manufacturers, and 26.3 percent overall.

The intention behind reporting these international and domestic data is to emphasize that these data are unavoidably incomplete in scope and do not provide information on many key participants in the various markets. The limitations inherent in using SEC filings to garner such data also point to the need for more granular information than the SEC database can reveal.

To assess the flow of funds through the distribution system, a Barclays

[13] Another study by Kanavos and colleagues (2011) found that distribution margins vary greatly at different levels of wholesale and retail segments among 27 member states of the European Union. However, none of these include distribution segments is comparable to health insurance and PBM markets in the United States.

Equity Research analysis using publicly available data from two PBMs (Express Scripts and CVS) estimated that, in 2015, an industry-wide total of $115 billion was either provided as discounts to or retained by those involved in the distribution of pharmaceutical products (i.e., those organizations between the manufacturers and the consumers). This was estimated to have been 27 percent of what gross sales would have been, based on the listed prices. The Barclays estimate of how this $115 billion is distributed is presented Figure 2-8.

In some cases, the Barclays analysis could not determine whether the funds were being retained or passed along in the supply chain because the analysts had no information from certain of the participants in this distribution system.[14] For example, the analysis found that $9 to $10 billion was either "retained by distributor or passed to dispenser" at the distribution level. Manufacturers directly paid fees to PBMs ($1.5 to $2.0 billion) and additionally retained $5 billion of rebates through the commercial insurance (nongovernmental) sector, with another $23 billion passed to Medicaid programs and $21 billion passed to Medicare. The final $31 billion in the commercial sector is described as "passed to payers" with no understanding of how much of this $31 billion was passed along to consumers in terms of lower drug prices (versus being retained by payers to cover costs or as profits).

In a separate analysis of 2015 data, the Berkeley Research Group (Vandervelde and Blalock, 2017) provided estimates of the distribution of gross revenues in the pharmaceutical distribution system. They began with gross sales information from manufacturers, estimating a total of $469 billion in 2015, and then estimated the portions received by branded manufacturers (47 percent) and generic manufacturers (23 percent), which implied a total of 70 percent received by manufacturers. It was estimated that others in the supply chain receive 27 percent of the total, with 4 percent consumed in other rebates and fees (see Figure 2-9).

This calculation diverges from that of Sood and colleagues (2017) in several ways. First, the Berkeley Research Group's method did not separate operating costs from profits. Second, its analysis began with total sales at gross list prices, whereas Sood and colleagues assessed the flow of funds only through retail sales involving commercial insurance plans. Sood and colleagues estimated that the manufacturer retained 58 percent of sales dollars, using as a base the actual amounts spent by consumers on retail sales (e.g., in pharmacies and other retail distribution outlets). Thus, the figure of 58 percent of sales calculated by Sood and colleagues (in effect, por-

[14] These gaps in available data cannot be repaired using existing data sources. One of the recommendations in this report focused on new data gathering is designed to remedy this defect, providing a direct method for assessing how much is retained by the distribution system and how much passes to consumers.

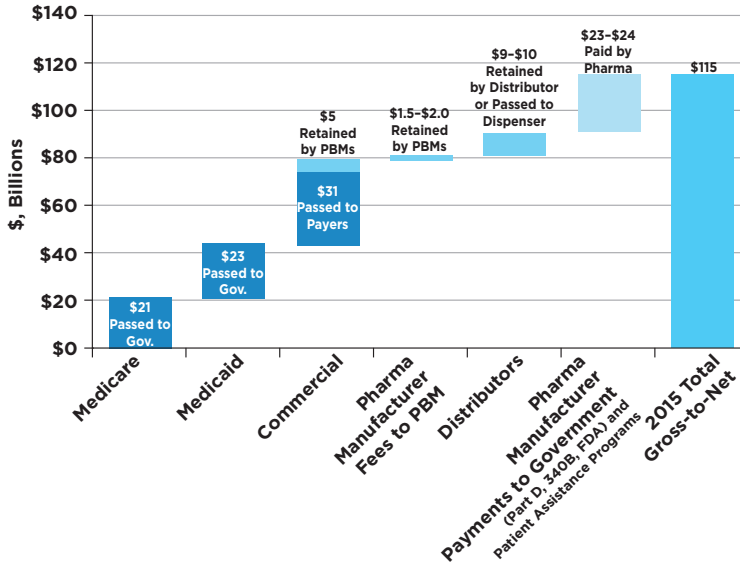
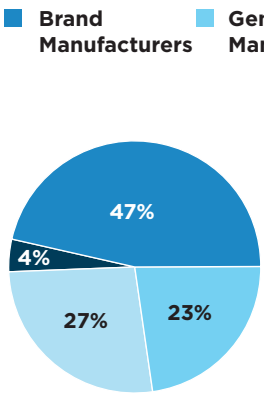


FIGURE 2-8 Total gross-to-net dollars contribution across the biopharmaceutical supply chain.
NOTE: FDA = U.S. Food and Drug Administration; PBM = pharmacy benefit manager.
SOURCE: Barclays, 2017, Figure 1.



	Net Expenditures $ (Billions)	%
Manufacturers		
Brand Manufacturers	218.6	47
Generic Manufacturers	107.6	23
Non-Manufacturer Stakeholders		
Supply Chain Entities	125.3	27
Other Retrospective Rebates and Fees	17.5	4
Total**	**469.0**	**100**

FIGURE 2-9 Share of 2015 net drug expenditures realized by manufacturers and intermediaries in the biopharmaceutical supply chain.
*Includes any retrospective rebates and fees not shared with the end payer.
**Components may not sum to total due to rounding.
SOURCE: Vandervelde and Blalock, 2017, Figure 3.

traying net sales after subtracting rebates given to PBMs and others) does not directly correspond to the 70 percent figure (gross revenue) calculated by the Berkeley Research Group.

A 2014 publication reported the proportion of total pharmaceutical costs attributable to the distribution system (comprising wholesalers and retailers) in different countries (QuintilesIMS, 2014). Current estimates of the populations of these six countries were used to calculate a population-weighted average of the data. The distribution-related costs in these six nations averaged 32.7 percent of end-user price based on a simple average and averaged 28 percent when a population-weighted average was used

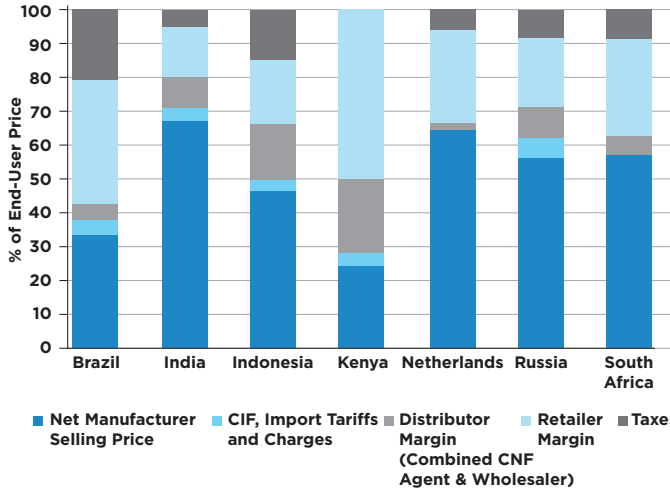


FIGURE 2-10 Price build-up across five therapy areas in seven countries.
NOTES: CIF = cost, insurance, and freight charges; CNF = cost, no insurance, and freight charges.
2013 population-adjusted average. The study's description of the countries chosen for the analysis stated:
Brazil: Upper-middle income country with large retail out-of-pocket market and a major market in the region.
India: Lower-middle income country with a large out-of-pocket market but undergoing change and implementing mechanisms to control the build-up of drug prices.
Indonesia: Lower-middle income country with little price regulation and relatively large out-of-pocket spending.
Kenya: Excluded by the committee for discussion in this report since the IMS study did not provide exact data on that country's costs. Furthermore, the data reliability for Kenya was very small (only 30 drug prices in the sample compared to thousands in other nations).
Netherlands: High-income country with a rational approach to pricing and margins, and useful as a baseline country for comparison purposes.
Russia: High-income market with a high level of out-of-pocket, mix of regulated and unregulated market.
South Africa: Upper-middle income country with a large proportion of the medicine market funded privately, but a highly transparent pricing system in place.
SOURCE: QuintilesIMS, 2014, Exhibit 12, p. 21.

(see Figure 2-10). The data from this report data came from a sampling of drug transactions in five significant areas of pharmaceutical products: antibiotics, diabetes, epilepsy, hypertension, and respiratory diseases. However, the analysis did not include other important areas of drug spending in the United States, most notably cancer and other specialty drugs.

In summary, each analysis differs in its methodology to estimate the potential amount captured by the intermediary participants in the biopharmaceutical supply chain. Part of the challenge in making these comparisons, as noted, is that various analyses employ different approaches to defining total drug spending, part is the differing assumptions made about the pass-through of discounts and rebates, and part is whether the issue is framed in terms of the share of list price or the share of the price ultimately paid by the patient and the insurers. Similar methodological differences also bedevil cross-country comparisons, as do varying approaches to the inclusion of sales and value-added taxes.

Thus, existing data do not adequately answer a question of fundamental interest: when a pharmaceutical company provides a discounted price, how much of that discount actually reaches patients at the other end of the distribution system? Without knowing the answer to this basic question, it is impossible to determine responsibility either for the levels of prices or their rates of increase over time. This lack of clarity has led to numerous situations in which different participants in the supply chain point to other participants as the source of high and increasing prices. One cannot know with reasonable clarity how much money is retained at various levels, or how much of that which is retained is due to operational costs and how much is profit. For example, while Sood and colleagues (2017) assembled this type of information, that analysis is limited by several important omissions: (1) it included only companies that are publicly traded (SEC data), and (2) it only assessed the distribution through the retail pharmacy sector for those with insurance. Thus, public programs such as Medicaid, veterans' benefits, TRICARE, and the 340B program, among others, are excluded, along with sales to clinicians who purchase and then directly administer prescription drugs.[15]

FINDINGS

Based on the material presented in this chapter, the following findings are offered:

[15] This same omission accounts for the difference between estimates that prescription drugs account for 10 percent of U.S. health care costs versus other estimates of 16 percent. The former estimate includes only the retail sales portion of total sales.

Finding 2-1: *The complexity, confusion, and conflicting information associated with the pricing of prescription drugs result in opaqueness of financial transactions among the participants in the biopharmaceutical supply chain.*

Finding 2-2: *Mandatory disclosure and public reporting of reliable information regarding financial flows and margins (which currently does not exist) would allow a fuller understanding of how participants in the biopharmaceutical supply chain operate and how they influence final prescription drug prices to the consumer. This would improve market performance and provide the basis for future policy changes as needed.*

Finding 2-3: *Various participants in the biopharmaceutical supply chain point to other participants as the main contributors to high and rising drug costs. The resulting discord and lack of meaningful information to evaluate those competing claims undermines the ability to confidently understand the root causes of price increases and when they are appropriate.*

Finding 2-4: *While some suggest that greater transparency across the biopharmaceutical supply chain could harm rather than benefit consumers, there is no compelling evidence to support this claim. Moreover, practices from other fields, such as banking, consumer loans, occupational safety, and automotive manufacturing, suggest that transparency does benefit consumers.*

Finding 2-5: *Most large employers self-finance their health insurance contributions for their employees and hence have a direct and significant interest in controlling health care costs.*

Finding 2-6: *Extensions of product exclusivity based on minor modifications to existing patents—known as "evergreening"—adversely affect consumers.*

Finding 2-7: *"Pay-for-delay" strategies employed by companies to keep generic competitors out of the market reduce access to reasonably priced generics.*

Finding 2-8: *In the United States, formulary control relies heavily on tiering, which can have mixed consequences. Placement of a drug in a higher tier can reduce adherence to the treatment plan, with potential harms to patient health, but the tiered price mechanism can also be used by insurers to negotiate better prices for branded drugs.*

Finding 2-9: *In the United States, the bargaining power of federal and state governments has been undercut by laws restricting what they may negotiate and exclude from coverage. Because prices tend to be lower when the purchaser has bargaining power that is at least comparable to that of the seller, the United States could achieve lower prices for prescription drugs by consolidating bargaining power and providing greater flexibility in formulary design.*

Finding 2-10: *Section 1861 of the Social Security Act, which requires that Medicare cover "reasonable and necessary" medical services, in conjunction with language in other statutes limiting the extent to which comparative effectiveness information can be used in Medicare coverage decisions, has precluded consideration of cost or cost-effectiveness in coverage decisions.*

Finding 2-11: *Value-based approaches to drug purchasing decisions and formulary control are well established in some other OECD countries where they are seen as critical to containing price pressures and ensuring affordability.*

Finding 2-12: *In the United States, although approaches for assessing the "value" of drugs have been developed and deployed in several clinical areas for a number of years, there remains considerable debate about the use of value-based approaches in the pricing and the purchasing of drugs, as well as for designing insurance benefits.*

Finding 2-13: *Rebates, discounts, and financial arrangements among biopharmaceutical companies, intermediaries, purchasers, and health care providers—coupled with tiered cost-sharing arrangements in health insurance plans—often do not benefit consumers even when intended to do so, and at times may even harm consumers and society at large.*

Finding 2-14: *Although the available data are not fully comparable, they indicate that intermediaries in the U.S. biopharmaceutical supply chain extract a higher fraction of total prescription drug spending than do the entities performing similar functions in other countries.*

The next chapter considers in greater detail some of the main factors influencing affordability. These range from pricing policies to market exclusivity, and from patient assistance programs to the availability and the clarity of information affecting the choices available to patients and their clinicians, and also presents related findings.

3

Factors Influencing Affordability

The affordability of prescription drugs in the United States is influenced by a complex and highly interactive set of factors. The factors that tend to increase the cost of drugs for patients include the following, each of which is discussed in turn in this chapter:

- High launch prices, with the price of the drug then often increasing over time.
- Inadequate competition when market exclusivity ends.
- The interaction of market power, health insurance, and the lack of effective incentives for controlling product price.
- Unequal bargaining power between buyers and sellers.
- Research, development, and marketing expenditures as well as other business expenses.
- Insurance benefit designs with significant patient cost-sharing provisions.
- Inadequate performance of patient assistance programs and other public programs intended to make medicines more affordable for patients.
- Lack of adequate information affecting choices regarding medicines.

PRODUCT PRICING

Patent law establishes the exclusive right for inventors to apply their work for a specified period of time, either through direct manufacturing or by licensing to others. During patent exclusivity, prices of products are typically

set higher that permit patent holders to realize greater profits than would be achievable in a competitive marketplace. Many observers of the biopharmaceutical sector characterize this pricing practice as "what the market will bear." Others rationalize it as properly and necessarily rewarding the pursuit of a high-risk, capital-intensive endeavor. That is, producers can be expected to set prices that are constrained only by how much consumers are willing to pay for a product that is protected by exclusivity.

The entry of generic drugs into the market provides competing products that are generally sold at much lower prices than the original branded product. Although the original branded product may continue to be offered at a high price, typically the lower cost of the generic will lead a large number of consumers to choose it. In recent years, between 80 and 90 percent of all prescriptions in the United States have been filled with generic products (Boehm et al., 2013; GPhA, 2015; Lee et al., 2016). However, if there is insufficient competition among the generic alternatives themselves, the prices of a drug might not drop to the anticipated competitive level. This particular issue is explored in a later section of this report.

A parallel issue relates to the particular manner in which drugs are actually priced in the United States (as described in Chapter 2). Specifically, manufacturers and distributors of drugs start with list prices at the time of launch and often modify them over time. However, in many cases a product's list price is immediately discounted by manufacturers and distributors in sales to pharmacy benefit managers (PBMs), insurance companies, wholesalers, retailers, and others. Unfortunately, there are few publicly available data about the nature of these discounts, so it is impossible to determine exactly how net prices for consumers are derived. The situation is made more complex by the fact that the net price may differ greatly among different consumers.

Biopharmaceutical manufacturers often state that too much attention is focused on the list price of drug, as opposed to the end cost to health plans and patients. However, in a system with a broad use of rebates and discounts, list price matters because it is the starting point for all negotiations in the supply chain. As discussed earlier, it also matters because (1) uninsured patients pay list price at the pharmacy, and (2) cost sharing for insured patients is sometimes defined as a fraction of list price. The effects of high list prices are discussed in the following sections, with branded, generic, and other drug products covered separately.

Branded Drugs

Although branded medications make up approximately 10 percent of all prescriptions in the United States, they account for nearly three-quarters

of prescription drug spending (GPhA, 2015). Spending for all retail prescription drugs accelerated significantly in 2014 and 2015, before slowing in 2016 (QuintilesIMS, 2017a). The spending rate was 10.3 percent, which rose to 12.4 percent between 2014 and 2015 before falling to 5.8 percent in 2016—still twice the 2.5 percent rate of growth in 2013 (QuintilesIMS, 2015a, 2016a, 2017a).

The cost of branded drugs is influenced by their launch prices—the prices set by the manufacturer for the new drugs when they first become available on the market—and the subsequent annual increases in their list prices. Recent data on anti-cancer drugs show that on average launch prices increased by about $8,500 per year over the past 15 years (Howard et al., 2015). Other studies have found similar increases in the prices of cancer drugs after their launch (Bach, 2009; Bennette et al., 2016; Shih et al., 2017).

A 2009 report from the U.S. Government Accountability Office (GAO) estimated that between 2000 and 2008, 416 brand-name drug products displayed "extraordinary" price increases (GAO, 2009). The 416 products represented 321 specific medications, with some medications being available in different drug strength and dosage forms; for example, the 416 products included eight different strength and dosage forms of the beta blocker Inderal. Most often the increases in price reported in the study were between 100 and 499 percent, but in a few cases, specifically for drugs used to treat such conditions as fungal or viral infections or heart disease, a drug's price increased by 1,000 percent or more.

The absolute price increases for branded drugs ranged from $0.01 per unit to $5,400 per unit. The unit price of a drug is, of course, only one factor in determining the cost of a full course of treatment for a medical condition. The cost for a full course of treatment for one drug used to treat one rare form of cancer increased from $390 to more than $3,000 during the study period (GAO, 2009). Figure 3-1 shows how the prices of 268 top branded drugs rose throughout the period 2006–2015, with the yearly increases being consistently higher than the increases in the overall consumer price index—sometimes much higher.

Spending on specialty medicines has nearly doubled over the past 5 years, clearly outpacing the consumer price index and accounting for more than two-thirds of the overall growth in spending on medicines between 2010 and 2015 (AHIP, 2015; QuintilesIMS, 2016a). One result of this increase is that Medicare beneficiaries face rapidly growing out-of-pocket payments for specialty drugs. This trend is likely to continue as the population ages and more treatments become available for difficult-to-manage diseases (Dusetzina and Keating, 2015; Dusetzina et al., 2017; Trish et al., 2016). On the challenge of how to go about financing very expensive

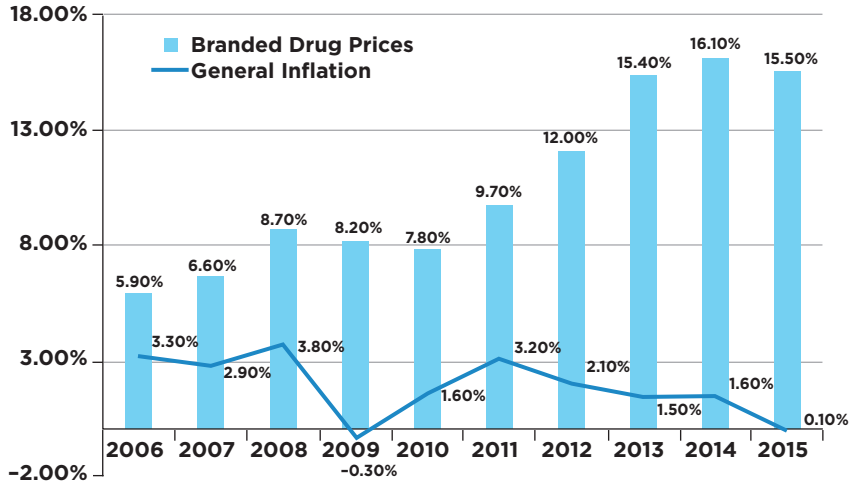


FIGURE 3-1 Average annual brand-name drug prices (a composite of 268 top drug products) compared with general inflation from 2006 to 2015.
SOURCE: Schondelmeyer and Purvis, 2016.

branded drugs, see Box 3-1. Whether existing or new drug therapies are actually effective in patients is another issue that must be considered.[1]

Generic Drugs

Once branded medications lose their patent exclusivity, generic versions can enter the market with approval from the U.S. Food and Drug Administration (FDA). Generic drugs are the same as the branded "innovator" drugs in terms of dosage, safety, strength, chemical composition, route of administration, quality, performance characteristics, and intended use (FDA, 2017a). When a generic enters the market, it tends to be priced more closely to the marginal cost of production, which often pressures the company that manufacturers the branded drug to lower the cost of that drug in

[1] Many therapies benefit only some of the patients who receive them. In recent years improved diagnostic tests have become particularly valuable, especially in oncology, for providing insights, based on an individual's genomic makeup and other biomarkers of his or her disease, into whether a particular therapy is likely to be of benefit (NASEM, 2016). Three issues may emerge in the future regarding these predictive diagnostics. The first issue involves the incentives of third-party payers to adequately compensate for diagnostics, which are often far more expensive to develop and apply than traditional laboratory tests. The second issue may arise from the increased use of companion diagnostics for rare diseases that affect only subpopulations. Third, as diagnostics advance the goal of precision medicine, the logical result will be that a given drug is prescribed for fewer patients.

order to remain competitive (Berndt and Aitken, 2011; Frank, 2007; GPhA, 2015; Grabowski et al., 2014; Greene et al., 2016; QuintilesIMS, 2016b).

People in the United States commonly pay lower prices for generic drugs than do people of other countries (Wouters et al., 2017). Generic drugs now account for up to 90 percent of all prescriptions written in the United States (GPhA, 2015; Grabowski et al., 2016). By comparison, in the early 1980s generics accounted for less than 20 percent of all prescriptions written and many profitable branded drugs with expired patents still did not have generic competitors (Frank, 2007). Analyses show that when generic drugs enter the market, they reduce the market share of the related brand drugs (Grabowski et al., 2014). If only a single generic producer enters the market, it does not necessarily reduce prices. Typically, once a drug has reached the end of its exclusivity period, the price of the branded drug may remain about the same during the period of exclusivity, or it may even drift upward, but as the generic prices decline, they capture a major portion of the market. It may take several competing generic companies to enter the market before the prices for the drug to reach their lowest possible level based primarily on cost of production.[2] Generic prices, not surprisingly, exhibit the largest reductions in markets where revenues are initially above average (Gupta et al., 2016; Olson and Wendling, 2013). Multiple producers of generic drugs also help prevent shortages should one firm ceases production. From the standpoint of ensuring ongoing production and competition in the market, mergers between competing firms that make identical or biosimilar products—either generic entrants or the original branded manufacturer—are not a desirable occurrence. The Federal Trade Commission has regularly challenged such mergers (FTC, 2017).

Two recent studies examined manufacturer entry, exit, competition, and the relationships among generic drug supply structures and inflation-adjusted prices. The first of these studies found that the median and the mean number of manufacturers was about two and four, respectively, and that the number of suppliers has been declining in recent years, due both to more exit and less entry of manufacturers (Berndt et al., 2017b). The second found that a very large portion of generic manufacturers have small portfolios consisting of less than five products, while a small number of generic manufacturers have very large portfolios with hundreds or even thousands of products (Berndt et al., 2017a). Approximately 40 percent of product markets were supplied by only a single manufacturer. The share supplied by one or two manufacturers increased over time and was larger

[2] The current backlog of unapproved generics at the FDA is a hurdle to generics pushing the costs of branded products down. Although the FDA's review times for generic drug applications have decreased since the implementation of the Generic Drug User Fee Amendment, there were 2,640 generic drug applications pending approval as of April 1, 2017 (FDA, 2017f).

BOX 3-1 Strategies for Financing Expensive Therapies with Broad Public Health Implications

Ordinarily we think of medical interventions as benefiting the patient who receives them, but some treatments have important spillover effects, or "positive externalities," for others. In such cases, it is arguably both economically rational and ethically justified for parties other than the patient to shoulder a large share of the cost. For example, employers and health insurance programs provide vaccines at low or no cost because of the population benefits of preventing infectious disease. Other examples of biopharmaceutical products that fall into this category of interventions include drugs that limit the spread of sexually transmitted diseases and smoking cessation medications that reduce others' exposure to secondhand smoke. For such products, arguments for eliminating financial barriers to treatment are compelling.

On rare occasions a therapy emerges that promises to cure those affected and thereby potentially eradicate the disease. These conditions are met only when a drug is very effective in curing patients, when the disease is transmissible, and, finally, when the disease is transmitted only through human vectors. It would not be possible, for example, to use such a therapy to eradicate mosquito-borne Zika or other viral and bacterial infections that have non-human carriers. When such a therapy appears, it may be desirable to use one-time financing to pay for enough treatments to bring the infection level so low that further human transmission either stops or is easily manageable in steady state. One recent example of such a very expensive therapy is medication to treat hepatitis C—a blood-borne infection that slowly destroys the liver and can lead to liver failure, cancer, and death (Chopra, 2014).

Hepatitis C is the leading cause of death from infectious diseases in the United States—responsible for more fatalities than HIV and tuberculosis combined (CDC, 2017a). Nationally, the number of reported hepatitis C infections has nearly tripled over the past 5 years (CDC, 2017a). In Ohio, infections have increased 10-fold during that same period, with nearly 120,000 individuals currently infected (CDC, 2017b; Rosenberg, 2017). While the majority of individuals currently infected with hepatitis C are baby boomers, the number of new infections is highest among 20- to 29-year-olds, largely driven by the increase in injection drug use related to the opioid crisis (CDC, 2017a).

There is no vaccine for hepatitis C, and for years, the available drugs were toxic and often ineffective. Several medications that clear the virus after 12 weeks of therapy became available in the past 3 years, revolutionizing care for infected individuals. Approximately 80 to 95 percent of patients treated with new direct acting antiviral treatments such as sofosbuvir experience elimination of blood viral loads consistent with cure[a] of the disease (Kohli et al., 2014). However, questions have arisen about the high list prices of the drugs (Brennan and Shrank, 2014). The list price for the first available drug was more than $80,000 per 12-week regimen or $1,000 per pill, and even at the typical state-discounted price of approximately $25,000 per 12-week regimen, the majority of those in need could not access these medicines (AASLD/IDSA, 2017). The drugs have remained very expensive even as multiple products have entered the market, with discounted prices still in the range of $15,000 to $20,000 (Rosenthal and Graham, 2016). It will be a decade or more before any of the available treatments lose patent protection and cheaper generics become available. The cost to manufacture the medicines is about than $3 per pill (Hill et al., 2014).

The recent introduction of these new antiviral treatments has challenged state budgets. Many states have used strict guidelines for determining which patients are eligible to receive hepatitis C treatment through state programs (Barua et al., 2015). For example, as of November 2017, more than half of states have restricted access to patients who have at least moderate liver damage and more than three-quarters of states require sobriety from drugs and alcohol, or enrollment in a substance use treatment program, before treatment can begin (Center for Health Law and Policy, 2017). However, delaying treatment can increase costs (NASEM, 2017).

States have been exploring strategies to expand the number of state Medicaid-insured patients able to obtain access to the new hepatitis C medications.[b] A recent report from the National Academies of Sciences, Engineering, and Medicine on measures to eliminate hepatitis B and C recommended several approaches for dealing with this issue (NASEM, 2017). A state or states, the report noted, could hold a voluntary competition to purchase a license for one of the existing medications at a heavily discounted price to specifically treat patients with hepatitis C through state Medicaid programs. However, the license would be voluntary so it is unclear whether any manufacturer would agree to do so. A waiver from the Centers for Medicare & Medicaid Services would also be required to pursue this option because current Medicaid rebate statute requires formulary coverage for all products made by manufacturers that enter into a federal rebate agreement (see later section on federal discount programs).

Approaches proposed by others include one-time financing that would involve amortizing the cost of the treatment at either the individual or the societal level (Montazerhodjat et al., 2016). At the individual level, this approach would be somewhat analogous to obtaining a home mortgage, but the analogy is imperfect. In particular, in the case of a mortgage the lender has marketable collateral that serves as a fallback if the borrower fails to repay the loan. However, when what is being paid for is human health, no such collateral exists. A comparable market with no collaterals is that of educational loans where the default rate has been 12 to 14 percent in recent years (AIER, 2017; Friedman, 2017), markedly higher than auto loans and credit card delinquencies.

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[a] A recent Cochrane systematic review of 351 publications of 138 randomized controlled trials (Jakobsen et al., 2017) has challenged the belief that a cure for hepatitis C has been achieved. The analysis concluded that direct-acting antivirals (DAAs) "seemed to reduce the risk of no sustained virological response. The clinical relevance of the effects of DAAs on no sustained virological response is questionable, as it is a non-validated surrogate outcome. All trials and outcome results were at high risk of bias, so our results presumably overestimate benefit and underestimate harm. The quality of the evidence was very low." This analysis, currently a subject of discussions in the public health community, ultimately reinforces the importance of assessing long-term outcomes as well as short-term surrogates to demonstrate the curative potential of the treatment, which may entail further research, development, and related costs.

[b] See, for example, the State Medicaid Alternative Reimbursement and Purchasing Test for High-Cost Drugs. See http://smart-d.org.

among non-oral drugs but varied across therapeutic classes. Generic drug prices also increased over time, particularly after 2010, following the implementation of the Patient Protection and Affordable Care Act (ACA) and the Generic Drug User Fee Amendments. The authors concluded that generic drug markets in the United States typically involve small-revenue products and are increasingly tending toward duopoly or monopoly supply. Taken together, these findings suggest that the conventional wisdom involving generic drugs in the United States—that competition among generic manufacturers, facilitated by buying power consolidation among insurers and other purchasers, results in increasing access to safe and effective treatments for chronic disease, offsetting at least to some extent the higher prices of newly launched and existing branded drugs (Aitken et al., 2016; Duggan et al., 2008)—may be less true now than previous studies suggested.

Abrupt price increases have been a matter of concern for generics as well. When the GAO examined the price histories of 1,400 generic drugs, it found 351 cases of extraordinary price increases within a single year (GAO, 2016b) (see Figure 3-2). For example, the cost of a generic antidepressant used to treat the symptoms of obsessive-compulsive disorder increased by more than 2,000 percent in 1 year, jumping from $0.34 per capsule in the first quarter of 2013 to $8.43 per capsule in the first quarter of 2014. Also, the price of a generic nonsteroidal antiinflammatory drug that can be used to treat rheumatoid arthritis or osteoarthritis increased by more than 2,000 percent, from $0.09 per capsule in first quarter 2010 to $1.94 per capsule in the first quarter of 2011 (GAO, 2016b). In some cases the prices of generics increased because of limited competition, while in other cases it was a result of delays in the review process by the FDA (GAO, 2016b; Greene et al., 2016). The lack of therapeutically equivalent drugs in the market limits competition and may contribute to extraordinary price increases (GAO, 2009). These issues further highlight the importance of having multiple producers of generic drugs. However, a recent lawsuit brought by the attorneys general of 45 states and the District of Columbia accused 18 companies and subsidiaries of colluding to fix prices for 15 medicines (Friefeld, 2017).

Biosimilars

A biosimilar is a biological product that contains a version of the active substance of an FDA-approved "reference" product (FDA, 2017b). The first biosimilar, a relative of somatropin (a growth hormone), was approved by the European Medicines Agency in 2006 (Simoens, 2011). Since then, 28 biosimilar products have been approved in Europe (QuintilesIMS, 2017b). Estimates of the overall cost saving that the European Union will experience

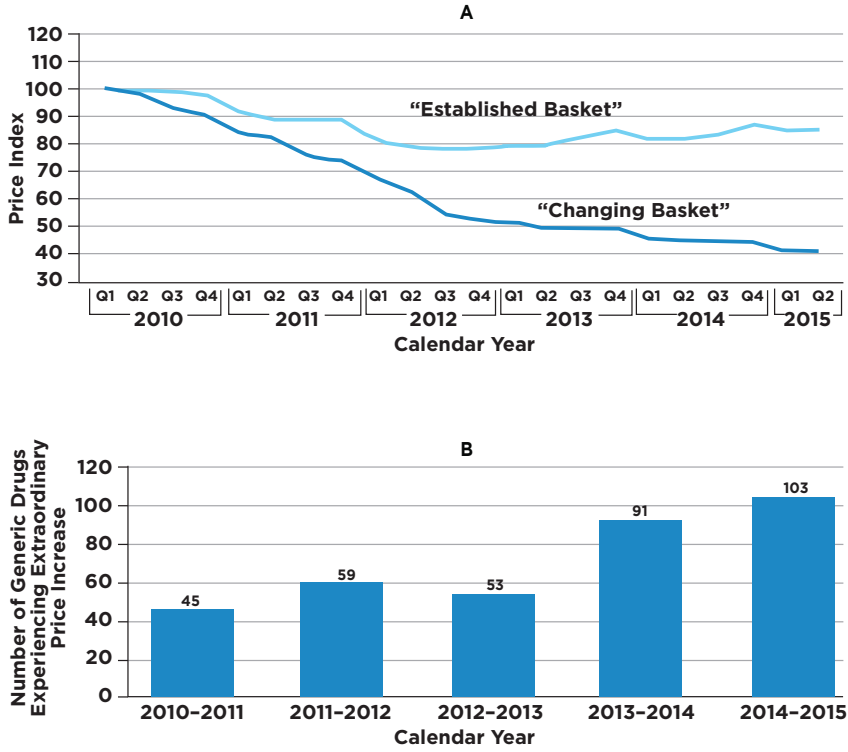

FIGURE 3-2 (A) Medicare Part D generic drug price trends for all generics and established generics (first quarter 2010 to second quarter 2015). The light blue line represents the composite trend of generic drugs ("established basket") present in the market throughout the analysis period, while the dark blue line represents those generics ("changing basket") that came into and exited during the period. (B) The number of established drugs under Medicare Part D that experienced an extraordinary price increase, first quarter 2010 to first quarter 2015.
NOTES: "For the changing basket of all generic drugs, the number of drugs included in each period varies from 1,733 to 2,124. For example, the period going from the first quarter of 2010 to the second quarter of 2010 has 1,733 drugs. A total of 2,378 unique drugs were included across our study period. To be considered an established drug, a drug had to be in the Medicare Part D claims data for each quarter from the first quarter of 2009 through the second quarter of 2015 and meet certain other data reliability standards. A total of 1,441 drugs met these criteria. Due to data availability at the time we conducted our study, the second quarter of our 2015 Medicare Part D claims data is limited to data from April and May" (GAO, 2016b, p. 11).
SOURCE: GAO, 2016b, Figures 2 and 3.

by 2020 from using biosimilars range from €11.8 billion to €33.4 billion (Haustein et al., 2012).

In the United States, however, biosimilars have not yet become a major part of the drug market. There are currently only five approved biosimilars in the United States, although there are more than 60 currently under development. The first biosimilar was approved by the FDA in 2015, a version of the leukocyte growth factor filgrastim (Neupogen); this was followed by three more approvals in 2016 and one thus far in 2017. In 2009 the Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated licensure pathway (351(k)) for products that are shown to be biosimilar to, or interchangeable with, a previously approved reference product.

The Congressional Budget Office (CBO) estimated that the BPCIA would result in a total cost reduction of $25 billion from 2009 to 2018. Savings to the U.S. government were projected to be $5.9 billion (CBO, 2008). An analysis by the RAND Corporation estimated that the use of biosimilar products across all therapeutic classes would result in savings between 2014 and 2024 of from $13 billion to $66 billion, depending on the amount of competition, with a best estimate of $44.2 billion (Mulcahy et al., 2014b). Among the deterrents to those wishing to bring biosimilars to market are uncertainty regarding regulatory requirements and also uncertainty about patent procedures (Hakim and Ross, 2017; Wong et al., 2017).

PRICE REGULATION

The patent law and health insurance systems in the United States are in concept similar to those in other developed countries. The United States, however, differs from most other nations with respect to the ability of the government to limit the prices of prescription drugs charged by manufacturers. While most other developed nations have governmental mechanisms for negotiating or controlling prescription drug prices, either directly or de facto (WHO, 2015), there is no nationwide regulation of drug pricing in the United States.

Table 3-1 summarizes the relevant pricing mechanisms used in five other developed nations with economies and legal structures similar to those in the United States. The tools employed in these countries include evaluating drugs using cost-effectiveness criteria and other related methods, imposing pricing limits or negotiations, and using formularies (including lists of "essential drugs," as are discussed in Box 3-2).

TABLE 3-1
Approaches to Drug Pricing in Other Countries

	Australia	Canada		Germany	India	United Kingdom
National Organization	Pharmaceutical Benefits Advisory Committee	Patented Medicine Prices Review Board	Canadian Agency for Drugs and Technologies in Health	Federal Joint Committee or the Institute for Quality and Efficiency in Health Care	National Pharmaceutical Pricing Authority	National Institute for Health and Clinical Excellence
Applicability	Public payers	All payers	Public payers except in Quebec (non-cancer drugs)	All insurers	All payers	National Health Service
Review Criteria	Comparative effectiveness, safety, and cost-effectiveness; projected usage and overall costs to the health care system	Therapeutic innovation; comparative pricing with respect to France, Germany, Italy, Sweden, the United Kingdom, and the United States	Comparative effectiveness, safety, and cost-effectiveness; patient experiences	Comparative benefit	National List of Essential Medicines prepared on the basis of efficacy, safety, cost-effectiveness, and common diseases	Clinical effectiveness and cost-effectiveness
Decision	Coverage (yes, no, limited)	Price reductions or rebates	Coverage	Price setting after first year on the market	Formulary inclusion or exclusion	Coverage
Binding	Yes	Yes	No	Yes	Yes	Yes

SOURCE: Adapted and expanded from Kesselheim et al., 2016.

BOX 3-2 Essential Medicines

According to the World Health Organization (WHO), essential medicines are "those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness" (WHO, 2017a). Lists of essential medicines have been developed to assist WHO member states in selecting and procuring medicines and in ensuring quality and reasonable cost (Laing et al., 2003). Since its development in 1977, the WHO list has been revised biennially to reflect new therapeutics, based on various factors including the need for the medicines, safety, efficacy, and comparative cost-effectiveness. The essential medicines on the list are divided into "core" and "complementary" categories. The core list contains safe, efficacious, and cost-effective medicines for priority conditions. The complementary list has essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, medical care, or specialist training is needed.

More than 100 countries have adopted the concept of an essential medicines list as a tool for developing a national formulary, but the lists put together by the individual countries generally differ from the centralized list produced by the WHO. Each country's list guides its drug reimbursement and insurance benefit design strategies. In many countries the implementation of an essential drug list is affected by such factors as pricing policy, the availability of essential drugs, reimbursement policies, government initiatives, patent and licensing, and the health care infrastructure (QuintilesIMS, 2015b). In the United States, the Patient Protection and Affordable Care Act requires that certain categories of drugs at the recommendation of the U.S. Preventive Services Task Force be included in a "preventive drugs list" that are to be made available to patients with little or no cost sharing (USPSTF, 2014). However, a complete list of essential medicines would include many drugs involved in treatment and cure of diseases and not just prevention.

Supporters of essential medicines lists argue that they help establish standards, common aims, and a baseline for health care delivery. Critics argue that centralized lists limit health care delivery, constrain professional autonomy, interfere with pharmaceutical markets, and reduce health benefits for patients (Reidenberg and Walley, 2004).

Australia

The Pharmaceutical Benefits Scheme (PBS) was established as part of the Australian government's broader National Medicines Policy in order to guarantee public access to (subsidized) essential medicine (PBS, 2017a). The PBS provides a list of drugs approved for coverage. To have a drug listed, its manufacturer must file an application with the Pharmaceutical Benefits Advisory Committee (PBAC), an independent body appointed by the Australian government that decides which medicines are approved and which are not (PBS, 2017b). Only those drugs on the PBS list are subsi-

dized by the Australian government. The PBAC regularly updates the list to include prescribing restrictions, maximum quantities, and price. When deciding whether to list a medicine on the PBS, the PBAC assesses the national disease burden, the medicine's clinical effectiveness, its safety, and cost-effectiveness compared with alternative treatments. Australia uses reference pricing[3] for generics and for groups of drugs with similar health and safety that can be used interchangeably. The maximum reimbursement for a medicine in a therapeutic group is based on the level of the lowest price in the approved group, and patients pay any difference between the price of the drug purchased and the reference price (Paris and Belloni, 2014).

Canada

The prices of medicines in Canada are determined by a combination of federal regulations and provincial negotiations. The price of every patented drug sold in Canada, both prescription and non-prescription, is regulated federally through the Patented Medicine Prices Review Board (PMPRB, 2017a).[4] The PMPRB performs an initial review of a new drug's price to determine if it is comparable to other products already sold in Canada. If the drug is comparable to an existing product, the price is not allowed to be greater than that of the existing drug. However, if it is not comparable, the price is allowed to be set at a point not greater than the median price in seven other industrialized countries: France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States. Further increases in drug prices are limited to the growth in the consumer price index (PMPRB, 2017b).

Germany

In Germany, the Act for Restructuring the Pharmaceutical Market in Statutory Health Insurance (AMNOG) established a mandatory benefit assessment of prescription drugs distributed in that country. The subsequent price negotiation process for new medicines is required to be completed within 1 year of product launch (Ruof et al., 2014). Under AMNOG, pharmaceutical companies can independently set the initial list price when they bring a new drug to market; however, they must submit a cost–benefit dossier in order for the drug to be fully reimbursed by all German insur-

[3] Reference pricing involves judging the therapeutic effectiveness of drugs within a disease group and reimbursing based on the least expensive option offering comparable effectiveness.

[4] The Canadian Agency for Drugs and Technologies in Health, in comparison, is responsible for making recommendations to inform coverage decisions of public drug schemes managed at the federal or the provincial level—except for Québec.

ance plans for the first 12 months. During that period, the Federal Joint Committee—the highest nongovernmental decision-making body of clinicians, hospitals, and health insurance funds in Germany—commissions a clinical comparative effectiveness review by the Institute for Quality and Efficiency in Health Care, a nongovernmental research body. Within 6 months of a drug's introduction into the market, the Federal Joint Committee, after receiving the results of the review from the Institute for Quality and Efficiency in Health Care, will determine the new drug's added benefits, if any, over existing drugs or treatments. The review criteria include benefits and risks for specific patient subpopulations. Each drug is given a final rating between 1 and 6, where 1 denotes "extensive benefit" and 6 means "less benefit" than an existing drug. A drug can receive different rankings for different patient subpopulations. Based on these ratings, the company then enters negotiations with the National Association of Statutory Health Insurance Funds to set the reimbursement price. One year after market launch, this reimbursement price replaces the initial list price of the drug.

Drug companies in Germany can choose to sell their products at higher prices; however, patients who want a newer, lower-ranked drug must pay the difference between the market price and the government's set reference price. Importantly, if a drug company charges an excessive rate for a lower-ranked drug in the first year of availability, the excess revenues must be returned to payers. A drug company can opt for a drug to not be assessed, in which case the drug's price is set through the German reference pricing system. Under the reference pricing system, the price is based on that of other drugs in the same therapeutic class, including lower-priced generic alternatives. Germany conducts more rigorous appraisals of new drugs than most other countries (Fischer et al., 2016) and has achieved significant savings in new drug spending. In 2015 Germany reported a savings of about $1 billion on new drug spending (Lauterbach et al., 2016).

India

In India, a major transition economy, the National Pharmaceutical Pricing Authority has the task of monitoring drug prices (India Department of Pharmaceuticals, 2017). By law, the authority fixes the maximum prices of items included in India's National List of Essential Medicines. Under current regulation, manufacturers are allowed to increase prices up to 10 percent annually for medicines that are not included in the national formulary. The pricing authority also recovers overcharge amounts from manufacturers of controlled drugs; monitors drug shortages and the prices of decontrolled drugs in order to keep them at reasonable levels; and collects data on individual companies' exports and imports, production, profitability, and market share of bulk drugs and formulations. India's National

List of Essential Medicines is based on efficacy, safety, cost-effectiveness, and common diseases of public concern in India (WHO, 2017b).

United Kingdom

The Pharmaceutical Price Regulation Scheme, which governs drug pricing in the United Kingdom, is a voluntary arrangement between the governments of the United Kingdom and Northern Ireland and the branded pharmaceutical industry, as represented by the Association of the British Pharmaceutical Industry (Association of the British Pharmaceutical Industry, 2017). Under this regulatory scheme, which has existed in various forms since 1957, pharmaceutical prices are not directly regulated; however, if a company exceeds the profit threshold set by the government, it is given an opportunity to justify its profits and adjust the thresholds.

If the National Institute for Health and Clinical Excellence (established in 1999 to provide guidance on the clinical effectiveness and cost-effectiveness of interventions and pharmaceuticals compared with current standard practice) does not consider a new medicine to be cost-effective, it does not recommend it for use by the National Health Service (Trowman et al., 2011).

RESEARCH AND DEVELOPMENT COSTS

Estimates of the research and development costs of a new drug vary widely (Morgan et al., 2011). Decisions regarding investments in biopharmaceutical research and development depend largely on drug manufacturers' assessment of future revenues. The greater the expected revenue from a prospective new drug, the more a drug maker will be inclined to develop it (GAO, 2009).

Spending on biopharmaceutical research and development has increased steadily over time (as addressed in the next section of this report). Revenues from the sales of prescription drugs must eventually pay for most of the costs of research and development, among other expenses, and a rise in research and development expenses will generally contribute to rising drug prices. The increase in research and development costs over time is attributable to several factors, particularly the extensiveness and cost of clinical trials, although it has been noted that the future may bring some opportunities for reducing such costs (Laurer et al., 2013).

A 2011 systematic analysis found that estimates of the cost of developing a single drug ranged from $161 million to $1.8 billion (Morgan et al., 2011). A 2016 analysis reported that the estimated cost to bring a new drug successfully to market is around $2.6 billion, with post-approval costs increasing the total to approximately $2.87 billion (DiMasi et al.,

2016). These figures are frequently cited by drug manufacturers in public and in policy discussions. A more recent analysis that considered 10 cancer drugs produced by 10 companies reported that the cost of developing a cancer drug was in the range of $157 million to $1.95 billion, with the median costs substantially lower—around $648 million, with the inclusion of opportunity costs bringing the total to $757 million (Prasad and Mailankody, 2017).

However, questions abound regarding the reliability of these studies and their estimates (Avorn, 2015; Goozner, 2017; KEI, 2014; Pitts, 2017; Wells, 2017). The basis of much of the information considered in the analyses of DiMasi and colleagues is undisclosed, and most studies have not been replicated, which raises concerns about the meaningfulness and validity of the estimates. The analysis supporting the more recent estimate from Prasad and Mailankody has been criticized for poor selection criteria. For example, critics note that their study underestimates the degree of failure in drug development by excluding larger biopharmaceutical companies that had a high percentage of cancer drug failures.

On occasion the total cost of drug development has been estimated using aggregate data on annual research and development costs reported by biopharmaceutical companies compared with the annual number of drugs approved by the FDA. Several challenges arise when using these highly aggregated data. For example, companies may conduct research and development that is not specifically related to developing novel drugs. Companies may also invest in product improvements, including the reformulation of existing drugs, as well as in analyses of the side effects of drugs already on the market. One advantage of such calculations is that they will generally take into account the large sums of money that drug companies invest in research and development on products that never reach the market. These are real costs that must be taken into account when calculating the costs of developing those products that are successful, and, indeed, publicly traded firms themselves must recognize these costs in portraying their overall financial status and also in pricing their products.

The research and development costs related to new molecular entities need to be separated from those devoted to products licensed from other firms. In the latter instance, the relevant research and development costs are reflected on the books of the licensor. Furthermore, estimates of the cost of capital that are reported in aggregated data generally do not account for the tax advantages of research and development expenditures (Riggs, 2004). In 1993, the Congressional Office of Technology Assessment estimated that the cost of research on a single drug through new drug approval was about $194 million in 1990 dollars ($363 million in 2017 dollars). The study used a marginal corporate tax rate of 34 percent, which reduced the actual cost of qualifying research and development (OTA, 1993).

The costs of abbreviated new drug applications (ANDAs) for generics have also been estimated. For oral tablets and capsules, the direct costs of ANDA applications are modest ($1 million to $5 million) compared with potential profitability (Berndt and Newhouse, 2012). Not much is known about the direct costs of obtaining ANDA approvals for infused or injected drugs.

In summary, the costs of research and development for biopharmaceutical development appear to have steadily increased in real terms over time, although it is difficult to know by exactly how much because estimates vary widely according to the analytical approach and the data sources used in making them. In a market-oriented economy, these increases in research and development costs would, over time, be expected to contribute to rising prescription drug prices.

PRODUCT PROMOTION AND DISTRIBUTION

Drug manufacturers have a direct interest in the choices made by patients and clinicians, and they have various ways to influence these choices. These include

1. *Discounts to PBMs and wholesalers*: Manufacturers commonly sell their products at discounted prices, most importantly through the system of PBMs that is now firmly established as part of the U.S. biopharmaceutical supply chain. In concept these discounts are passed through (at least in part) from the PBMs to the consumer via the consumer's prescription drug insurance plans—primarily through the choices of prescription drug tier and the differing copayments often associated with each drug. Greater discounts would generally be expected to lead to lower consumer copayments at the end of the supply chain. However, it is not clear that this occurs in practice.
2. *Marketing of products*: Marketing by biopharmaceutical companies contributes to higher prescription drug expenditures through two avenues. First, studies indicate that marketing increases prescription drug use (Alpert et al., 2015; Donohue et al., 2007). Second, the costs of marketing are part of the overall cost structure of drug manufacturers and thereby place upward pressure on prices.

The exact amount that the biopharmaceutical industry spends on product promotion remains undisclosed and thus must be inferred, to the extent possible, through secondary sources of information. A recent analysis of annual financial reports and Securities and Exchange

Commission (SEC) filings of 12 large pharmaceutical companies found that between 2003 and 2015 expenditures on marketing and administration[5] (a figure that includes executive pay) increased noticeably and exceeded research and development investments by up to 80 percent. Figure 3-3 displays one estimate of marketing expenditures and research and development expenditures over time.

3. *Direct-to-consumer advertising of pharmaceutical products*: A more recent practice by pharmaceutical companies, direct-to-consumer advertising, has attracted considerable attention among those concerned with the objectivity of the process of prescribing drugs. It is noteworthy that among developed nations, the marketing of prescription drugs through direct-to-consumer advertising is legal only in the United States and New Zealand (Mackey and Liang, 2013). In recent years, direct-to-consumer advertising in the United States has grown rapidly (Wilkes et al., 2000). The Internal Revenue Code makes direct-to-consumer advertising tax deductible as a business expense, as is the case for most advertising in other industries. Recent estimates indicate that in 2016, spending on direct-to-consumer advertising was about $5.2 billion, the bulk of which was used for television promotions (Robins, 2016) (see Figure 3-4). These estimates, as compiled by Nielsen, exclude spending on Facebook, Twitter, and other digital media.

The steady growth in such advertising places increasing demands on clinicians to accommodate patient requests for advertised products that may be more costly than other treatment options (or, alternatively, to expend time explaining why an advertised medication might not be the best option for the patient). This in turn adds to the ultimate cost of drug treatment. A recent analysis of direct-to-consumer advertising concluded that these marketing efforts increased drug take-up and use—with 70 percent of the increased use arising from new patients—but also increased adherence to prescription plans (Alpert et al., 2015).

Some studies have found that direct-to-consumer advertising can increase patients' knowledge about treatment options and may enhance the clinician–patient relationship, while others have identified effects that tend to offset these potential benefits (Lexchin, 2017; Mailankody and Prasad, 2017; Wilkes et al., 2000). In short, direct-to-consumer advertising has the potential to educate patients about conditions and their potential treatments; however, the practice may also result in unjustified demands

[5] SEC filings (10-K forms) show only a blend of marketing and administration costs, thus making it difficult to isolate marketing costs as a separate item.

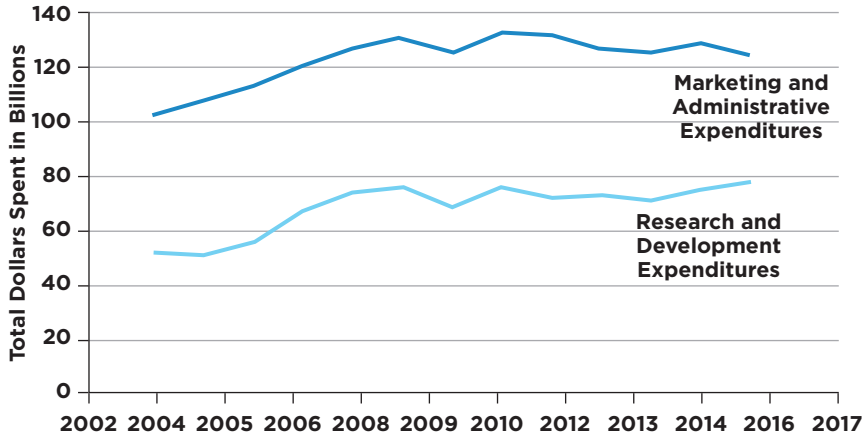

FIGURE 3-3 Comparison of total aggregate research and development and marketing-plus-administrative (including executive compensation) expenditures by 12 large pharmaceutical companies from 2003 to 2015.
SOURCE: Data retrieved from Belk, 2017. See http://truecostofhealthcare.org/pharmaceutical_financial_index (accessed November 15, 2017).

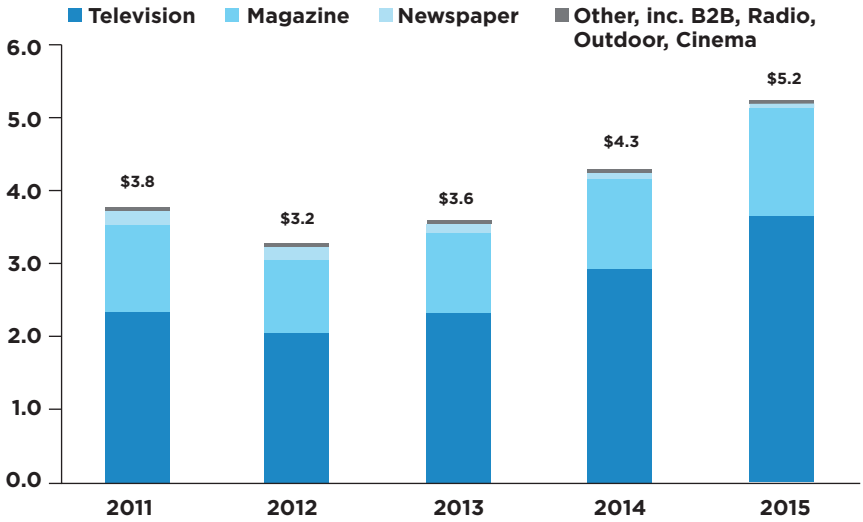

FIGURE 3-4 Spending on direct-to-consumer advertising of prescription drugs, in billions of dollars, by source.
NOTE: Digital outlets not included.
SOURCES: Natalia Broshtein/STAT, from Robbins, 2016; data from Nielsen.

for expensive branded medications. The conversations triggered by this advertising may increase the pressure of clinician–patient conversations, which are already affected by short visit times, and one result may be overprescribing.

Studies of the effect of advertising on prescribing practices have shown that such advertising increases sales, reduces the underuse of some medicines needed to treat chronic conditions, and leads to some overuse of prescription drugs (Donohue et al., 2007). A randomized controlled trial to study the influence of patients' requests for direct-to-consumer advertised antidepressants found that patients' requests had a material effect on clinician prescribing practices for major depression and adjustment disorder (Kravitz et al., 2005). A Canadian report showed that in recent years a significant amount of money has gone toward drugs that offered "little to no therapeutic gain. This result calls into question whether doctors read journal advertisements or see sales representatives to acquire information about important medical therapies" (Lexchin, 2017, p. E724).

For more than a century there have been efforts in the United States—including legislation, regulations, and advocacy—to control the marketing and advertising of pharmaceuticals directly to consumers (Mogull, 2008). Recently, the American Medical Association called for a complete ban on direct-to-consumer advertising, arguing that the "growing proliferation of ads is driving demand for expensive treatments despite the clinical effectiveness of less costly alternatives" (AMA, 2015). The Congressional Budget Office (2011) examined the potential effects of a moratorium on direct-to-consumer advertising of new prescription drugs and concluded that:

- Drug manufacturers would probably expand their marketing to clinicians to substitute for at least some of the banned advertising to consumers.
- The number of prescriptions filled would probably decrease for some drugs, but for other drugs the number of prescriptions might be little changed, owing both to the likely substitution of other types of promotions and to other factors that influence a drug's reach in the prescription drug market.
- Any change in prescription drug prices would depend on changes in demand; however, prices for new brand drugs that normally would be part of a direct-to-consumer advertising campaign could increase, since sales would be reduced.
- A moratorium could affect public health. The exact result would depend on whether the benefits of fewer unexpected adverse health events were greater than the health costs of possibly reduced use of new and effective drugs.

While the results of studies of the effects of direct-to-consumer advertising are somewhat inconclusive or at least mixed, drug advertisements remain pervasive and influence the manner in which clinicians prescribe. Because advertising is demonstrably effective in stimulating consumer demand for branded drugs and adds to the cost of doing business, such direct-to-consumer advertising likely contributes to the nation's high prescription drug costs.

The FDA regulates the content of this advertising, seeking to ensure a fair balance in describing benefits and risks and making certain that the risks are included in a prominent statement (Ventola, 2011). Although proposals exist to ban direct-to-consumer advertising of drugs, the constitutional protection of free speech in the United States may constrain such efforts.[6] The U.S. Supreme Court has regularly ruled that commercial speech is protected by the First Amendment.

Marketing practices such as direct-to-consumer advertising aside, there are several other ways that manufacturers influence the debates and discussions in the biopharmaceutical sector, some of which are described in Box 3-3.

4. *Direct rebates to consumers*: Another mechanism used by pharmaceutical manufacturers to affect the choices of patients and prescribers is the provision of direct payments to patients upon proof that they are actually using the specific drug. These payments have two key features. First, they almost universally are

[6] An often compared scenario is the federal legislation that banned advertising of tobacco on television and radio beginning in 1971. In 1967, the Federal Communications Commission ruled that the "fairness doctrine" be applied to cigarette advertising, which meant that television stations that broadcasted tobacco advertisements were required to give equal time to showing anti-smoking messages, during prime time as well as during children's programs, leading up to the Public Health Cigarette Smoking Act of 1969, which banned cigarette advertisements on American radio and television.

After the ban, the tobacco industry increased advertising in other media, but the total volume of advertising by the industry decreased. In parallel, broadcast media no longer were compelled to run anti-smoking messages, and their removal may have contributed at least briefly to increase smoking rates. The anti-smoking advertisements were mandated by the Federal Communications Commission in response to the strong evidence of harm caused by tobacco, a unique situation.

The ban also appears to have reduced competition in the industry, allowing the firms selling cigarettes prior to the ban (the incumbent firms) to maintain higher prices than they would have if they had been challenged by market entrants. Without the ban, market entrants might have attracted consumers away from the incumbent firms using television and radio advertising. The financial advantage to incumbent firms may explain why the tobacco industry did not challenge the advertising bans (Eckard, 1991). The reduced cost of advertising may also have increased tobacco industry profits, a situation that might be repeated in the biopharmaceutical sector.

employed by makers of on-patent drugs—often in situations where competition exists from either generic or other branded drugs. Second, they are generally directed at patients with prescription drug insurance plans, using such language as "if you need help with your copayments." Such rebates have the effect of counteracting higher-tier (larger) copayments set by PBMs and health insurance plans, thereby increasing annual insurance premiums for all enrollees in prescription drug plans but reducing the drug cost to the individuals receiving the rebate. A comparison of Figures 2-5

BOX 3-3 Other Forms of Financial Influence in the Biopharmaceutical Sector

Patient advocacy organizations have longed played an influential role in shaping health policy in the United States (Rothman et al., 2011). A recent study, however, has shown that 8 out of 10 patient advocacy organizations receive substantial philanthropic support or other forms of financial support from biopharmaceutical and medical device companies (McCoy et al., 2017). This study also found that a majority of patient advocacy organizations did not disclose the sources of their financial support and that only a few of the organizations even had any institutional conflict-of-interest policies.

The limited disclosure practices of the patient advocacy organizations make it difficult for members of the public to know how significant the funding is that these organizations receive from the biopharmaceutical industry (McCoy et al., 2017).[a] While many have argued that accepting money from the pharmaceutical industry does not diminish the effectiveness of the advocacy groups (Kent, 2007), others firmly believe that the receiving money from the companies undermines the independence of the organizations meant to serve the interests of the patients they represent (Mintzes, 2007).

Moreover, despite the growing outrage over price spikes in an already complex and opaque drug pricing system, a recent investigative report found that drug manufacturers fund or recruit academic economists and health care experts as spokespersons to help justify high drug prices to the general public and to policy makers (Waldman, 2017).

These two examples should not be interpreted as examples of direct contributors to increasing drug prices. Their purpose is merely to indicate that the major financial influence of the biopharmaceutical enterprises spreads far beyond the direct supply chain (not to mention the significant contributions made by companies to the political campaigns in the United States and how aggressively firms invest in lobbying efforts). This situation further complicates the drug pricing and affordability debate.

and 2-6 illustrates these mechanisms. One recent analysis estimated that copay coupons increase branded drug sales by 60 percent or more, almost entirely by reducing the sales of generic competitors, and that branded drug manufacturers receive a return of between four-to-one and six-to-one on every dollar spent on copay coupons (Dafny et al., 2016a). Analyses have also concluded that copay coupons increase costs for all enrollees in prescription drug insurance plans (Dafny et al., 2016a; Ross and Kesselheim, 2013).

[a] Consider, merely as an illustration of this challenge, a recent article that was originally published in *STAT News* (September 1, 2017) titled "How Pharma Sales Reps Help Me Become a Better Doctor." The author of this piece noted that "I continue to find visits from pharmaceutical representatives to be beneficial to myself and to my patients. Yet, I worry that lawmakers could eventually implement further restrictions on these interactions that could *de facto* ban communications between pharmaceutical companies and doctors."

The article described the author as a member of a patient access alliance, a membership organization describing itself as "comprised of policy-minded physicians who advocate for patient access to approved therapies and appropriate clinical care" and "non-physicians, including corporations and associations." The *STAT News* article further noted that "The alliance supports regulations that expand manufacturers' ability to discuss off-label uses, particularly those that are accepted in compendia and practice guidelines or reimbursed by the government and insurers."

In other words, it is an organization dedicated to advocacy for the expanded marketing of "off-label" uses of drugs—that is, for indications that have not been approved by the FDA. (FDA approval is essentially a license to market a drug for the approved indication, which is defined in the drug label. Health care professionals can prescribe a drug for other indications "off-label," but manufacturers are prohibited from marketing drugs for any purpose other than those stated in the FDA-approved drug label.)

The alliance is heavily financed by its "associate members," a majority of which are large publicly traded pharmaceutical corporations or the trade organization representing them. None of the alliance's posted annual reports contain any financial information about its dependence on pharmaceutical manufacturers for support. Indeed, these annual reports are devoid of any financial reporting at all.

Shortly after the publication of this article, *STAT News* retracted the piece, citing, among other reasons, that the author "received more than $300,000 in recent years from pharmaceutical companies, including one he mentioned in the article." Moreover, the retraction notice also added that the article's central "anecdote was inaccurate."

IMPORTATION OF MEDICINES

One strategy that has long been advocated as a way of reducing prescription drug prices and countering drug shortages (see the section on drug shortages) in the United States is to import prescription drugs—especially generics and biosimilars—from other countries. The rationale is that importing lower-cost drugs from other countries with high-quality production systems (and, potentially, government limits on price increases) would cause U.S. manufacturers to be faced with greater competition and encourage them to reduce prices.

A related strategy is "reimportation," or having U.S. wholesalers and pharmacies import and sell branded drugs that were produced in the United States but sold in other countries where prices are lower, as long as the FDA has approved a version of the same drug for domestic use.[7] Essentially, the goal of reimportation is to negate drug manufacturers' differential pricing across countries—and, in particular, the pattern of charging more in the United States than in other countries for the same drug (Outterson 2005). Such programs could in principle also be established by state or local governments.

The importing and the reimporting of prescription drugs have been perennial proposals in the U.S. Congress over the past two decades. A number of states and localities have experimented with pilot programs, which have generally encountered legal challenges. Despite the longstanding interest, efforts to legalize the practice have not been successful.

The Food, Drug, and Cosmetics Act (FDCA) prohibits the importation of prescription drugs made in the United States by anyone other than the manufacturer—with the exception of drugs approved by the secretary of the U.S. Department of Health and Human Services (HHS) for emergency care. Another legal obstacle is that it is nearly impossible for drugs made for non-U.S. markets to satisfy the FDCA's requirements relating to drug approval and labeling (CRS, 2008; Terry, 2004).

Importation and reimportation run the risk of enforcement actions for introducing "misbranded" drugs into U.S. markets. The federal Controlled Substances Act also bears on reimportation in that it prohibits the unlawful distribution of prescription drugs, such as narcotics and opioids, that meet the statutory criteria for controlled substances (CRS, 2008).

In 2000, Congress passed the Medicine Equity and Drug Safety Act

[7] "Personal reimportation" proposals focus on making it easier for individual U.S. consumers to buy and import drugs from other countries. Personal reimportation is not permitted by law, but the U.S. Department of Health and Human Services has historically exercised its discretion not to enforce this prohibition against individuals bringing medications into the United States for personal use (Reichertz and Friend, 2000). This report's focus is on broader-scale reimportation proposals, which have greater potential for population-level impact.

that authorized the FDA to allow the reimportation of prescription drugs from a specified group of countries. The U.S. Congress again authorized reimportation in the Medicare Modernization Act, this time narrowing the list of acceptable countries to Canada. But neither act was implemented, due to opposition by the HHS secretary. Both statutes required the secretary to certify that reimported drugs would be safe and would significantly reduce costs. No secretary has yet been prepared to do so. Thus, importation and reimportation remain prohibited. Several subsequent legislative proposals have failed to clear these and other obstacles (Bluth, 2017).

Historically, the FDA has opposed reimportation out of concerns about its ability to ensure a safe drug supply (Bhosle and Balkrishnan, 2007; Terry, 2004). Although reimportation discussions often assume that the drugs would be imported from Canada, if a sufficient supply could not be obtained there it could become necessary to import from countries with a less robust record of preventing counterfeit, contaminated, expired, and mislabeled drugs from reaching the market. Moreover, drugs may be falsely labeled as originating in the United States or a Canadian pharmacy (Bhosle and Balkrishnan, 2007). FDA commissioners have consistently expressed skepticism about the agency's ability, with its current financial and technological resources, to ensure the safety and authenticity of a much larger volume of imported drugs (Bhosle and Balkrishnan, 2007). Others note, however, a lack of evidence that Canadian drugs are less safe or that concerns about adulteration and other problems are unique to imported drugs (Kamath and McKibbin, 2003; Outterson, 2005). The proponents of importation have argued for further pilot studies of controlled importation systems, noting that the reimportation ban values drug safety absolutely, at the expense of financial access, and arguing that safety concerns have been overstated.

Even if importation or reimportation, or both, were allowed, it is not clear how much they would reduce drug costs for U.S. consumers. The outcome would depend largely on (1) the countries from which drugs may be imported or reimported, and (2) the strategic responses of U.S. drug manufacturers. The CBO (2003) has estimated that allowing reimportation from 25 countries would save $40 billion over 10 years; however, other research has concluded that the savings would be considerably smaller, about $1.7 billion annually (Danzon et al., 2011).

A key question is how large a supply of drugs Canada and other approved countries would make available for export back to the United States (or, in the case of generics, allow them to be imported by the United States at lower prices). The CBO has concluded that the savings would not be substantial if reimportation were limited to Canada because drug companies probably would not increase their Canadian sales enough to allow a significant propor-

tion of American-made drugs to be reimported from Canada (Kaiser Health News, 2009).

It is also possible that manufacturers could penalize countries and firms that exported products back to the United States or that imported generics and biosimilars to the U.S. market. Firms could, for example, raise the prices of drugs sold in Canada, or penalize wholesalers that reimported drugs by raising the prices of the drugs they sell to those particular wholesalers in the United States. There is anecdotal evidence of penalizing behavior on the part of U.S. manufacturers: in 2004, GlaxoSmithKline and Pfizer announced that they would limit sales of their drugs to Canadian pharmacies that resold them to individual U.S. consumers (CRS, 2008). A larger question is whether importation and reimportation would spur manufacturers to reduce their investment in research and development.

DRUG SHORTAGES

In recent years there have been numerous high-profile reports of inadequate supplies of generic drugs that have served as the standard of care for some diseases. For example, shortages have been reported for two critical cancer drugs, Doxil and Methotrexate, a medication used as backbone therapy to treat pediatric cancer (Harris, 2012); various antibiotics, including doxycycline (Stone, 2015); and saline bags, which are used throughout inpatient and outpatient treatment (McGinley, 2017).

Although the number of new drug shortages has declined since 2011, prominent shortages exist among generic injectables and other drugs for cancer and cardiovascular conditions (ASHP, 2017a; GAO, 2014, 2016a), and drug shortages have been known to lead to adverse events and even increased patient morbidity and mortality (Duke et al., 2011; Gu et al., 2011; Kaakeh et al., 2011; Kaiser, 2011; McKenna, 2011). The more constrained supply of such drugs has also led to higher prices for these drugs (GAO, 2014; IOM, 2013).

Shortages, threatened and actual, often result from lapses in manufacturing quality (Fox et al., 2014; GAO, 2016a; Stomberg, 2016). For example, the immediate precipitating factors behind the shortages reported since 2009 (largely for infused and injectable drugs) include a lack of high-quality manufacturing processes and facilities and a lack of necessary compounds and raw materials (GAO, 2014; Pew, 2017; Stomberg, 2016; Woodcock and Wosinska, 2013). The lapses in manufacturing quality and the shortages in the of necessary or adequately manufactured raw materials that can lead to supply interruptions of certain drugs and other products regulated by the FDA are not new, but appear to be more frequently reported in recent years. For example, in 2008, the FDA reported that at least 81 deaths and 785 serious injuries were thought to be linked to a

raw heparin ingredient imported from China (FDA, 2012). This led to the withdrawal of the product from the U.S. market for a period of time and consequently there was an inadequate supply to meet American demand.

Yet, according to a recent report from the American Society of Health-System Pharmacists, the immediate causes for more than one-half of drug shortages reported in 2016 were unknown (ASHP, 2017b). In some circumstances, unexpected consumer demand or an outbreak of a rare illness can contribute to drug shortages (ASPE, 2011; Fox et al., 2009; GAO, 2014; IOM, 2013; Pew, 2017). In addition, a federal report noted that class-wide shortages in 2011 were likely due to a rapid and sizeable increase in the scope and volume of products produced without a corresponding increase in overall manufacturing capacity (ASPE, 2011). The constrained supply of these drugs and the high costs of entry for manufacturers willing and able to produce these molecules for sale in the U.S. market also contribute to threatened and actual drug shortages (ASPE, 2011; Berndt et al., 2017a,b; Fox et al., 2009; IOM, 2013). The FDA response to periodic drug shortages has largely been to either pull or push more manufacturers into supplying U.S. demand for these products.

The growing trend to outsource drug manufacturing and to source base ingredients from non-U.S.-based manufacturing facilities, along with the highly publicized incident of adulterated heparin manufactured in China that evaded inspection by a resource-constrained FDA (U.S. Congress, 2008), led to key aspects of the Generic Drug User Fee Amendment (GDUFA), first enacted in 2012 (Conti and Berndt, 2017a). Specifically, GDUFA funded the FDA's redesign of its inspection program and the associated user fee schedule to meet these new challenges.

More recently, under the Safety and Innovation Act of 2012, the FDA required drug manufacturers to provide early notification of any manufacturing interruptions or production changes that could lead to a supply disruption or the discontinuation of a product. Subsequently, the FDA improved its efforts to prevent shortages by expediting application reviews and inspections, exercising enforcement discretion in relevant cases, and helping manufacturers respond to quality control issues in drug manufacturing (Chen et al., 2016; GAO, 2016a).

WASTE AND COST DUE TO UNUSED DRUGS IN THE SUPPLY CHAIN

Every year drugs worth billions of dollars that have been purchased by health care organizations (e.g., retail pharmacies, hospitals, nursing homes) and patients are discarded. Some of this waste in the system could be eliminated by changing the way drugs are packaged and labeled. For example, vials of infused drugs are often available only in a single dose size that is

sufficient to treat a physically large patient. As a result, the remaining drug must be discarded when a smaller patient is treated. Because 18 of the top 20 infused cancer drugs are sold in just one or two vial sizes, 10 percent of the purchased drug amount is discarded on average (Bach et al., 2016). Manufacturers propose dose sizes for marketing, and the FDA only reviews the request for safety considerations (FDA, 2015). However, in Europe, where governments play a more active role than the United States does in drug pricing and distribution, many of these medicines are distributed in smaller vial sizes, reducing the potential for waste.

Many medicines are also discarded because of expiration dates (Allen, 2017). Since 1979 the FDA has required drug manufacturers to provide evidence of product stability, by subjecting drugs to various environmental variables such as temperature, humidity, and light, but there are no requirements for long-term testing. Pharmacies routinely discard stocked drugs when they reach their expiration date, but many drugs, if stored properly, are stable long beyond the expiration date on the label (Cantrell et al., 2012, 2017; Lyon et al., 2006). The strongest evidence comes from the FDA's Shelf Life Extension Program (SLEP) (FDA, 2017c), which is funded by the U.S. Department of Defense to support the maintenance of its stockpiled drugs, worth billions of dollars. In a study of 122 different medication products, nearly 90 percent met the requirements for an extension; the average additional extension length by SLEP was 5.5 years, and some lots were extended by more than 20 years (Lyon et al., 2006).

Extending shelf life could not only reduce waste in the system, but also address shortages. The FDA recently posted updated expiration dates for batches of several different injectable drugs to help address ongoing critical shortages of these drugs used in critical care (FDA, 2017d). The American Medical Association and other entities have called for routinely collecting more data on long-term stability and revising expiration dates as appropriate (Diven et al., 2015). An independent organization could conduct more testing similar to that done by the FDA extension program. Information from the extension program also could be applied to properly stored medications.

Drugs worth billions of dollars are discarded each year by nursing homes and other long-term care facilities when they are no longer needed by residents (Allen, 2017; Coggins, 2016). A few states and nonprofit organizations have set up programs to collect, sort, and redistribute these unused drugs to reduce waste and costs to patients. However, in many areas no such programs exist (and in some cases are even illegal), so valuable drugs are simply discarded.

INSURANCE DESIGN

A key factor affecting the affordability of health care for individuals and families is whether a patient has health insurance. After the implementation of the ACA, the number of people with health insurance increased substantially, but approximately 10 percent of the population under age 65 has no health insurance—and hence no coverage for prescription drugs. Furthermore, not all of those with health insurance have insurance coverage for prescription drugs. This latter circumstance applies to both the under-65 population and those on Medicare. Fee-for-service Medicare helps cover the cost of prescription drugs for people who enroll in a Part D drug plan (see Figure 3-5), but enrollment is voluntary and only 42 million of the 57 million Medicare beneficiaries have Part D coverage (KFF, 2017b). However, of the remainder, some have drug coverage through employers, the U.S. Department of Veterans Affairs, and other "creditable" sources (those that offer coverage as good as is provided by Part D), but a small share (about 12 percent) of Medicare beneficiaries lack a creditable source of drug coverage (MedPAC, 2017a). As of 2017, 99 percent of covered

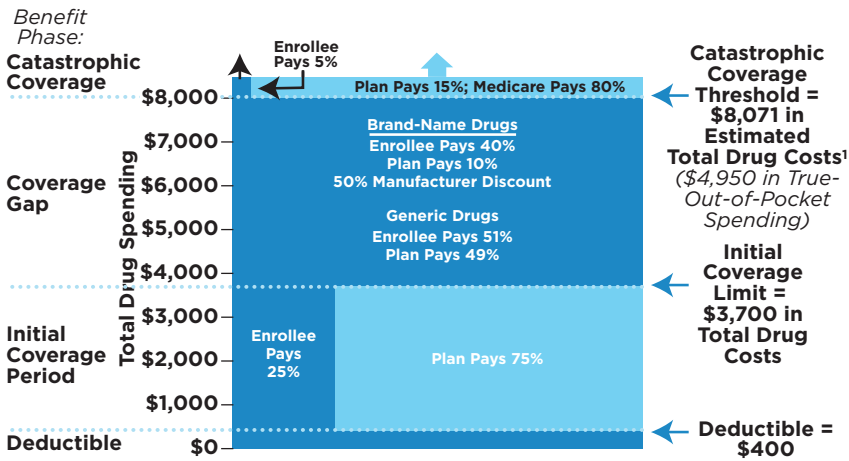

FIGURE 3-5 Standard Medicare prescription drug benefit, 2017.
NOTES: Some amounts rounded to nearest dollar. [1]Amount corresponds to the estimated catastrophic coverage limit for non-low-income subsidy (LIS) enrollees ($7,425 for LIS enrollees), which corresponds to a true out-of-pocket spending of $4,950, the amount used to determine when an enrollee reaches the catastrophic coverage threshold in 2017.
SOURCE: KFF, 2017.

employees worked for a firm whose largest health plan covered prescription drugs (KFF and Health Research & Educational Trust, 2017).

Recent changes in insurance design in the United States reflect the rising costs of not only drugs but all sectors of health care (*Consumer Reports*, 2016). As the costs of health care have risen, employers and insurers have modified benefit designs as a way to keep premiums as low as possible, with the goal of balancing cost and access. The escalating list prices of many branded drugs, especially specialty drugs and those that lack a competitor, have been a particular challenge in recent years.

As a result, even among those with insurance benefits, the out-of-pocket costs for premiums, deductibles, and copays can be substantial, and the design of the coverage and cost sharing can significantly affect the financial burden arising from prescription drug spending. Studies have found dramatic reductions in coverage generosity and shifts to percentage-based cost sharing for high-priced drugs over time (Doshi et al., 2016a; Dusetzina, 2016; Jung et al., 2016; Polinski et al., 2009; Yazdany et al., 2015), limiting options for patients to obtain plans that provide generous coverage for drugs. The specifics of pharmacy benefit design have the potential to be an important public health tool for improving patient treatment and adherence (Goldman et al., 2007) and can have a major effect on access to prescription medications (Delbanco et al., 2016).

The effects of high out-of-pocket spending can be significant for patients and their families. Increased cost sharing can reduce patient uptake and adherence to treatments, including specialty drugs (Alexander, 2003; Doshi et al., 2016a,b; Dusetzina et al., 2014; Fischer et al., 2011; KFF, 2015; Olszewski et al., 2017; RAND Health, 2006; Streeter et al., 2011; Winn et al., 2016). Nearly one-quarter of the Americans who participated in a 2015 survey reported that they had difficulty affording their prescription medicines. And nearly one-quarter reported that they or a family member had not filled a prescription that they had been provided, had skipped doses, or had reduced their dosage because of cost (KFF, 2015). One study of commercially insured adults with chronic myelogenous leukemia found that having higher out-of-pocket costs reduced patient adherence to therapy by 42 percent and increased the discontinuation of therapy by 70 percent (Dusetzina et al., 2013). A 2014 study on primary care found that approximately 31 percent of patients did not fill their prescriptions within the first 9 months after receiving them from a doctor. Additionally, the study found that patients with higher copayment fees, recent hospitalizations, severe comorbid conditions, or some combination of these three factors were less likely to fill their prescriptions (Tamblyn et al., 2014). Various studies confirm that poor adherence leads to negative clinical outcomes and increased health care costs (e.g., Roebuck et al., 2011).

Even for insured patients, the use of prescription drugs often entails a large out-of-pocket expense because of the high coinsurance rates that often apply to expensive drugs, particularly if the patients use specialty drugs or multiple high-cost brand-name drugs. For example, traditional Medicare currently places no upper limit on the total amount an individual may end up spending on cost sharing for Medicare-covered services. For services offered under Medicare Part B, including clinician-administered drugs, the beneficiaries (or their supplemental insurance plans) are responsible for 20 percent of the cost (MedPAC, 2016), and there are no catastrophic coverage limits. In 2014, virtually all Part D formularies required coinsurance of between 25 and 33 percent for cancer drugs, the maximum allowed by the Centers for Medicare & Medicaid Services (CMS) (Dusetzina and Keating, 2015). This can translate to hundreds or even thousands of dollars annually in out-of-pocket costs for higher-cost medications.

Individuals with employer-sponsored or other types of private health insurance also face challenges with prescription drug costs. As noted above, in response to increasing costs across all sectors of health care, insurance companies have raised deductibles, increased monthly premiums, imposed or increased copays and coinsurance, and transferred high-cost drugs to more expensive formulary tiers (Claxton et al., 2017; *Consumer Reports*, 2016). Among employer-sponsored plans, deductibles grew from 4 percent of cost-sharing payments in 2004 to 24 percent in 2014; coinsurance increased from 3 to 20 percent over that same period (Cox, 2016). A patient's costs often depend on the tiered structure by which many health plans organize the drugs that are covered by their formularies.

Private health insurance plans have been moving to three- or four-tier coinsurance or copayment structures that require a smaller degree of cost sharing for generics and a greater degree for higher-cost drugs especially when there are therapeutically equivalent options (KFF, 2014). Plan tiers often include preferred, non-preferred, and generic drugs, and each tier of drugs can represent a different level of cost sharing or class of drugs, such as specialty drugs (KFF and Health Research & Educational Trust, 2017). However, every plan, whether Part D or an employer-sponsored pharmacy benefit, has an exception process that permits coverage of a drug not on formulary or reduce out-of-pocket cost if a physician provides information about side effects the patient has experienced from a lower-tiered drug or offers another medical reason for switching.

As noted in Box 2-1, most large employers self-finance their health insurance contributions for their employees and hence have a direct and significant interest in controlling health care costs. As of 2017, 91 percent of employees covered by employer-sponsored insurance plans were in a plan with tiered cost sharing (KFF and Health Research & Educational Trust, 2017). The ubiquity of such plans can influence how much individuals cov-

ered by specific employer-sponsored plans pay due to the variation in cost sharing. The Kaiser/Health Research & Educational Trust 2017 Employer Health Benefits Survey of workers covered by employer-sponsored plans found that, among those in plans with at least three tiers of cost sharing, the average copayment per drug was $11 for the first tier and $110 for the fourth tier. The average coinsurance was 17 percent for first-tier drugs and 38 percent for third-tier drugs. Specialty drug tiers tend to drive up cost sharing even further, with an average copayment of $101 and an average coinsurance rate of 27 percent for drugs on a specialty tier. In addition to copayments and coinsurance, health plans can apply an additional deductible to drugs that is separate from the general annual deductible. In 2017, 15 percent of workers with prescription drug coverage had to meet a prescription drug–only deductible (KFF and Health Research & Educational Trust, 2017).

Health plan decisions regarding which drugs to include in their formularies—and in which tiers—also reflect the influence of PBMs, whose negotiations often occur with minimal transparency or data on rebate amounts, raising concerns about their impact on patients' out-of-pocket spending (*Health Affairs*, 2017b). However, Part D plans do enable consumers to determine and compare the out-of-pocket costs of a drug in the "preferred pharmacy network," "non-preferred networks," and mail-order services.

"High-deductible health plans" are also becoming more common in the U.S. insurance marketplace as health care costs rise (Claxton et al., 2016). These plans require a higher deductible than most health plans, in exchange for a lower monthly premium. High-deductible health plans require consumers to cover 100 percent of their health care costs up to a certain amount—the deductible—at which point their insurance coverage and other cost-sharing arrangements begin. In 2016, nearly 30 percent of individuals in employer-sponsored plans were enrolled in a high-deductible health plan (Claxton et al., 2016). Recent work has begun to explore the clinical and economic benefits of high-deductible plans in the long run (Fronstin et al., 2013).

Out-of-Pocket Spending and Specialty Drug Access

Many oral drugs used to treat complex conditions such as HIV, multiple sclerosis, rheumatoid arthritis, cancer, and hepatitis C are costly, and the increasing use of deductibles and coinsurance in the pharmacy benefit offered by insurance plans may lead to significant financial hardship for patients needing treatment. Medicare beneficiaries are exposed to high costs in two primary ways. First, enrollees who take drugs covered on a Part D plan's specialty tier face coinsurance rates of between 25 percent

and 33 percent of the drug's total price during the initial coverage phase. In 2017 the Part D standard benefit has a $400 deductible and 25 percent coinsurance up to an initial coverage limit of $3,700 in total drug costs, followed by a coverage gap (see Figure 3-5). During the gap, enrollees are responsible for a larger share of their total drug costs than in the initial coverage period, until their total out-of-pocket spending in 2017 reaches $4,950. After enrollees reach the catastrophic coverage threshold, Medicare pays for most (80 percent) of their drug costs, plans pay 15 percent, and enrollees pay 5 percent of total drug costs. Second, even patients who reach the catastrophic coverage threshold of Medicare Part D can be exposed to high costs because the threshold is not a hard cap on out-of-pocket costs. For medications costing tens of thousands of dollars or more per year, patients can spend more out of pocket during the catastrophic phase than in the other benefit phases combined (Hoadley, 2015). A recent analysis found that 3.6 million Medicare beneficiaries had total drug spending above the Part D catastrophic threshold in 2015, and of those, one million incurred out-of-pocket drug costs above the threshold (KFF, 2017a).

Two examples illustrate the extent to which Part D enrollees can be exposed to serious financial risk, despite the Part D benefit's catastrophic coverage, when the underlying price of the drug they take is very high. For Harvoni, a breakthrough treatment for hepatitis C, a patient enrolled in Part D in 2016 faced total out-of-pocket costs of $7,153 for a course of treatment, but 61 percent of this total was incurred in the catastrophic coverage phase. For Revlimid, a cancer drug, a patient enrolled in Part D in 2016 faced total annual out-of-pocket costs of $11,538 for this drug alone in 2016, 76 percent of which was in the catastrophic coverage phase of the benefit. (The price for Revlimid has since increased dramatically, to more than $18,000 per fill; thus, in the catastrophic phase under Part D, enrollees will pay more than $900 per month for this drug [Court, 2017].)

One way to strengthen financial protections for Medicare beneficiaries with very high drug costs would be to eliminate enrollees' cost sharing above the catastrophic coverage threshold, thereby making the current catastrophic coverage threshold an absolute limit on out-of-pocket spending under Part D. This proposal has been recommended by the Medicare Payment Advisory Commission (MedPAC, 2016). To mitigate the concern that pharmaceutical companies might respond by simply raising their list prices, one strategy might be to increase the share of total costs that Part D plan sponsors pay in the catastrophic coverage phase of the benefit (up from the current 15 percent), giving them a stronger financial incentive to negotiate larger rebates for higher-priced drugs and to take more steps to manage the use of these drugs by their enrollees, which could produce savings for enrollees, Medicare, and the plans themselves.

PATIENT ASSISTANCE PROGRAMS

Patient assistance programs supported by drug manufacturers serve to lower patients' out-of-pocket spending by covering the cost of all or part of their out-of-pocket expenses when they buy brand-name medications. This practice may bring the price that patients pay for branded medications closer to—and in some cases lower than—the price of generic alternatives, but it does not change the cost to the insurer. In fact, such practices serve to increase costs to insurers and therefore, the premiums charged by the insurer. These practices also lessen the insurer's ability to price discriminate (through the use of tiers in the formulary), as patients with access to these programs will often opt for branded products over generics and, more generally, choose drugs not "preferred" by the plan (Ubel and Bach, 2016).

The popularity of patient assistance programs among both patients and manufacturers has increased over time (Daubresse et al., 2017; Ross and Kesselheim, 2013). Assistance programs are delivered through a variety of mechanisms, including coupons, drug savings cards, manufacturer assistance programs (provided through the drug maker), access networks that create disease-specific funds, and disease-focused foundation programs. Payments are generally distributed via clinicians' offices or, increasingly, directly to the patient through the mail or online (Dafny et al., 2016b). Support can include providing medications or payments directly to individuals. Eligibility for support from these sources varies by insurance status and income. Some types of copayment assistance are not allowed, including the use of manufacturer coupons to pay for drugs obtained through Medicare Part D benefits.

While helpful in some ways, patient assistance programs encourage patients to use higher-cost branded products, since generic manufacturers do not typically offer assistance programs. Patients with very high deductibles or with high coinsurance requirements may find it difficult to pay the out-of-pocket costs to obtain high-priced drugs. In such cases, patients may need to access assistance programs in order to offset the out-of-pocket costs of starting and adhering to therapy, regardless of their insurance status. Each program is a unique, unregulated, private offering by a pharmaceutical company for an individual product. The application process can be onerous for patients and clinicians, with a high probability of rejection, commonly based on patient income level and insurance coverage. There is little information available to evaluate the impact of patient assistance programs so few studies have examined the proportion of patients served, the extent of aid provided, the criteria for qualifying for aid, and the estimated financial cost to society (Felder et al., 2011).

Drug manufacturers tend to use coupons to promote the use of branded expensive products when less expensive alternatives are available (Dafny

et al., 2016b; Ross and Kesselheim, 2013). One analysis estimated that copay coupons increased branded drug sales by 60 percent or more, almost entirely by reducing the sales of generic competitors, and that they had the potential to undermine the efforts of prescription drug insurance plans (Dafny et al., 2016a). Federal policies prohibit the use of manufacturer coupons in paying for medications paid for by Medicare Part D because it is considered a violation of anti-kickback statues and it raises costs to the government (OIG, 2014).

FEDERAL DISCOUNT PROGRAMS

Medicaid Drug Rebate Program

The U.S. Congress created the Medicaid Drug Rebate Program (MDRP), which went into effect in 1991, resulting from the Omnibus Budget Reconciliation Act of 1990 in an attempt to address the rising cost of prescription drugs in the Medicaid program. In the MDRP, the drug manufacturer enters into a rebate agreement with the HHS secretary in return for Medicaid coverage of all products made by this manufacturer, as well as payments for covered outpatient drugs provided through Medicare Part B. This has essentially created an open formulary in Medicaid. CMS reports that about 600 manufacturers have entered into such an agreement (CMS, 2017a).

Unlike most rebates for prescription drug spending, the rebates obtained through the MDRP are not negotiated, but are defined by statute. However, many components used to calculate the rebate are proprietary, and as a result, it is difficult to calculate exactly how much Medicaid spends on a particular drug. This contributes to the lack of transparency surrounding drug pricing. Statutory rebates are set by the U.S. Congress and enacted into law, and there have been changes over time. States are free to negotiate supplemental rebates on top of the statutory rebates.

The basic rebate calculation for single-source drugs and innovator multiple-source drugs[8] is set by statute and is set separately for non-innovator, multiple-source drugs. For single-source and innovator multiple-source drugs, the unit rebate amount is equal to the greater of either the product of Average Manufacturer Price (AMP) times 23.1 percent or the difference between AMP and the Best Price (defined as the lowest

[8] "Innovator drugs" include both single-source (typically a brand-name product that has no available generic versions) and multiple-source (typically a brand-name product that has available generic versions) products. "Non-innovators" are typically generic versions of multiple-source drugs (OIG, 2009). Statute sets different rebate percentages for certain types of single-source and innovator multiple-source drugs: clotting factors and drugs approved by the FDA exclusively for pediatric indications.

price the manufacturer charges any wholesaler, health maintenance organization, retailer, health care provider, government entity, or nonprofit organization in the United States during that rebate period). For non-innovator, multiple-source drugs, the unit rebate amount is equal to the product of AMP times 0.13. The rebate on innovator drugs includes an adjustment to account for price inflation; however, this adjustment is not included in the rebates for non-innovator drugs. There are some important exceptions to the "best price" provision, including prices charged in the 340B program to the U.S. Department of Veterans Affairs, the U.S. Department of Defense, Medicare Part D, and Indian Health Service. This seemingly minor part of the MDRP has a major implication: outside of these exceptions, manufacturers are very reluctant to provide rebates for single-source or innovator multiple-source drugs large enough to trigger the "best price" provision because it would create a lower price for the entire Medicaid program (*Health Affairs*, 2017a).

Rebates are paid by drug manufacturers on a quarterly basis to states and are shared between the states and the federal government. Prior to the ACA, rebates through the MDRP were only available for drugs provided in fee-for-service settings. Under the ACA, drugs provided in managed care settings are also eligible for rebates and as a result, states have increasingly been providing the Medicaid prescription drug benefit through managed care.

In large part due to the market entry of very expensive hepatitis C drugs, Medicaid expended $57 billion on prescription drugs in 2015, compared to $42 billion in the previous year (*Health Affairs*, 2017a). States have been left vulnerable to the high costs of branded drugs that have little competition (McConnell and Chernew, 2017). The National Association of Medicaid Directors has called for expanding the tools that states can use to design and manage Medicaid's optional prescription drug benefits, including providing states with the flexibility to exclude some FDA-approved drugs from coverage (NAMD, 2017). Recently, Massachusetts submitted an amendment to its 1115 demonstration waiver to CMS that would allow the state to have a closed formulary.[9] However, in response to this waiver request, some advocates have emphasized the importance of specifying exclusion criteria in order to ensure that patients with serious conditions on Medicaid are not denied needed effective treatments for their conditions.

The 340B Program

Prior to the implementation of the MDRP in 1991, manufacturers often provided discounts on their drugs to safety net providers. However,

[9] Commonwealth of Massachusetts, MassHealth Section 1115 Demonstration Amendment Request, September 8, 2017. The waiver request is pending as of November 2017.

after the establishment of the MDRP, there was concern that manufacturers would be less willing to provide additional discounts to providers serving largely uninsured or underinsured populations. The U.S. Congress addressed this potential unintended effect of the MDRP with the 340B program, a drug discount program named after the section[10] in the law that created it (*Health Affairs*, 2017a). The stated goal of the 340B program is to enable these providers "to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services" (HRSA, 2017).

Section 340B requires certain drug manufacturers to provide outpatient drugs to qualified medical care providers, called "covered entities," at prices not higher than Medicaid is able to obtain, net of rebates (GAO, 2011; *Health Affairs*, 2014; HRSA, 2015). Covered entities can seek additional rebates on top of the 340B discount. 340B discounts and potential additional price concessions are not included in the Medicaid best price (*Health Affairs*, 2017c). The law instructs the HHS to enter into a pharmaceutical pricing agreement (PPA) with drug manufacturers as a stipulation for their drugs to be covered under Medicaid. If a drug manufacturer signs a PPA, it agrees that the prices charged for covered outpatient drugs to covered entities will not exceed 340B ceiling prices as defined by statute. The Health Resources and Services Administration (HRSA) calculates the ceiling prices quarterly using pricing data reported to CMS. The 340B ceiling price is calculated by subtracting the Unit Rebate Amount from the AMP. In practice, this results in the 340B price being about 20 to 50 percent off the drug's AMP. Drugs included in the 340B program generally consist of outpatient prescription drugs and drugs administered by clinicians in an outpatient setting, excluding vaccines.

HRSA administers the 340B program and is responsible for the oversight of various stakeholders, including covered entities and pharmaceutical companies. The ACA expanded the types of covered entities eligible to participate in the 340B program, including critical-access hospitals, rural referral centers, sole community hospitals, and freestanding cancer centers. Furthermore, in 2010, HRSA allowed 340B entities to sign agreements with more than one outside pharmacy—known as contract pharmacies—to provide the covered drugs. Contract pharmacies are employed by some hospitals and clinics to expand services outside of hospital walls (HRSA, 2010).

By design, 340B program participation provides qualified entities the opportunity to generate revenue from administering and dispensing prescription drugs, financed by pharmaceutical manufacturers, insurers, and paying patients (Conti and Bach, 2014). The program does not require enti-

[10] Section 602 of Public Law 102-585, the Veterans Health Care Act of 1992 enacted section 340B of the Public Health Service Act (PHSA) Limitation on Prices of Drugs Purchased by Covered Entities, codified at 42 U.S.C. 256b.

ties to pass the drug discounts along to the patients they treat in the form of lower out-of-pocket costs, nor does it require passing those discounts in the form of lower reimbursements to the insurance plans that cover affected patients. It also does not require these entities to limit the patients who receive the discounted drugs to those who are uninsured or underinsured.

As noted earlier, 340B discounts are not counted in the manufacturers' best price, and they are also exempt from formulas that set reimbursement for fee-for-service Medicare Part D and Part B, in order to better reflect their acquisition costs. These exemptions in turn influence the costs of drug therapies among fee-for-service Medicare beneficiaries and the commercially insured. Patient deductibles and coinsurance payments associated with prescription drugs reflect the reimbursement set by the insurer to the pharmacy or the clinic; these are unaffected by 340B discounts.

Debate about the program has intensified recently, due in part to the large number and the significant diversity of providers receiving the discounts and their safety net roles (GAO, 2011; OIG, 2011; von Oehsen et al., 2012). Outpatient clinics participating in 340B are, by definition, serving vulnerable patient populations. These participants include federally qualified health centers, critical access hospitals, rural referral centers, specialized clinics (including black lung clinics, comprehensive hemophilia diagnostic treatment centers, Title X family planning clinics, sexually transmitted disease clinics, tuberculosis clinics, Native Hawaiian health centers, tribal/urban Indian health centers) and Ryan White HIV/AIDS Program grantees. In 2015, these standalone safety-net clinics were outnumbered by hospitals, their affiliated outpatient clinics, and contract pharmacies participating in 340B (OIG, 2014).

Particular scrutiny has focused on acute care nonprofit hospitals. In 2014, roughly one-third of all acute-care not-for-profit hospitals in the United States qualified as covered entities under the 340B program (Conti and Bach, 2014), and they are thought to have accounted for approximately 48 percent of the national outpatient hospital visits (Mulcahy et al., 2014). In contrast to the clinics, acute care, nonprofit hospitals and their affiliated outpatient clinics participating in the 340B program are not required to demonstrate that they provide community benefits in the outpatient setting. To be eligible for 340B discounts, HRSA requires only that hospitals provide inpatient services to Medicaid and low-income Medicare beneficiaries (to the degree that their Medicare disproportionate share patient percentage[11] exceeds the eligibility threshold of 11.75 percent) (GAO,

[11] Enacted by statute in 1986, Medicare's disproportionate share adjustments were intended to provide additional reimbursement for hospitals that incur higher-than-average costs per case because they serve a significantly disproportionate share of low-income patients (CMS, 2017b). The disproportionate patient percentage is equal to the sum of the percentage of

2011). However, in the years since the program's inception, the structure of hospitals in the United States has dramatically changed, with nonprofit hospitals increasingly displaying characteristics of for-profit hospitals (Bai and Anderson, 2016; Horwitz, 2005; IOM, 2000), and standalone hospitals pursing mergers and affiliations with other hospitals and hospital systems and outpatient provider groups (Baker et al., 2014; Cutler and Scott Morton, 2013).

Evidence about the impact of 340B revenue on safety net and community need engagement among qualifying hospitals is largely anecdotal (340B Health, 2016; Kantarjian and Chapman, 2015; Wallack and Herzog, 2011). GAO conducted a cross-sectional comparison of 340B-qualified Medicare disproportionate share hospitals with non-340B hospitals in 2012 using publicly available data from Medicare hospital cost reports (GAO, 2015). The report found that 340B hospitals provided more uncompensated care than did non-340B hospitals and also had lower profit margins than non-340B hospitals, in part because they provided more uncompensated and charity care. A more recent report found that hospitals participating in 340B in 2015 exhibited widely varying financial stability and safety net care provision (Nikpay et al., 2017). Some 340B disproportionate share hospital (DSH) program participants operated at a substantial loss, but at least one-quarter of participants operated with a comfortable margin. Many of the hospitals with the highest operating margins were also those that provided the least uncompensated care, while the hospitals that provided the most uncompensated care had the lowest operating margins. Furthermore, there was little correlation between county-level uninsured rates and the adjusted DSH patient percentage.

Finally, some 340B hospitals and clinics built large networks of contract pharmacies after HRSA released its 2010 guidance. As contract pharmacy arrangements have proliferated, especially with national chains including Walgreens, Rite Aid, CVS, and Walmart, these agreements have come under scrutiny. They are not subject to routine independent audits like other 340B program providers and manufacturers. Furthermore, contract pharmacies are not required to demonstrate that they serve vulnerable populations at all, nor are they required to show that they meet the core program objectives to qualify for discounts. In 2014, the HHS Office of Inspector General released a study regarding contract pharmacies that was conducted by interviewing a "purposeful sample" of 30 administrators and representatives of covered entities (OIG, 2014). The report noted that covered entities using contract pharmacies do not always offer the discounted 340B price

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Medicare inpatient days attributable to patients eligible for both Medicare Part A and the Supplemental Security Income plus the percentage of total inpatient days attributable to patients eligible for Medicaid but not Medicare Part A.

to uninsured patients and that covered entities did not "conduct all of the oversight activities recommended by HRSA."

Under current statute, neither HRSA nor CMS collects information from qualifying entities or drug manufacturers regarding which drugs are being purchased through the 340B program, the amount of 340B-derived revenue generated by qualifying entities, or how revenues are used to benefit vulnerable patient populations. Reports from several pharmaceutical manufacturers suggest that sizable proportions of national product sales (10 to 20 percent) are currently subject to 340B discounts. The sales of drugs through one program vendor totaled $12 billion in 2012, and $2 billion of Genentech's sales flowed through the 340B program in 2016 (Fein, 2017). A 2011 GAO report documented that some covered entities in the 340B program generated revenue that "exceeded drug-related costs," while others did not (GAO, 2011). GAO also analyzed spending on oncology drugs covered under Medicare Part B in 2012, comparing hospitals that were or were not qualified to participate in the 340B program (GAO, 2015). Part B spending on those drugs was substantially higher at 340B hospitals than at non-340B hospitals. These differences did not appear to be explained by the limited number of hospital characteristics examined or by patients' health status.

Stakeholders have expressed concern that the scale of the program has increased without a subsequent correlation in resources dedicated to oversight. In the past several years, HRSA has been working to release a comprehensive update to the program's definitions, covered entity qualifications and program participation requirements for covered entities and manufacturers, sometimes referred to as the omnibus Mega-Reg (HRSA, 2015). Of particular concern has been the strengthening of oversight by HRSA and CMS to adequately enforce existing prohibitions on diversion and duplicate discounts among covered entities and contract pharmacies (GAO, 2011). Diversion is when a 340B drug is given to an ineligible patient or resold by the covered entity. Under current statute, eligible patients are defined as those who receive regular medical care at covered entities or who participate in an AIDS drug-purchasing assistance program and who are not insured by Medicaid, although there are some exceptions. Duplicate discounts occur when a covered entity receives the 340B discount and the state receives a Medicaid drug rebate, also from the drug's manufacturer, on the same unit. While manufacturers can audit covered entities for suspected unauthorized use of 340B drugs, covered entities do not have any audit authority and they must petition HRSA to investigate manufacturers or turn to the judicial system when purported violations in 340B pricing occur; therefore, another focus of these efforts has been to strengthen oversight of possible manufacturer overcharges. The ACA required a new dispute resolution process and greater pricing transparency by establishing a 340B

pricing database; however, while HRSA has started these initiatives, it has not finalized them. In February 2017, the Trump administration cancelled the release of the Mega rule (Ellison, 2017), effectively pushing 340B reform into the purview of CMS and the U.S. Congress. In November 2017, HHS finalized a rule that would reduce Medicare Part B's reimbursement for hospital outpatient clinics' use of 340B-discounted drugs and increase oversight of the program. This change will also result in reduced out-of-pocket payments for Part B beneficiaries undergoing outpatient drug-based treatment (HHS, 2017).

RARE DISEASES

The special protections afforded to drugs that prevent or treat rare diseases also influence their availability and may have an impact on their affordability as well. The Orphan Drug Act was passed in 1983 as an amendment to the Federal Food, Drug, and Cosmetic Act. A 1984 amendment to the act defined rare diseases as those affecting "less than 200,000 persons in the United States" and for which "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from the sale in the United States."[12] Based on the 2017 U.S. population, that translates to approximately 6.1 in 10,000 people. The European Union identifies a rare disease as a condition affecting no more than 5 in 10,000 people (Gammie et al., 2015).

Since 1983, more than 600 drugs and biological products have been brought to market with the act's assistance (FDA, 2017e). Fewer than 10 such industry-sponsored products entered the market in the decade preceding the act (FDA, 2017e). Over the past 5 years, orphan drug approvals have increased exponentially (Evaluate Pharma, 2017). In 2016, nearly half of the new medications approved were orphan drugs, including two that are indicated for diseases with no approved treatments (FDA, 2017e).

The program provides a number of benefits to the sponsors of FDA-designated products for rare diseases (FDA, 2017e), including an additional 7 years of market exclusivity. Participating firms also benefit from more open study protocols (with fewer eligibility criteria), which are intended to increase access of affected patients to the medications, and these firms may also receive modest FDA grant support to investigate treatments for rare diseases. The regulatory review process for orphan drugs is expedited, and clinical trials can enroll smaller numbers of patients than would otherwise be acceptable in registration trials. The manufacturers of orphan drugs can

[12] Health Promotion and Disease Prevention Amendments of 1984, Public Law 98-551, 98 Stat 2815 (1984), § 4.

also qualify for tax credits to help support testing. Furthermore, the act allows manufacturers to claim a tax credit[13] in the taxable year of up to 50 percent for expenses paid or incurred by the sponsor on human clinical trials required to obtain FDA approval (FDA, 2017c). These factors tend to substantially reduce the development costs for orphan drugs compared with what traditional drugs cost to develop (HHS, 2016). However, sponsors are required to request orphan drug designation from the FDA before filing a new drug application (FDA, 2017e).

Drugs for rare diseases often have higher prices because of the small size of the eligible patient population and because there are generally few if any competitors to address what is most often a high unmet need. Orphan drugs are also more likely to be biologics, which tend to be less susceptible to generic competition (Thomson Reuters, 2012). The median cost per patient is 5.5 times higher for orphan drugs than for non-orphan drugs (Evaluate Pharma, 2017). In 2016, the median annual cost for an orphan drug in the United States was more than $32,000, although the 10 therapies used by the most patients averaged less, at $14,909 (QuintilesIMS, 2017). Among the top 100 drugs in the United States, the average cost per patient per year for orphan drugs was $140,443 in 2016, compared with $27,756 for a non-orphan drug (QuintilesIMS, 2017).

From 2015 to 2016, orphan drug sales increased 12.2 percent to $114 billion, compared with an increase of 2.4 percent (to $578 billion) for non-orphan drug sales (Evaluate Pharma, 2017). In 2016, of the total drug sales ($450 billion) in the United States, approximately 7.9 percent of total spending was for orphan indications of approved orphan drugs, up from 3 percent in 1993 (QuintilesIMS, 2017). By 2020, estimated worldwide sales are projected to reach $209 billion (approximately 21 percent of prescription sales excluding generics) (Evaluate Pharma, 2017).

The Orphan Drug Act has recently come under increasing scrutiny for several reasons, including (1) the fact that orphan drug status has been bestowed on some drugs that were already available (and thus did not need orphan drug program benefits to make it to market), and (2) the way that some manufacturers have selected a subset of eligible patients to qualify for orphan drug status and then extended the scope of the drug's use to a broader population that exceeds the Orphan Drug Act limits of 200,000 potential patients—a practice termed by critics as "salami slicing" (Daniel et al., 2016; Kesselheim et al., 2017; Loughnot, 2005; Pulsinelli, 1999).

Some drugs receiving orphan drug status have in fact become "blockbuster" successes, with more than $1 billion in annual sales. These include Vioxx, Cialis, and Botox. Rituximab, the highest-selling orphan drug to

[13] A bill introduced in the U.S. House of Representatives in October 2017 would eliminate this tax credit (H.R. 1, Subtitle E, section 3401).

date, is a biologic (monoclonal antibody) originally intended for treating lymphoma. It is now used to treat a wide variety of conditions, including non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and several skin disorders. In 2016, 7 of the 10 best-selling drugs in the United States had at one time received orphan drug status (Evaluate Pharma, 2017).

Some drugs have received multiple orphan designations, each of them creating a new 7-year market exclusivity. For example, Gleevec has received 9 separate orphan drug designations and had a reported $3.3 billion in sales for 2016 (Novartis, 2017). A 2017 investigation found that 70 drugs (more than 10 percent of the total approved for orphan status) had received their status after having already been approved for marketing by the FDA (Tribble and Lupkin, 2017). This group included the blockbuster drugs Crestor (for cholesterol control), Abilify (for psychiatric disorders), and Humira (for rheumatoid arthritis). The investigators found that another 80 drugs had received multiple orphan designations and that, overall, approximately one-third of all orphan drug approvals either had been for repurposed drugs already marketed or had received multiple orphan drug designations (and hence multiple program benefits). According to another recent analysis, 98 drugs with orphan status also had non-orphan indications. Of those, 54 received a non-orphan indication first and 10 received both orphan and non-orphan indications simultaneously (QuintilesIMS, 2017).

While special incentives are unquestionably needed to justify firms pursuing drugs with very small markets, empirical evidence indicates that the current orphan drug program may be misused.

OTHER INFLUENCES

Awareness of Costs

In order for clinicians and patients to make optimal choices relating to drug therapies, both must have reliable information regarding the benefits and costs of both the drug under consideration and other treatment options. However, given the large and expanding array of choices, expecting even experienced clinicians to have a full grasp of the benefits and the risks of all reasonable alternatives is at best problematic, while the patients themselves can be expected to know and understand far less than the providers.

Price-informed care has been shown to reduce unnecessary medical spending (Stammen et al., 2015). However, at present, clinicians are generally unaware of the actual cost of medications—either to health insurers or to the patients (Schutte et al., 2017). A review of studies of clinician awareness of medication costs found that clinicians were able to estimate

drug costs within 25 percent of the true cost less than one-third of the time. Clinicians tended to underestimate the cost of expensive medications and to overestimate the cost of cheaper medications (Allan et al., 2007).

Clinicians' unfamiliarity with medication costs is not due to a lack of interest or concern. The vast majority of prescribers report that it is important to manage the patient's out-of-pocket medication costs (Shrank et al., 2006a). But the challenge is not a simple one: developing an awareness of prices is complicated by the existence of multiple formularies, differences in list prices, and differences in individual patients' insurance plans. A decade ago, prescribers reported that they were already facing challenges dealing with the overwhelming quantity of medical information (Shrank et al., 2006a), and the situation has likely intensified. Hence, clinicians are unlikely to respond favorably to anything that requires them to deal with multiple prices for each patient's medication unless the information is provided in an efficient, user-friendly fashion at the point of care.

The use of high-cost medications can be reduced if prescribers have ready electronic access to information relating to the medications that are prompted by the diagnosis, in addition to relevant summaries of product safety and cost pertaining to the insurance plan (McMullin et al., 2005). An increasing number of firms are creating Web- and smartphone-based applications that can be used by prescribers and patients to view drug cost information based on list prices. However, these list prices generally reflect what the patient would pay without insurance and may be very different from what the actual out-of-pocket payments would be according to the patient's insurance plan.

Patients themselves are often unaware of the amount that they will pay for their medications. The "sticker shock" at the pharmacy leads to lower fill rates for prescriptions, and some patients extend their medications by reducing dosages. Some health plans and PBMs are attempting to improve patients' access to medication cost information. Insurance companies are creating Web portals designed to help patients learn about which medications will be covered under their plans with a lower copayment, when cheaper alternatives exist, and whether patient assistance programs are available (Humana, 2017). A complicating factor for both patients and the insurers is that insurers typically do not have access to information about rebate and discount agreements between manufacturers and PBMs.

Also, more prescribers are requesting that pharmacists routinely be involved in the process of reviewing the costs of medications (Ross, 2016). Indeed, the Medicare Modernization Act established the requirements that Part D sponsors[14] must offer each enrolled beneficiary a minimum level of

[14] CMS contracts with sponsors (insurers) to provide the Medicare Part D prescription drug benefit.

medication therapy management services that includes interventions for both the Medicare beneficiaries and prescribers. The sponsors must also offer at least once per year an interactive person-to-person comprehensive medication review by a pharmacist or other qualified provider. They must also perform quarterly medication reviews with follow-up interventions when necessary, focusing on patients with high expected out-of-pocket costs who have multiple chronic conditions and who are taking multiple medications. These strategies have been linked to reductions in medical costs (Ramalho de Oliveira et al., 2010) and improvements in medication adherence (Pringle et al., 2014).

State Laws on Prescription Form Language

State laws that specify the language used in prescription forms can also influence prescriber behavior. Even in situations when a generic medication is available, prescribers can mandate that a brand medication is dispensed by indicating "dispense as written" on the prescription. However, due to the increased cost of brand medications, the use of "dispense as written" has been shown to reduce the likelihood that the patient will actually purchase the medication and, consequently, take the needed medication. A pharmacy claims analysis found that patients with a tiered pharmacy benefit who received a generic medication were 62 percent more likely to use their medications appropriately than those who had been prescribed more expensive medications (Shrank et al., 2006b). Another analysis estimated that if the 5 percent usage of "dispense as written" observed in the study sample was extrapolated to the United States as a whole, the result would be an additional $1.2 billion in out-of-pocket spending by patients and an additional $7.7 billion in drug costs for health systems (Shrank et al., 2011).

The design of the prescription pad itself can influence the likelihood that a prescriber uses the "dispense as written" designation. If the provider must check a box in order to designate "generic substitution is permitted," more prescriptions are filled with branded medications. Conversely, if the prescriber must check a box saying "dispense as written," then more prescriptions are filled with generic drugs (Helmons et al., 2014). This result is consistent with the literature on behavioral sciences that shows how answers to a question can be "framed" by the manner in which the question is presented. Some approaches to reducing the use of "dispense as written" designations that are being tested include improving the education of providers and patients on the clinical equivalence of generic medications, and imposing financial penalties on clinicians by health plans (Shrank et al., 2011).

Patients may themselves request that a brand medication be dispensed rather than the generic equivalent when they reach the pharmacy. An

analysis of state Medicaid programs with "mandatory" generic substitution programs compared states that required patient consent for generic substation versus those that did not require patient consent. The study found an increased use of branded medications in states that required patient consent. States that required patient consent paid on average an additional $15 per prescription (Shrank et al., 2011).

Payments to Prescribers

The norms of medical professionalism obligate clinicians to make prescribing decisions that are in their patients' best interests. Payments to clinicians by pharmaceutical manufacturers, which include speaking honoraria, travel expenses, and paid meals are seen by some as creating a conflict of interest. These payments could potentially lead clinicians to favor medications from a sponsor over non-sponsored medications, even when the sponsored medications are less effective or more expensive. A 2009 Institute of Medicine report concluded that industry payments to clinicians were likely to create conflicts of interest that were not outweighed by the positive benefits of working with drug makers, such as continuing education (IOM, 2009). The report recommended that clinicians not accept industry payments, and that industry (including pharmaceutical companies) refrain from offering payments to clinicians. This report also recommended public reporting and disclosure of potential conflicts of interest although this is not a sufficient remedy by itself.

The Open Payments program (also known as the Physician Payments Sunshine Act) within the ACA requires industry to disclose payments made to clinicians in a public database. The Physicians Payments Sunshine Act has increased the visibility of the prevalence of industry payments to clinicians and the association between industry payments and prescribing behavior. A recent study of clinicians in Massachusetts, using data from the Sunshine program on payments, found an association between payments by statin manufacturers to clinicians and an increased likelihood of prescribing branded statins. Furthermore, payments for the educational training of clinicians were associated with a 4.8 percent increase in the rate of brand-name prescribing (Yeh et al., 2016). Another study found that having received an industry-sponsored meal was associated with higher likelihood of prescribing branded pharmaceuticals across a range of therapeutic classes (DeJong et al., 2016). Findings from these studies show a potential influence of such benefits on prescribing choices.

In principle, disclosure has the potential to reduce conflicts of interest by creating greater scrutiny of financial relationships between clinicians and industry. However, it seems likely that most patients have limited knowledge about transparency tools (including the Open Payments database), so

the use of these tools by patients is likely to be limited (Ross, 2017). And, contrary to what one might expect, the disclosure of conflicts of interests can increase the amount of biased recommendations offered by clinicians and reduce skepticism from patients, who may believe that disclosure increases trustworthiness (Loewenstein et al., 2012). In focus groups about the open payments system, clinicians have expressed general appreciation for such transparency (Chimonas et al., 2017).

Steps to further limit pharmaceutical industry influence on clinicians have been limited. Some health systems have rules that limit interactions between drug company representatives and health system employees. These include anti-detailing policies, which prohibit direct marketing to these employees. One study found that the adoption of these policies in an academic medical center reduced the controversial practice of providing off-label prescriptions (uses that have not been approved by the FDA) of antipsychotic medications to children (Larkin et al., 2014). Some states had adopted laws, including transparency laws, that preceded the federal open payments legislation and bans on clinicians accepting gifts. One study found that the market share of new, costly drugs was substantially lower in such states than in states without the laws (King and Bearman, 2017). While legal concerns have been raised about the commercial speech rights of drug manufacturers to promote their products, a key legal issue is whether laws that restrict some corporate speech act to advance the public's interest (Kesselheim and Avorn, 2008).

Prescriber Reimbursement

Another potential conflict of interest arises from the current percentage-based reimbursement system for drugs administered in outpatient clinics, under which the use of higher-priced drugs results in higher payments to providers. Specifically, under the buy and bill arrangement in which clinicians are reimbursed for the average sales price of the drug plus 6 percent plus an administration fee, the spread between the payer-reimbursed price and the acquisition cost of the drug generates revenue for standalone and hospital-affiliated clinics (Conti et al., 2013; Howard et al., 2015; Malin, et al., 2013; Polite et al., 2014; Shahinian et al., 2010). In oncology, where the infused or injected administration of drugs in the outpatient setting is very common, a substantial fraction of practice revenues may depend on the use of these drugs.

As a consequence, studies suggest that oncologists' drug choices are responsive to drug-based profit margins (Conti et al., 2012; Jacobson, 2006; Jacobson et al., 2010). When Medicare reimbursements for these drugs were reduced under the Medicare Modernization Act (MMA), the volume of chemotherapy use increased—which suggests that the total dol-

lars received remained the same for prescribing doctors (Jacobson et al., 2010). Furthermore, eligibility for special discounts on the acquisition costs of these drugs that do not affect payer reimbursement for their use may act to alter the incentives for community providers to remain independent. For example, hospital-affiliated outpatient practices that qualify for 340B discounts can purchase drugs at reduced cost while still receiving full reimbursement for them in addition to their ability to charge facility fees. Conversely, community oncology practices that do not qualify for 340B discounts operate on lower per person-per treatment margins derived from the administration of the drugs they purchase, including the revenue generated from buy-and-bill reimbursements and the ability to charge facility fees (Polite et al., 2014). These disparities in revenue-generating incentives may act to encourage the consolidation of health care providers (Baker et al., 2014; Cutler and Scott-Morgan, 2013). For example, there has been significant growth in 340B eligibility among outpatient clinics affiliated with 340B-participating hospitals preceding and following ACA implementation. As a result, GAO estimates that 340B discounts apply to 50 percent of cancer drugs sold and paid for by Medicare Part B (GAO, 2015). For drugs dispensed or used by clinicians at a hospital-affiliated clinic or an outpatient infusion center affiliated with a hospital, these providers also charge payers facility fees, which may amount to 50 percent or more of the drug's acquisition cost. As the site of care for outpatient infusion services has increasingly shifted toward hospital-owned or affiliated practices in recent years, spending associated with this form of care has grown (MedPAC, 2017b).

Unlike drugs covered under insurers' pharmacy benefits, the coverage of drugs under the medical benefit is essentially guaranteed for indications approved by the FDA and for many off-label uses as well (Bach, 2009; Conti et al., 2013; Scheingold et al., 2017). Formularies and other supply-side coverage restrictions based on evidence of clinical benefit or cost-effectiveness are not commonly used to restrict wasteful spending on these drugs. Many state laws, affecting about three-quarters of the U.S. population, require insurance coverage of infused and injected cancer treatments if their use is recognized in drug compendia, the peer-reviewed literature, or both (Bach, 2009; IOM, 2013). However, the quality of information in compendia is often variable and adequate evidence is often lacking (Abernethy et al., 2010). This complex legal and regulatory framework makes it difficult for payers to use comparative effectiveness evaluations in reimbursement decisions for cancer drugs (Pearson, 2012). Thus, under buy and bill, medical providers face incentives to use expensive prescription drugs, often in combination, whenever indicated (Howard et al., 2015). This system also creates a disincentive to substitute lower-priced drugs that offer patients equivalent outcomes or to substitute generics for more costly branded drugs (Conti et al., 2012).

Buy and bill also creates incentives for high pricing of drugs covered under the Part B benefit. As noted by Brock (2010), manufacturers know that expensive new cancer drugs will not be denied coverage by payers on the basis of cost, so they have no incentive to set prices to meet any cost-effectiveness standard. CMS posts a new average sales price every quarter based on information submitted by drug manufacturers 6 months earlier. As a result, clinician reimbursement remains stagnant for two quarters after drug acquisition costs rise, posing a financial risk for outpatient practices (Conti et al., 2013). Howard and colleagues (2015) argued that the launch prices of these drugs are high and have grown over time in part because manufacturers understand the risks practices face if prices rise after launch.

Over the years, there have been many proposals to minimize the influence of drug-derived revenue on clinician prescribing behavior in the Medicare program (Bach, 2009; Polite et al., 2014). This was one motivating rationale behind the MMA's revision of Medicare Part B payment to average sales price—this policy explicitly linked reimbursement to the drugs' actual acquisition cost, including the availability of volume-based discounts and rebates. Proposed alternative methods for setting alternative reimbursements under Medicare Part B have included invoice pricing, least costly alternative reimbursement, the bundling of drugs into episode-of-care payments, shifting Part B drugs to the Medicare Part D benefit, and the revision of the failed Competitive Acquisition Program enacted under MMA (Polite et al., 2014, 2015). Under the Bipartisan Budget Act of 2015, CMS will implement Section 603, which specifies that services provided at off-campus hospital outpatient departments that began billing under the Medicare outpatient prospective payment system on or after November 2, 2015 will no longer be reimbursed under outpatient rates (CMS, 2016). This site-neutral payment policy was designed to reduce Medicare spending on off-campus hospital outpatient department services that could be performed at a physician's office for a lower rate. These changes will be phased in over 4 years beginning in 2017. Payments for services provided at off-campus hospital departments that began billing Medicare before this date are not covered under this policy (OIG, 2014).

In 2016, the CMS Innovation Center created new authority for payment demonstration projects and unveiled plans for the Medicare Part B Drug Payment Model. This demonstration was intended to test in two phases the effect of alternative payment models on Part B spending across therapeutic categories. In the first phase, an alternative to the 6 percent markup would be tested by including a lower-percentage markup, offset by a flat daily supplemental payment of $16.50. In the second phase, payment alternatives such as reference pricing (pegging reimbursement to the least expensive available drug in the class) and outcome-based risk sharing (pro-

viding higher reimbursement for more favorable patient outcomes) would be introduced. The CMS demonstration was designed to be cost-neutral in the short run, but ultimately to identify models that would produce greater system cost savings (Schrag, 2016). The Part B demonstration was canceled before implementation began (Dolan, 2016). However, there is a relevant demonstration project under way in the Oncology Care Model, wherein clinician practices have entered into payment arrangements that include financial and performance accountability for episodes of patient care surrounding chemotherapy administration.

FINDINGS

Based on the material presented in this chapter, the following findings are offered:

Finding 3-1: *Position statements provided by various participants in the drug pricing debate reveal numerous instances of potential conflicts of interests, including various combinations of financial relationships among biopharmaceutical companies, patient advocates, academic researchers, health care professionals, and their representative organizations.*

Finding 3-2: *Publicly available evidence shows that the biopharmaceutical industry has higher profitability than other comparable sectors in the economy.*

Finding 3-3: *There is a widespread disagreement about the actual costs underlying biopharmaceutical research and development and the proper methods to calculate them.*

Finding 3-4: *When branded drugs go off patent and a generic supplier enters the market, prices for those medications usually decline; with two or more generic suppliers, the market prices generally decline significantly.*

Finding 3-5: *Mergers between companies that produce both branded and generic drugs treating the same condition can, in absence of other competition, have anti-competitive effects that often result in undesirable price increases.*

Finding 3-6: *Delays and backlogs in the U.S. Food and Drug Administration approval of generics and biosimilars curtail market competition and thereby increase the likelihood of higher drug prices.*

Finding 3-7: *In the absence of evidence of harm (as opposed to the concerns surrounding potential harm) with respect to importation of generics and biosimilars when competition is lacking, and given the potential cost-savings for patients, policy experiments related to generic and biosimilar importation could be useful.*

Finding 3-8: *Essential medicines lists by other OECD countries have been generally helpful in managing the availability and affordability of drug therapies.*

Finding 3-9: *Drug shortages occur regularly and can lead to adverse outcomes for patients.*

Finding 3-10: *The list prices provided by manufacturers can significantly affect patients' drug costs and access. This affects retail purchases of both insured and uninsured patients, as well as drugs purchased by clinicians and hospitals and administered to patients directly.*

Finding 3-11: *Current insurance benefit designs for prescription drugs often expose consumers to considerable financial risk and can unfavorably affect patients' medication adherence.*

Finding 3-12: *Large biopharmaceutical companies spend substantially more on marketing and administration than on research and development that could lead to new drugs.*

Finding 3-13: *Direct-to-consumer advertising of prescription drugs has increased substantially over time and can adversely influence consumer choices.*

Finding 3-14: *While copay coupons provided by pharmaceutical companies can expand patient access to high-cost medications, they also increase the percentage of prescriptions that are filled with branded drugs, increase overall drug spending, and drive up individuals' insurance premiums.*

Finding 3-15: *Programs promulgated under the Orphan Drug Act—which were originally designed to foster the development of innovative drugs for rare conditions—have expanded well beyond their original intent and are counteracting efforts to make medicines more affordable.*

Finding 3-16: *Section 340B of the U.S. Public Health Service Act had the stated intent of improving the access of low-income populations*

to medicines at discounted rates; however, it is unclear whether the benefits of the program flow to the intended vulnerable populations. As implemented, the program has expanded well beyond assisting low-income patients and may therefore be acting to increase the cost of medicines paid by insurers and patients.

Finding 3-17: *Current insurer reimbursement policies for clinician-administered drugs in the outpatient setting minimize incentives for medical providers to select treatments and settings for patient care that are the most cost-effective. These policies may serve to inflate the prices of these drugs charged by manufacturers and other members of the supply chain who profit from the current system, and put patients at clinical and financial risk.*

Finding 3-18: *In order for both consumers and clinicians to make well-informed decisions regarding prescription drug therapies, reliable and objective information is needed—including information on potential clinical outcomes, the comparable effectiveness of alternative treatments, and out-of-pocket and overall costs to the patients. Some but not all of this information is available today; particularly lacking is information regarding costs.*

4

Strategies to Improve Affordability and Availability

Without the major advances in biopharmaceutical research and development that have taken place over the past several decades, there would have been far fewer of the tangible improvements in public health that our society has enjoyed. Researchers and developers in the biopharmaceutical sector share the societal goal of bringing useful products to patients who need them. Nevertheless, many aspects of how drugs are developed and delivered to the public today have made it more difficult to achieve that goal and threaten to dampen the promise of the field.

In developing policy solutions to the challenges in the biopharmaceutical supply chain, high priority should be place on optimizing the health and well-being of the people—including relief from the burden of unaffordable medical bills. It is important to reward private industry for supporting research and development, which are high-risk endeavors with serious financial consequences in the case of failure. The government has played and continues to play a significant role in improving the understanding of human health and diseases by supporting basic and translational research and new technology development and by fulfilling regulatory responsibilities. Investments by the government should benefit the public that financed them. Today, there is a critical need for policy changes that will ensure the availability and affordability of medicines for patients who need them.

CONCLUSION

There is little value in new drugs that patients cannot afford—and there is no value in drugs that do not exist. Thus, there is a fundamental tension

between ensuring the availability of new drugs in the future and ensuring the affordability of those drugs that exist today. Based on the 32 findings listed in Chapters 2 and 3, the overarching conclusion is that **improving patient access to effective and affordable medicines is an imperative for public health, social equity, and economic development; however, this imperative is not being adequately served by the biopharmaceutical sector today.** This sole conclusion is intended to refocus and refresh the priorities of the entire biopharmaceutical sector as well as to serve as the basis for the following eight recommendations and the implementing actions that accompany each.

RECOMMENDATIONS

As is often the case in providing policy guidance on complicated matters, each recommendation is invariably accompanied by counterarguments. Similarly, it is not always possible to obtain all of the relevant information before providing policy guidance. These caveats certainly apply to the issue of making drug therapies affordable to patients. Identifying which policies need to change and in what ways is only complicated by the complexity and opacity of the biopharmaceutical sector. Dismissing the option of doing nothing, this report offers recommendations based on the preponderance of the available evidence.

Wherever possible, the recommendations indicate the relevant federal agencies that have legal authority to implement the accompanying actions, along with other participants as appropriate. However, there are situations where there is no agency with the definitive legislative authority to carry out certain recommended actions. Thus, this report urges that the U.S. Congress, where necessary, grant the legislative authority to the relevant agencies essential to executing the actions recommended in this report.

Recommendation A:[1] Accelerate the market entry and the use of safe and effective generics as well as biosimilars, and foster competition to ensure the continued affordability and availability of these products.

Implementation Actions:

A-1. The U.S. Department of Justice and the Federal Trade Commission should vigorously deter manufacturers from paying other producers for the delayed entry of generics and biosimilars into the market.

A-2. The U.S. Department of Justice and the Federal Trade Commission should expand the enforcement of policies that preclude

[1] Supporting findings for Recommendation A include 2-6, 2-7, 3-4, 3-5, 3-6, and 3-7.

mergers and acquisitions among companies possessing significant competing generics and biosimilars—either by preventing the mergers or acquisitions or by requiring divestiture of potentially competing drug products to independent entities.

A-3. The U.S. Patent and Trademark Office should identify specific means to reduce "evergreening" of drug exclusivity via new patents or extensions on existing drugs.

A-4. The U.S. Congress should authorize the U.S. Food and Drug Administration to seek reciprocal drug approval arrangements for generics and biosimilars between the regulatory agencies of the United States and the European Union, and such countries as Australia, Canada, Japan, and New Zealand.

A-5. The U.S. Congress and the U.S. Food and Drug Administration should actively seek to reduce barriers to generic market entry and promote the expeditious market entry of additional domestic and international providers of generics and biosimilars, particularly including those not marketed by the original patent holder.

A-6. State legislatures should develop policies to restrict the use of the "dispense as written" practice by prescribers that may unnecessarily impede the use of generics and biosimilars.

Recommendation B:[2] Consolidate and apply governmental purchasing power, strengthen formulary design, and improve drug valuation methods.

Implementation Actions:

B-1. The U.S. Congress should modify existing legislation so as to allow the U.S. Department of Health and Human Services, acting as a single entity, to directly negotiate prices with producers and suppliers of medicines, including acting on behalf of any relevant state agency that elects to participate in the process.[3]

B-2. The U.S. Department of Health and Human Services should test and further refine methods for determining the "value" of drugs and identify approaches to support value-based payments, formulary design, and negotiation of prices with biopharmaceutical manufacturers and suppliers.

B-3. The U.S. Congress should authorize the U.S. Department of Health and Human Services, related federal agencies, and asso-

[2] Supporting findings for Recommendation B include 2-8, 2-9, 2-11, and 2-12.

[3] Alan Weil dissents from Recommendation B-1. In his view, this implementation action is not supported by the report's findings and there is no evidence of its likely effects.

ciated private payers to expand flexibility in formulary design, including selective exclusion of drugs such as when less costly drugs provide similar clinical benefit.

B-4. The U.S. Congress should amend the Medicaid Drug Rebate Program—authorized by Section 1927 of the Social Security Act—to allow for exclusion of certain drugs from coverage under the rebate provisions.

B-5. The U.S. Department of Health and Human Services through the Centers for Medicare & Medicaid Services should expand demonstration projects that test alternative payment models for prescription drugs and assess the impact of such models on health care outcomes and costs.

Recommendation C:[4] Assure greater transparency of financial flows and profit margins in the biopharmaceutical supply chain.

Implementation Actions:

C-1. The U.S. Congress should require disclosure of information on a quarterly basis, at the National Drug Code level from:

- **Insurance plans that cover prescription drugs about the average net prices paid for drugs, including patient cost sharing.**
- **Biopharmaceutical companies about average net volume of and prices for drugs across each active sales channel, including discounts provided to pharmacy benefit managers and insurance plans.**

The U.S. Department of Health and Human Services should obtain, curate, and publicly report this collected information at the National Drug Code level on a quarterly basis. The U.S. Department of Health and Human Services should conduct analyses of these data and inform relevant congressional committees. In addition, the Federal Trade Commission should examine these data to identify and act on any anti-competitive practices in the market.

C-2. The U.S. Department of Health and Human Services should require biopharmaceutical companies to submit an annual public report stating list prices; rebates and discounts to payers, including changes thereto; and the average net price of each drug sold in the United States. The U.S. Department of Health and Human Services should also inform the relevant congressional

[4] Supporting findings for Recommendation C include 2-1, 2-2, 2-3, 2-4, 2-14, and 3-2.

committees of all net drug price increases that exceed the growth in the consumer price index for the previous year.

C-3. The U.S. Department of the Treasury should revise Form 990 and expand the disclosure requirements on all sources of income by organizations in the biopharmaceutical sector that are exempt from income tax under the Internal Revenue Code.

Recommendation D:[5] Promote the adoption of industry codes of conduct, and discourage direct-to-consumer advertising of prescription drugs as well as direct financial incentives for patients.

Implementation Actions:

D-1. The U.S. Congress should disallow the tax deductibility of direct-to-consumer advertising of prescription drugs as a business expense.

D-2. Manufacturers and suppliers should adopt industry codes of conduct that reduce or eliminate direct-to-consumer advertising of prescription drugs and should increasingly support efforts to enhance public awareness of disease prevention and management.

D-3. The U.S. Congress should prohibit patient coupon programs, in which biopharmaceutical companies give payments or discounts to consumers who fill prescriptions for the company's drug, except in cases where no competing drug is available in the market.

Recommendation E:[6] Modify insurance benefits designs to mitigate prescription drug cost burdens for patients.

Implementation Actions:

E-1. The U.S. Congress should establish limits on the total annual out-of-pocket costs paid by enrollees in Medicare Part D plans that cover prescription drugs by removing the cost-sharing requirement for patients who reach the catastrophic coverage limit.

E-2. The U.S. Congress should direct the Centers for Medicare & Medicaid Services to modify the designs of plans offered through Medicare Part D and governmental health insurance exchanges to limit patients' out-of-pocket payments for drugs when there is clear evidence that treatment adherence for a particular indica-

[5] Supporting findings for Recommendation D include 3-12 and 3-13.
[6] Supporting findings for Recommendation E include 2-10, 3-10, 3-11, and 3-13.

tion can reduce the total cost of care, as determined by the U.S. Department of Health and Human Services.

E-3. The U.S. Congress should direct the Centers for Medicare & Medicaid Services to specify that when patient cost-sharing is calculated as a fraction of drug prices in insurance policies through Medicare Part D and governmental health insurance exchanges, this calculation should be based on net prices, not list prices. All state and private prescription drug plans should be encouraged to follow this approach.

E-4. The U.S. Congress should require the Centers for Medicare & Medicaid Services, when determining patient cost-sharing rates, to specifically include the costs and the clinical effectiveness of prescription drugs and available treatment alternatives. This evaluation should address, where feasible, the total costs of care rather than simply the costs of the drugs themselves.

Recommendation F:[7] Eliminate misapplication of funds and inefficiencies in federal discount programs that are intended to aid vulnerable populations.

Implementation Action:

F-1. The U.S. Congress should expand the authority of the U.S. Department of Health and Human Services to provide increased oversight and regulation of the 340B program to assure that participation by covered entities, contract pharmacies, and drug manufacturers is consistent with the intent of the original legislation. Oversight should include systematic collection and assessment of data from qualified medical providers and participating drug manufacturers regarding the volume of drug purchases eligible for 340B discounts, revenues generated from 340B program participation, and safety-net services funded by these revenues.

Recommendation G:[8] Ensure that financial incentives for the prevention and treatment of rare diseases are not extended to widely sold drugs.

Implementation Actions:

G-1. The U.S. Congress should revise the Orphan Drug Act to achieve its original intent by:

[7] Supporting finding for Recommendation F is 3-16.
[8] Supporting finding for Recommendation G is 3-15.

- **Promoting agreements between biopharmaceutical companies and the U.S. Department of Health and Human Services that enable the department to obtain favorable concessions on launch prices, annual price increases, and other practices important to public health.**
- **Ensuring that drugs with orphan designation receive program benefits under the act only for the target rare disease, not for ancillary non-orphan indications.**
- **Eliminating unnecessary sub-classifications of disease categories that create artificial eligibility for orphan drug status, and limiting eligibility to only one orphan condition per drug.**
- **Directing the U.S. Food and Drug Administration to limit the market exclusivity awarded to orphan drugs to one 7-year extension.**

Recommendation H:[9] Increase available information and implement reimbursement incentives to more closely align prescribing practices of clinicians with treatment value.

Implementation Actions:

H-1. Payers should establish payment policies for drugs administered by clinicians in medical practices and hospitals that do not differentiate for the site of care (site neutral payment).

H-2. Hospitals, vendors of electronic health records, insurers, and professional societies should ensure that clinicians have readily accessible and routinely updated information regarding drug cost and efficacy to support sound prescribing decisions at the point of care. This information should include the relative clinical benefits of alternative treatment regimens and the relative financial costs of treatment settings to both patients and payers.

H-3. Payers should eliminate the practice of reimbursing clinicians and standalone and hospital-based clinics on the basis of list prices for drugs covered under the Medicare medical benefit, and replace the current reimbursement model with fixed fees that support clinical care and the costs of storing and administering these drugs.

[9] Supporting findings for Recommendation H include 3-12, 3-17, and 3-18.

H-4. Clinicians, medical practices, and hospitals should substantially tighten restrictions on pharmaceutical detailing visits, the acceptance and use of free drug samples, special payments, and other inducements paid by biopharmaceutical companies to clinicians, medical practices, and hospitals. Professional societies, trade organizations, and insurers could play an important role in accomplishing this objective.

A NATIONAL IMPERATIVE

Individuals make difficult trade-offs between spending their income to purchase prescription drugs and providing other necessities for their families. In addition to the health challenges they face, patients must also contend with the financial burden that comes with medical care needs that may sometimes last a lifetime for them or their families. From an individual to the national level, the growing cost of health care—and of pharmaceuticals in particular—has produced a new urgency because of the effects of these growing costs on the country's ability to meet other societal obligations while remaining economically competitive. Devoting such a large share of the nation's fiscal resources to this one particular human need limits investments in other national priorities, from education to infrastructure to the environment, thus affecting international competitiveness, jobs, quality of life, and standard of living.

The biopharmaceutical sector is critically important to public health, social equity, economic development, and, in some circumstances, the national security of the United States. Furthermore, bringing new medications to the market and placing them in the hands of patients has proven to be a laborious, complicated, and expensive process.

Ideally, an effective biopharmaceutical system would need to: focus on prevention as well as on treatments and cures; stimulate robust research and development on drugs that enable major improvements to human health; rapidly adapt to new scientific discoveries; adopt technologies, systems, and practices that improve health care; provide effective drugs that are affordable to all patients, including the disadvantaged; be affordable to society as a whole; sustain itself financially over time; and ultimately, improve the health of the nation.

With these characteristics as a reference, developing strategies to deal with the complexities of the biopharmaceutical sector will require the consideration of approaches beyond, for example, simple price control—a controversial topic in its own right. Thus, this report does not recommend enacting direct controls or setting limits on drug prices—a strategy adopted by many high-income nations that allows individuals in these countries to pay comparatively lesser prices for drugs but frequently does not sup-

port new drug development to the extent realized in the United States. This report also does not recommend or encourage certain more invasive options that have been advocated by others, such federal appropriation of intellectual property. This report opts for a more nuanced, less disruptive set of recommendations that include such factors as increased transparency and consolidated price negotiation by the U.S. Department of Health and Human Services.

Some of the actions recommended for implementation could potentially reduce expected revenues for manufacturers and intermediaries in the biopharmaceutical sector. However, reductions in corporate revenues do not necessarily lead to reductions in investments for research and development. Despite the commonly made assertion by the biopharmaceutical industry that potential reductions in revenues would lead inevitably to reductions in research and development, there are many choices the companies could make in response to such reductions. Such actions include moving funds allocated for product marketing and promotion to research and development, reducing stock buy-back programs, limiting administrative expenses such as executive compensation, and reducing lobbying expenditures.

Ultimately, this report addresses subject matter that arguably more closely involves behavioral, organizational, and political elements than scientific factors, and it highlights the fundamentally different views that exist on these issues—as was observed in the input to the committee from various experts and interested stakeholders, within committee deliberations, and in the external review of the report drafts. A system as complex as the current biopharmaceutical sector is rife with opportunities for unintended effects, so continued and diligent monitoring will be essential. An urgent and concerted effort on many fronts will be required to resolve the affordability and the availability of medicines.

Nonetheless, each month of delay in implementing important reforms adds another month of hampered access to medicines. As a major public health issue, the effects of the unaffordability of prescription drugs to people in the United States are very clear: they ultimately harm the health of individuals, sometimes even resulting in death. If the actions recommended in this report are implemented, it should be possible to achieve a significantly improved system for making drug therapies affordable to patients. The time to act is now.

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A

A Dissenting View

Michael Rosenblatt and Henri Termeer[1]

We are grateful for the contributions of our colleagues on this committee. We had hoped that the committee, after so much analysis and deliberation, would arrive at a consensus. Instead, we find the need for us to prepare this dissenting view. Our hope is that our view offers an alternative and effective set of recommendations that are sufficient to achieve the objectives of the committee. We believe that the committee's recommendations, if actually implemented, will lead to unintended consequences that will damage the health of people in the United States and damage the health of an industry whose innovations are essential to addressing unmet medical needs in the future. Our dissenting perspective

[1] Henri Termeer passed away during the advanced stages of this report's development. This dissent, therefore, reflects the draft at the time of Termeer's death. Only editorial changes, without any change to the core arguments, were made by Michael Rosenblatt. The main text of this report underwent further revisions in response to review, but Rosenblatt made the decision not to further revise this dissenting viewpoint in order to retain the original spirit and authentic co-authorship of this piece. Termeer and Rosenblatt emphasized that they wrote this piece not with the intent of solely presenting an "industry perspective." Rather, their intention was to provide a balanced view derived from insights and experiences in more than one sector, and to reflect their shared commitment to always place patients first.

Portions of this dissent are drawn from two publications by the authors:
Rosenblatt, M. 2014. The real cost of high-priced drugs. *Harvard Business Review*. https://hbr.org/2014/11/the-real-cost-of-high-priced-drugs (accessed November 13, 2017).
Rosenblatt, M., and H. Termeer. 2017. Reframing the conversation on drug pricing. *NEJM Catalyst*. https://catalyst.nejm.org/reframing-conversation-drug-pricing (accessed November 13, 2017).

provides: (1) background on why the biopharmaceutical industry is important to the health of Americans and our economy, (2) proposed principles to guide the generation of an effective set of recommendations, (3) specific recommendations that replace some present in the current draft, and (4) comments on the potential impact of implementing the recommendations.

THE SOCIETAL IMPACT OF BIOPHARMACEUTICALS

The introduction of the first antibiotics—sulfanilamide, streptomycin, and penicillin—launched the modern era in biopharmaceutical therapies. These early "miracle drugs" began saving lives from the instant of their availability. For penicillin, which was discovered in the United Kingdom, production at a scale of billions of units was achieved by a consortium of 20 pharmaceutical companies as part of the effort of the Allies to achieve victory in World War II.

Since then, a range of different medicines and vaccines has transformed health and society. Diseases with public health dimensions, such as hypertension, lipid disorders, diabetes, and osteoporosis, now have foundational (although imperfect) treatments. In recent years, previously neglected rare diseases that afflict only small numbers of people (but which have large impacts on individuals and their families) have been benefitting from innovative therapies.

AIDS was a major epidemic in the 1990s, filling one-quarter of the beds in some hospitals. The AIDS diagnosis was considered worse than a diagnosis of cancer because AIDS was universally fatal. The human loss was catastrophic. The financial burden was crushing: unabated, AIDS was projected to bankrupt the health system. But within a decade of researchers identifying the virus that caused the disease, new medicines had been developed that stopped the epidemic in its tracks. Today, AIDS has essentially been transformed into a chronic disease with a near-normal life expectancy. It is hard to picture our society if the AIDS epidemic were still continuing today.

It is important to note that the key AIDS therapies originated from the U.S. biopharmaceutical industry. The only reason that a rapid and effective response could be made was the existence of an innovation infrastructure in the United States, which meant that AIDS research did not need to start from scratch. Universities and industry were well positioned to translate scientific insights into new therapies from the moment they were made. A critically important lesson that emerged is that we must not damage this innovation infrastructure; without it, finding a treatment or cure for Alzheimer's and other diseases is hopeless.

Among the most dramatic advances in recent decades have been the development of drugs that cure some childhood and adult cancers, the development of drugs that cure hepatitis C, and the development of vaccines

that prevent hepatitis B. The recent National Academies of Sciences, Engineering, and Medicine publications *A National Strategy for the Elimination of Hepatitis B* and C (2017) and *Eliminating the Public Health Problem of Hepatitis B and C in the United States* (2016) put forward a plan to eliminate these two diseases by 2030. The reason that this plan is realistic is the ability of this country's innovation infrastructure to come up with a steady stream of inventions, and this in turn is made by possible by the existence of various incentives.

The impact of vaccines on health has been enormous: Deaths from viruses have been prevented for millions of children globally. The polio epidemic was ended, and vaccines that prevent cancer have been created (cervical cancer via immunization against human papilloma virus strains). In the United States, it is virtually impossible to find a single individual whose personal health or that of a loved one has not benefitted from a medicine or vaccine.

This is the richest period in history for the sciences that are fundamental to medicine. We are well positioned—thanks to our universities, hospitals, and industry (and the interactions among them)—to generate insights and discoveries. Furthermore, we are experienced in translating these insights and discoveries into innovations that truly benefit health. But the scientific enterprise is fragmented and highly vulnerable to a decline in investment in any of the interacting sectors.

In truth, biopharmaceutical research and development is just beginning to take advantage of the explosion of knowledge in science. Unfortunately for patients living today with diseases for which there is no treatment, the era of modern medicine has yet to begin.

WHERE DO OUR MEDICINES COME FROM?

The pharmaceutical and biotechnology industries use insights from research conducted by researchers in universities, government, and other private enterprises to develop new medicines. Inventing a new drug is the longest, most expensive, most regulated, and most risky undertaking of any product-development process in any industry. Nine out of 10 drug candidates that enter clinical trials fail, and only 2 out of 10 recover the cost of capital. Nevertheless, industry in the United States continues to reinvest approximately 10 to 20 percent of its revenues in research and development. This amount outpaces the National Institutes of Health (NIH) research budget by nearly two to one. Even for those familiar with other research-based industries, it is difficult to appreciate just how challenging it is to create a new drug and how real the odds are of failure.

Many point to the reliance of industry on NIH and other government-sponsored basic research. The process of inventing drugs starts with fun-

damental insights, usually obtained in universities and research institutes. Industry relies on these insights, but these discoveries are a long way from actually inventing a drug. Industry supports government-sponsored research through the payment of taxes and the licensing fees it pays for patents (generated through government-funded research) held by universities. It is also worth noting that public funding of basic research likely would not be at its current levels but for the promise that such research will lead to new therapies for the U.S. population.

The biopharmaceutical industry is critically important to improving and maintaining public health and is essential for a future with less disease. The United States is the "medicine chest" for the world. Two-thirds of new drugs in the past decade and more than 80 percent of the drugs in the world's biopharmaceutical pipeline today emerge from the United States. The biopharmaceutical industry is one of the few sectors of the national economy that has a favorable balance of trade.

Drug discovery and development is not like going to the moon. It is not an engineering problem that can be solved by assembling a team of capable engineers and providing sufficient resources. Rather, creating a drug is a problem completely subject to human biology with all its intrinsic complexity, variability, and unpredictability. Drugs work by introducing an agent that perturbs in a favorable direction a physiological process that has taken a wrong turn. Confounding such interventions are the interlocking systems of human biology. The challenge is to favorably perturb the selected pathway without distorting others. If drug invention were simply an engineering problem, then by now we would have a vaccine for AIDS (35 years after the beginning of the outbreak) and a cure for Alzheimer's disease.

New medicines and vaccines are generated and enter clinical practice by a process that is far from perfect but which is not fundamentally broken. Despite its complexity and unpredictability, the current system generates a flow of medicines to address unmet medical needs—the U.S. biomedical enterprise understands the process and it works.

ROLE OF INNOVATION

"Innovation" is an overused term. There is no doubt that innovation is needed in every component of health care: hospitals, clinics, and nursing homes, among others. Most innovations are aimed at improving efficiency while enhancing the quality of medical care. Drugs and vaccines, however, are fundamentally different: they are inventions that we can touch and feel. Society faces an imminent tsunami of health care costs from Alzheimer's and other mental diseases. Among the baby boomer generation, one in nine people will develop Alzheimer's. There are currently 47 million people living with dementia worldwide, a number projected to double every 20

years. Today's $200 billion annual U.S. expenditure on Alzheimer's will balloon to $1 trillion by 2050, siphoning resources from education, social welfare, defense, roads, and other vital areas. Does anyone seriously believe that the impending crisis can be averted by building more efficient hospitals, better health care delivery systems and nursing homes, and higher-quality home care?

The Alzheimer's example illustrates that it is the cost of disease that is expensive. Health care costs are escalating because we are unable to treat or cure so many diseases. Society has only one possible solution: new drugs that change the course of Alzheimer's by arresting, delaying, or preventing the disease. But the record of failure, despite billions of dollars invested, illustrates the need for continued incentives to assume high risk and drive invention: in more than 400 clinical trials of more than 35 agents intended to treat Alzheimer's in the past decade, the failure rate was more than 99 percent. Only 7 percent of the clinical trials have been government-funded; industry has spent $100 billion on Alzheimer's research and development.

During the several-month period in which the committee deliberated, two promising Alzheimer's drugs (from Eli Lilly and Merck & Co., Inc.) experienced major setbacks in clinical trials—setbacks that came after one to two decades of research investment. Given the track record, it is reasonable to ask: who would gamble their own time and money on inventing the next agent without adequate incentives? Yet, Alzheimer's research and development programs continue to receive industry investment. Despite the high-profile setbacks, there has been learning. And with each iteration, the chances of success increase. The extraordinary costs of failure across therapeutic areas must be included when computing the investment needed to generate a successful drug. Even more expensive for society is the cost of doing nothing, and doing nothing would be a moral failing.

Clearly, an effective prevention, treatment, or even cure for Alzheimer's disease would be of great value to patients, their families, and society. But what if we tried to place a price tag on such an agent today? Given the extraordinary cumulative investment already made and now continuing and the risk involved, capping a price today would inhibit future investment. Such an approach also fails to recognize that while the initial price of an Alzheimer's drug might be high, the price will come down dramatically with time (initially from competition and later from generics, as discussed next)—no legislation is needed. It is incentives that are needed to stimulate continued investment. Alzheimer's disease is but one example. We are not at the end of drug discovery; we are just at the beginning. We need new medicines for cancer, cardiovascular diseases, Parkinson's disease, diabetes, and more rare and neglected diseases.

THE ROLE OF PATENTS

This report describes patents as "legal monopolies."[2] The implication is that patent law permits something that otherwise is illegal. And the sense of the report is that the patent mechanism has somehow been co-opted inappropriately by the biopharmaceutical industry. Patents and the protection of intellectual property are the foundation of the modern U.S. economy. Edison obtained patents for electricity and light bulbs—there is a reason that so many utilities have "Edison" in their name. Similarly, we would not have telephones and telephone companies called "Bell" but for patents. The list continues to today and includes computers, iPhones, etc. Patents indeed provide for exclusivity or a "monopoly" for a single biopharmaceutical product, but not for a whole class of therapeutic agents. A reason that drug prices generally fall over time is that patents are narrow enough that other, often closely similar products, can enter the same arena and compete. The competing products are themselves patented. In the U.S. economy, it is straightforward: without patents, there would be no investment; without investment, there will not be any innovation. It is important to remember that patents do not obligate the patent holder to maintain exclusivity. The patents for AIDS drugs were placed in a "patent bank" to enable companies to access them for production for patients in the developing world.

WHAT IS THE PRICE OF A DRUG?

In the United States, even with the recent introduction of expensive cancer and hepatitis C drugs, prescription drugs account for 10 to 15 percent of the total cost of health care, a figure that has been constant over the past 50 years. The prices of drugs in different therapeutic categories rise and fall over time. Yesterday, AIDS drugs were receiving attention; today it is cancer. Tomorrow, it will be a different disease. But the average across categories remains remarkably stable. To provide one example for comparison purposes, the worldwide revenues from one of the new immune oncology drugs, pembrolizumab (Keytruda)—whose list price is approximately $150,000 for a full course of treatment—were $1.4 billion in 2016. In comparison, the revenues of just one cancer hospital in the United States, Memorial Sloan Kettering in New York, was $3.6 billion.

Most of the current discussion on drug prices focuses selectively on the list price of a drug on the day of its introduction into the market. The

[2] As noted in the previous footnote of this appendix, some mismatches remain between the current content of the main report and this response. This is because the main report underwent several rounds of revisions after the dissent was completed. Rather than having one author continue to respond to new revisions, the integrity of the co-authorship of the dissenting statement was maintained. This section on patents is an example of these mismatches.

discussion narrowly revolves around immediate cost to the system. In order to make informed analysis and recommendations, however, we need to expand the boundaries of the pricing discussion in several dimensions: long term versus short term, value versus cost (not list price), and global versus only the United States.

A discussion on pricing needs to begin with the question: What is the price of a medicine? There is no simple answer. Prices for the same drug vary within different sectors of health care in the United States, across regions of the globe, and over time. The launch price falls dramatically with patent expiration. But usually there is also competition along the way that produces large intermediate declines in price. The current debate on drug pricing does not take these built-in substantial falls in price into account; instead it focuses exclusively on a drug's price on day 1. For most new drugs, the patent expires approximately 10 to 12 years after market introduction. At that time, the price generally falls to pennies on the dollar.

Atorvastatin (Lipitor), a leading statin for treating elevated cholesterol, was introduced at more than $5 per tablet. When it became generic, the price fell by 95 percent to 31 cents per tablet. Many prescriptions for a statin in the United States are for generic atorvastatin, a situation likely to continue for the foreseeable future. Alendronate (Fosamax) for osteoporosis was $2.60 daily, but is now 28 cents. These low prices will persist in perpetuity. So what is the accurate cost of these medicines to society—the price on day 1, or the price over decades?

This report states that the value of medicines cannot be calculated at this time because we lack the tools. It is true that "all in" value or savings cannot be readily or accurately determined fully. But there are approximations that are worthy of attention and provide guidance. The U.S. Congressional Budget Office demonstrated that a 1 percent increase in spending on prescriptions yields a 0.2 percent decrease in expense across the much larger base of medical services. This translates to roughly a two-fold return for every dollar spent on drugs, validating the notion that medicines save lives and money.

Informed by these views, it is time to look at medicines not in isolation as a single piece of the health care puzzle, but rather as part of an interlocking system with the patient at its center.

THE FINANCIAL PERFORMANCE OF THE BIOPHARMACEUTICAL INDUSTRY

During our deliberations, the committee sought information on the financial performance of the biopharmaceutical industry. Graphs depicting performance over the most recent 16-year period (with comparison to a cross-section of all U.S. industry) were obtained and included in an earlier

draft of the report.[3] The data, shown below, reveal that the biopharmaceutical industry, on average, performed better than the average of aggregated U.S. industries from 2000 to 2011. But for the past 5 to 6 years, the operating margins and return on capital for the biopharmaceutical industry were considerably worse than the broad industrial average (see Figures A-1 and A-2). This important information, with implications about the potential impact of acutely changing the research-driven biopharmaceutical business model, was not included in the subsequent draft to which this dissenting view responds.

Some will point out that there are companies in the biopharmaceutical sector that perform well above average. That is true. But there are also companies that perform well below average; that's the reason average performance is calculated.

PRINCIPLES AND FINDINGS

This committee was tasked with "ensuring patient access to affordable medicines." Each word in this task is essential. In our view, carrying out recommendations that move money around the complex web of health care or that create revenues or savings for one component without reducing costs to patients would be a futile exercise. The high cost of drugs experienced by patients is not simply and solely the result of biopharmaceutical industry pricing. Pharmacy benefit management (PBM) companies and other intermediaries in the supply chain contribute to patient "out-of-pocket" costs and limit access, as does the unique and idiosyncratic structure of health insurance (both government and private). Unless the interlocking dynamics of this complex system are probed by modeling or pilot programs, the recommendations contained in this report will likely create unintended consequences with long-term impacts on public health.

We note that the report uses the terms "consumer" and "patient" interchangeably. In our view, there is an important difference. Consumers have discretion. In a market, they can choose to buy one product or another or forgo altogether making a purchase. Patients are not in so fortunate a position; patients are financially exposed and vulnerable in a way that is quite

[3] The committee compared the aggregate 16-year trend of selected market parameters (price earnings ratio, gross margin, operating margin, return on capital, basic earnings per share, and the earnings before interest, tax, depreciation, and amortization [EBITDA]) from 2000 to 2016 for the Standard and Poor's (S&P) 500 index and the S&P Pharmaceuticals Select Industry Index. The S&P 500 is widely regarded as the most meaningful single gauge of large-cap U.S. equities and includes 500 leading companies that capture approximately 80 percent of market capitalization. The S&P Pharmaceuticals Select Industry Index comprises stocks in the S&P Total Market Index that are classified in the standard pharmaceuticals sub-industry of the global industry classification. This former index contains 38 companies.

different than a typical consumer. They have a disease that almost always requires that they purchase or copay for a medicine. And the doctor, not the patient, via a prescription determines which product the patient must use (unless a generic version is available). So we, instead, focus our contribution on "patients" and their experience obtaining medicines through insurance and intermediaries.

Making policy recommendations based on the introductory price of drugs fails to recognize the changes in price that occur for virtually all drugs over time. Looking exclusively at the price of a drug on day 1 is viewing reality through a distorted lens. Usually within 12 to 18 months after market entry, competition is introduced and prices fall considerably. (For example, the cost of hepatitis C drugs fell 40 to 60 percent when the first competitor entered the market.) After 10 to 12 years, when a patent expires, the price falls by 95 percent (or more) as generics enter the market. No other component of health care falls so dramatically, not hospital or physician fees. With patent expiry and the switch to generic, society inherits a kind of "annuity": a valuable drug that remains very low-priced for the remainder of its useful life.

We also note that not every patient with a disease needs to be started on a new medicine as soon as it is available. It should be possible to plan the introduction of a medicine into clinical use. Planning to eliminate hepatitis B and C—as called for by the National Academies reports noted earlier—by 2030 is ambitious, but feasible. Planning for elimination by 2020 is not, for both logistical and market reasons. And allowing some time for competition to enter will naturally address some of the financial challenges.

OUR OBSERVATIONS AND SUGGESTED GUIDING PRINCIPLES FOR RECOMMENDATIONS

1. We should remember that every component of the U.S. health care system is more expensive—often by a factor of three to five—than health care systems elsewhere in the developed world. Even dramatic reductions in the cost of medicines will not alone fix the high cost of health care in the United States. A magic wand that made all prescription drugs free of charge would still leave the United States with the most expensive health care system in the world by a wide margin.
2. Out-of-pocket expenses for health care for people in the United States, even those with insurance, are too large, often ruinously so. The notion that forcing patients to have "skin in the game" for prescription drugs will lead to better outcomes and less health expenditure is controversial at best and has been proven incorrect for some common chronic diseases (e.g., diabetes). Any policy

recommendation in this area should connect the dots between the proposed intervention and financial relief to patients.

3. Given the current structure of insurance, with its premiums, deductibles, and copays, even dramatic reductions in drug prices will translate into little financial relief for patients.
4. Research and development is crucially important. It is essential that policy recommendations not sacrifice the future translation of medical advances into new therapies. As a matter of principle, recommendations should either stimulate investments in research and development or be neutral. Given the long-term investment required to invent a drug or vaccine, policies also need to provide stability. Inhibiting investments in research and development would be a mistake with long-term consequences.
5. Recommendations should be modeled before they are made, and pilot programs should be run before full implementation. We cannot afford to make casual recommendations about an ecosystem and industry of critical importance to society.
6. PBMs, 340B hospitals and clinics, and other intermediaries operate with large margins often based on perverse incentives. Little of the savings extracted from manufacturers' discounts and rebates to PBMs are passed on to patients. And those patients least able to afford medicines, namely the uninsured, pay the highest (list) prices.
7. Insurance in the United States is a misnomer; we operate a "cost-sharing" system in which patients directly carry much of the financial burden. Compared with the health insurance provided in virtually every other country in the developed world, our insurance coverage falls short, especially for prescription drugs, and it seems likely that in the future even more expense will be shifted to patients via deductibles and copays.
8. Branded drugs have a limited time on the market as unique products. Competition drives down the cost of drugs, as does the expiration of patent protection. The research and development–driven biopharmaceutical industry is fundamentally different from the generic drug industry. By analogy, those who design new cars are fundamentally different from those who manufacture "after market" replacement parts. The generic industry fulfills 90 percent of drug prescriptions in the United States. Accordingly, it should receive its own set of specific recommendations. The same is true for biosimilars.
9. There has been bad behavior in both the research and development–driven and generic industry. There have been many yearly and semi-yearly double-digit price increases for branded drugs. Neither

price abuse of old drugs with unique market positions nor price abuse of generic drugs should not be tolerated.

10. The impact of recommendations needs to be assessed not only individually but also in aggregate. Recommendations that might appear individually to have moderate effects can collectively overshoot the mark. Taken together, the biopharmaceutical sector is not unusually profitable (as can be seen in Figures A-1 and A-2).

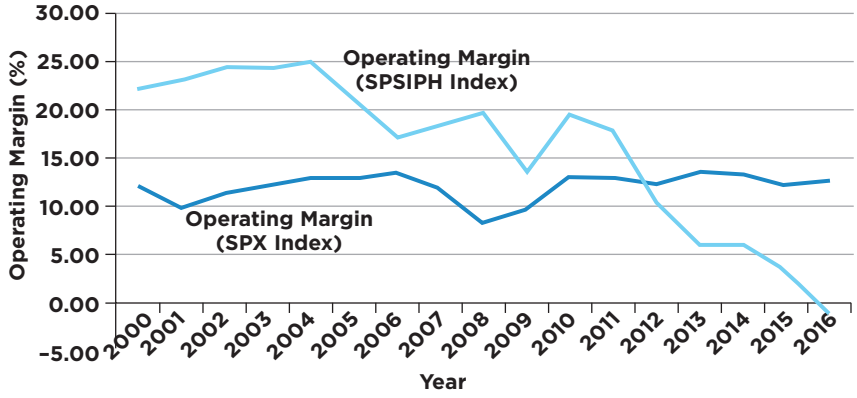

FIGURE A-1 Comparison of the operating margin trend for the S&P 500 and S&P Pharmaceuticals Select Industry, 2000–2016.
SOURCE: Data retrieved from Bloomberg Terminal .NetFrameworkV4 (March 2017).

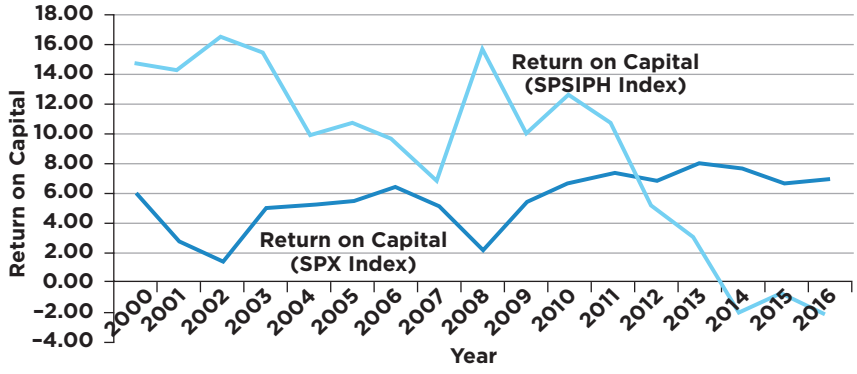

FIGURE A-2 Comparison of the return on capital trend for the S&P 500 and S&P Pharmaceuticals Select Industry, 2000–2016.
SOURCE: Data retrieved from Bloomberg Terminal .NetFrameworkV4 (March 2017).

Removing too much margin will affect its ability to invest. A collection of recommendations that reduce research and development investment by the pharmaceutical, biotech, and venture capital industries should not be made.

11. Ascribing motives and making presumptions and generalizations about the values of an entire industry should not be part of any serious policy recommendations. Veiled threats of future actions, which likely would never be used by the U.S. government, are not helpful in the context of an already intense debate. Advocacy for cooperation and collaboration is likely to be more productive when making recommendations that will require sacrifice across many components of the health care sector.

RECOMMENDED ACTIONS IN THIS REPORT AND OUR ASSESSMENT

1. Transparency is needed at a level that is sufficient—but no more than sufficient—to influence the market forces on key components of the supply chain. The committee has a recommendation calling for publicizing the details provided about relevant financial transactions that go beyond the basic information that is needed and that should be made available. The big three PBMs control approximately 80 percent of prescriptions in the United States and enjoy large margins in their business. They now receive approximately 40 percent of the revenues of the total payment for drugs. Their research and development investment and risk over time do not compare with that of the biopharmaceutical industry, yet they enjoy almost half the revenue from the sale of prescription drugs. Furthermore, they have perverse incentives: the higher the price of the drug, the more profit they make.

   The report fails to realize the large opportunity to reduce drug costs that would result from changes in the U.S. system of PBMs. There is no reason to pay for distribution of a drug based on a percentage of its price. Imagine if one paid FedEx, UPS, or the U.S. Postal Service for delivery of an item based on the value of the package rather than a flat fee. Consider the savings to society if Amazon started a prescription drug delivery business (which might happen). The lack of transparency of PBMs and the nature of their business model permeates almost all aspects of the cost of drugs in the United States. For example, when Mylan raised the price of an EpiPen (generic epinephrine) to $600 per device, there was deserved public outrage. But how many people understood that $300 of the $600 went to PBMs like Express Scripts?

Assessment: Potentially, this represents the largest opportunity among the committee's recommended actions. Transparency would help bring the margins of PBMs and 340B hospital and clinic plans toward a range that is more commensurate with the value they deliver. It might also lower prices from the biopharmaceutical companies. And transparency likely will reduce bad behavior and abuse in the market. Participants in the markets will perform better. If properly structured, this would pass savings on to patients. Importantly, it would not inhibit investments in research and development.

2. Medicare should have the right to negotiate purchase prices of medicines. In reality, prices are already negotiated for a large portion of Medicare Part D through the private insurance companies that provide coverage under Part D to patients.

Assessment: This recommended change alone will create a great change in the dynamics of the market compared with the current situation. Combined with transparency, this recommended action will go a long way toward reducing drug costs; in fact, these two recommended actions alone may prove sufficient to achieve the objectives regarding the cost of medicines. Other government buyers, such as the Veterans Health Administration and Medicaid, should continue to be able to negotiate. This new environment would mirror the private market, which has multiple buyers, each of which negotiates independently. However, allowing all government health plans to negotiate as a single block would establish a near monopoly that would translate into functional price controls. This, in turn, would be likely to have a devastating effect on long-term, high-risk investment.

3. The generic drug industry needs both promotion and further regulation. It has worked exceedingly well at bringing less expensive, but quality-controlled drugs to the United States. However, some monopoly situations have occurred and have been abused. The U.S. Food and Drug Administration should be strengthened to enable more rapid entry (and reduce the backlog) of safe generics into the U.S. market—a good thing for generic companies. The same is true for biosimilars. Generic companies enjoy special legal protection. Given these circumstances, it is reasonable to require generic companies to provide notice (e.g., 1 to 2 years) before terminating the availability of a drug.

Assessment: A stable supply of generic drugs will be available. Monopoly situations and abuse will be diminished. And the incentive for research and development–driven companies to replace products lost to patent expiration will persist or even be intensified.

4. Sickness strikes rich and poor alike. The U.S. insurance system provides only partial coverage and places an inordinate financial burden on the poorest in society. Public and private insurance plans need to be revised and coverage improved. The ongoing shift of drug costs to patients' out-of-pocket expenses must stop. "Doughnut holes" and "tiered pricing" are totally disconnected from good medical practice—they are pure economic constructs and are not oriented to improving health (for many people, they do the opposite). Some of the recommended actions in the report are modeled on the National Health Service of the United Kingdom. People in the United States envy the lower drug prices there. But people of the United Kingdom are often the last or one among the last in Europe to have access to a new drug. For the U.K. subpopulation with cancer, life expectancy is 2 to 4 years shorter than in the United States. Importantly, in national health systems like those in the United Kingdom and other European countries, medicines are provided to patients with no out-of-pocket expense. Access to medicines is severely restricted by the financial burden borne by patients. Patient access would improve dramatically if the financial obligation for patients were truly limited.

Assessment: This is a large opportunity to increase access, improve health, and simultaneously drive innovation. Patient access to affordable medicines will increase. Currently, out-of-pocket cost is a major factor in non-adherence to prescriptions. Non-adherence has been documented to result in poorer health outcomes. With more patients covered, adherence and health will go up. And with increased insurance coverage, industry will have greater incentives to discover drugs for unmet medical needs.

5. Efforts should be made to level the playing field for drug pricing in the developed world. Currently, the United States bears a disproportionate burden for the cost of drugs and the support of innovation, while Europe and other regions do not pay a fair share.

Assessment: Drug prices in the United States might stabilize; European prices would increase. And the biopharmaceutical industry in the United States would be better able to provide drugs at or below cost to the poorer regions of the world.

6. The Orphan Drug Act should be revised, but not exactly in the complicated way recommended by the committee in this report. The act has been very successful in spurring the invention of drugs for rare diseases, but has also created some unintended conse-

quences. The major problems can be readily addressed just by lowering the current requirement to a number lower than 200,000 afflicted patients. An analysis needs to be performed to select the correct number based on medical knowledge and epidemiology, not just economics. This is especially important as we enter the era of precision medicine where new subpopulations of people within a disease category will be identified.

Assessment: Orphan drug designation confers special privilege in the marketplace in terms of exclusivity and opportunity for high prices. Now that the legislation has been in place for more than 30 years, it appears that the limit of 200,000 patients may be too generous and may dilute the intended impact. A lower number would be more in line with the original intent, stimulating initiatives to find drugs for those with rare diseases while enabling market forces to influence price on more new drugs than in the past.

7. Each action recommended in this report needs to be modeled for benefits, trade-offs, and potential unintended consequences. Furthermore, for many recommended actions, pilot programs should be tested after modeling and prior to implementation. Along the same lines, modeling of the impact of the aggregated recommendations needs to be performed.

Assessment:

- Recommendations that provide financial relief to patients will receive top priority.
- The additive or potential synergistic impact of the set of recommendations taken together will be understood.
- Innovation is fragile and too important to diminish or curtail. Modeling and piloting will lessen the chances of unforeseen outcomes.

RECOMMENDED ACTIONS WE CANNOT ENDORSE

We list actions recommended in this report that we cannot support and provide our rationale for opposing them. We doubt that these actions would prove necessary if the actions we recommend in our dissent are implemented.

Each one of the following recommended actions listed below shares common features. If implemented, they would:

- Increase uncertainty about recovering already high-risk research and development investment.

- Substantially decrease the operating margin of the research and development–driven biopharmaceutical industry.
- Decrease or cease venture capital investment in creating new biotechnology companies.
- Decrease the ability to finance existing biotechnology companies.
- Decrease investments in research and development, leading to fewer new therapies and poorer health, as well as an overall long-term increase in health care costs.

The following are the recommended actions that we cannot endorse:

1. Permitting government programs to negotiate individually will create a more conventional and dynamic market, but allowing the government to act as a single buyer across all programs would produce a near monopoly and functional price controls.
2. Allowing the government to exclude a drug from its formulary based on cost alone raises serious moral and ethical issues. Imagine that a new drug is created that effectively treats a condition for which there never has been an effective treatment. Under these circumstances, it is hard to imagine the federal government or insurers telling patients or parents of affected children that the drug will not be made available.

   Exclusion will also discourage investment in research and development. Companies currently assume risk in the research and development portfolio based on being able to (imperfectly) predict the returns on investment. The conditions conducive to investment have always been precarious, but the possibility of a zero return for a drug demonstrated to be safe and effective adds an entirely new dimension of unpredictability and risk. Undoubtedly some medically important research programs would not receive investment as a result.
3. Allowing the U.S. Food and Drug Administration (FDA) to permit importation. The FDA already permits importation of generics and biosimilars. It is the addition of "therapeutically equivalent" products that is new. Is the intention to import drugs made abroad that would be in violation of patents if brought into the United States? If so, we oppose this for the reasons stated at the beginning of this section. If that is not the intention, then importing generic and biosimilar products should be sufficient, and no new recommendation is required other than to encourage speed in the FDA importation approval process without sacrificing the evaluation of safety and efficacy.

Perhaps the intention is to allow enforced therapeutic substitution based on high costs. But substitution of one drug for another creates serious problems. It is not as easy as simply changing the oil in your car or substituting one bottle of pills for another. Imagine that a patient is adequately and stably controlled on a medication for high cholesterol or diabetes. Changing the patient to another medicine will involve communication about the new medicine. In many cases, the doctor will want to see the patient after the switch to make sure that the patient is not experiencing side-effects from the new medicine. In almost all cases, blood tests will be needed to determine if the patient's condition is under control on the new drug. If good control is not obtained, the dose will need to be adjusted, or the patient will need to be switched to yet another medicine. All these maneuvers will cost the health system money. Furthermore, there is evidence that approximately 10 percent of patients who are asked to switch wind up discontinuing the medication; they are then untreated for a condition that requires treatment. This contributes to poorer outcomes and increased costs long term.

4. Special arrangements to import branded drugs is a recommended action by the committee. Drug importation raises safety and practical issues. Four prior commissioners of the FDA have advised strongly against importation. Drug safety cannot be ensured, nor can the stability of the supply. How could a foreign country consistently provide supplies of medicines to the population of the United States that is many times larger than its own? Importation channels also facilitate the entry of counterfeit medicines—both a medical and economic problem in many other countries. Finally, importing drugs based on price translates into importing the pricing mechanism of other countries. Functionally, it translates into importing price controls into the United States.
5. The committee also reminds both the government and the industry that the government holds "march in" rights in certain situations. Such action would be an extraordinary precedent with implications for many industries, not just the biopharmaceutical industry. Marching in, if implemented, would chill for many years, perhaps for decades, the inclination to invest in research and development and to create new biotechnology companies. (Certain South American countries provide vivid examples.) Meanwhile, the outlier behavior that might trigger such action most probably would have soon self-corrected as a result of market pressure and public pressure based on past history.

6. The recommended actions to substantially reduce or curtail direct-to-consumer advertising need to be better understood before making a recommendation. How much does direct-to-consumer advertising contribute to the cost of drugs? Would legislation in this arena be worthwhile in relation to the savings generated? Does direct-to-consumer advertising inhibit patient access or enhance it? The "juice may not be worth the squeeze." And can anything be done without violating the First Amendment of the U.S. Constitution? Even in the presence of direct-to-consumer advertising, it is physicians, not patients, who ultimately decide whether or not to write a prescription. We would want to know much more before endorsing a recommendation in this arena.

OUR CONCLUSIONS

The recommended actions provided in this report could have important societal impacts on health and the cost of health care—impacts that we hope will be positive. We endorse or modify those recommended actions that promise to promote health while generating economic benefit, especially for patients, all the while stimulating research and development investment for the future. However, in our view, several of the report's recommended actions would produce a decline in research and development investments, ultimately leading to increases in health care costs.

Patients are often the "silent partners" without representation in discussions or negotiations concerning pricing. Patients are the most vulnerable financially, especially considering the structure of insurance coverage and its ability to obligate patients to pay despite having no voice. So, in any recommendations we need to keep patients in the spotlight and connect the dots so that any savings that are generated lead to financial relief for patients and improve access to needed medicines and vaccines.

The report's collected recommendations have such potential impact that they should be modeled and piloted before full-scale implementation. Directives for modeling and piloting should have accompanied many of the report's recommendations. Also, an assessment needs to be made of the dynamics and the impact of the collection of recommendations in aggregate. Furthermore, an understanding needs to be obtained of the trade-offs of current versus future benefits.

Whatever is ultimately concluded and recommended, abuse—as seen in the cases of Valeant, Turing, and Mylan—is unacceptable. In each of these examples, the companies chose bad strategies. But the inappropriate behavior was exposed rapidly, and the consequences were severe. So the system worked. Exposure was more rapid and more effective than legislation would likely have been. The examples of these bad business practices

serve as deterrents to other companies considering similar approaches. And when the system does not self-correct, measures should be taken to stop abuse.

Instead of accepting the full set of recommended actions offered by this committee, we have offered in this piece a different set that excludes several of its recommended actions. Our recommended actions include several of the same elements, modified in order to achieve sufficient impact without the same degree of accompanying damage. We wrote this dissent in the hope that it will be favored as a more attractive alternative to achieving the goal of ensuring patient access to affordable medicines.

B

A Minority Perspective

Rena Conti, Stacie Dusetzina, Martha Gaines, Rebekah Gee, Victoria Hale, Peter Sands, and Alan Weil

The charge to this committee was to "address drug price trends, improve patient access to affordable and effective treatments, and encourage innovations that address significant needs in health care." The recommendations in the report are an important step in this direction. We endorse them. However, they do not go far enough. To fulfill our charge of providing recommendations that will ensure access to affordable drugs, we need more ambitious approaches to transparency, value assessments, and pricing.

The committee's report shines a powerful spotlight on the myriad ways in which actors within the biopharmaceutical development, production, and distribution system exploit information asymmetries, misaligned incentives, and market power to maximize profits, often to the detriment of individual patients or society as a whole. Even as the biopharmaceutical industry delivers enormous benefits through the development of new drugs with significant clinical value, the shortcomings of our current approach are apparent. Too many patients cannot afford the drugs they need.

The committee's recommendations take a piecemeal approach to addressing specific flaws in the current system. These changes, if adopted, will remove some market distortions, but will leave many others in place that will continue to be exploited to the detriment of patients. To achieve a more patient-centric system, we need a more comprehensive approach.

MAKING THE BIOPHARMACEUTICAL MARKET WORK FOR PATIENTS

The report claims that "an inherent conflict exists between the desire of patients . . . for affordable drugs and the expectations of . . . biopharmaceutical companies for a competitive return on investment." Framing the problem this way leads to a false choice between affordable access to patients and reasonable financial rewards to biopharmaceutical companies. We reject this premise.

By contrast, we believe a well-functioning biopharmaceutical market is precisely what is needed to achieve the committee's charge. The current biopharmaceutical market displays so many market failures and distortions that marginal improvements in market functioning will be insufficient to achieve the goal of affordable drugs. Taking the view that the method for achieving patient access to affordable drugs is to redesign the regulatory framework that defines the market, we identify three specific areas where the committee's recommendations should be stronger. They are in the areas of transparency, value assessments, and pricing.

TRANSPARENCY

Markets only function effectively when customers have choices: They can switch to another product, or buy nothing. In the biopharmaceutical market, formularies are the mechanism for making these choices. Yet, the current approach to the design and operation of formularies has two significant flaws. First, there is little transparency regarding how formularies are developed. Clinical considerations are paramount, but the methods by which formulary developers make clinical judgments are unknown to the patient. The degree to which financial interests affect choices by pharmacy benefit managers is also unknown. Second, because many formularies, particularly in government-sponsored programs, are legally or effectively precluded from excluding drugs, they rely heavily on tiering: applying different levels of cost sharing to different drugs. Patients cannot exert any force in the market when they are given a price with no relevant information to evaluate their choices.

The committee's transparency recommendations focus on financial flows among manufacturers, intermediaries in the supply chain, clinicians, hospitals, and payers. But transparency regarding the criteria used to determine coverage, pricing, and formulary decisions is also critical. In a market with high levels of information asymmetry and where patients are heavily affected by decisions made by professionals and systems that are opaque to them, payers and other intermediaries should be required to disclose the

methods they use to design and manage formularies and to reveal where and how their decisions relate to their own financial interests.

VALUE ASSESSMENTS

Purchasers in a marketplace make choices based on the value they place on the products they are buying. In other advanced economies, value-based assessment of drugs is seen as a vital tool in formulary design and drug price negotiations. Decisions around coverage, prices, and formulary inclusion are made on the basis of formal assessments of efficacy, comparative effectiveness, and value relative to cost. In the United States, formal adoption of value-based approaches is hampered by legitimate disagreements regarding how to measure value and further compounded by political concerns regarding anything perceived to be rationing care. Yet, since all purchasers must make their decisions on the basis of something, the result is opaque and obscure practices with implicit value assessments that cannot be subject to scrutiny by patients and their clinicians. So long as the methods purchasing intermediaries, hospitals, and payers use to make coverage, pricing, and formulary decisions are opaque, patients and policy makers cannot know whether current arrangements provide value that outweighs the costs to patients and the health care system.

The committee appropriately recommends further testing and refinement of methods for determining the "value" of drugs and using those methods in formulary design and payment policy. This recommendation understates the maturity of those methods as used around the world today and by American payers, intermediaries, physicians, and hospital systems. Its tentative tone belies the reality that, in the absence of such methods, patients are left at the mercy of coverage and pricing decisions that are completely unknown to them. To make the market more patient-oriented, public and private purchasers should adopt value assessment methods, use them systematically, and make them transparent.

PRICING

Our committee chair points out in his preface that drugs that do not exist are of no value. This view captures the importance of sustaining incentives for innovation. Yet, the committee's report does not go far enough in considering how the current drug pricing regime distorts both the incentives for investment in research and development and the way the drugs are deployed once launched.

Current mechanisms for setting drug prices can yield prices that are either too high or too low for achieving optimal public health or optimal investments in innovations that promote public health. Many drugs, par-

ticularly for infectious diseases, create significant positive externalities (e.g., improving the health of others) that are not built into the price. Manufacturers set prices in part based on ability to pay, which is highly variable depending on whether the patient has private insurance, public coverage, or no insurance, even though the disease burden is not evenly distributed across these populations.

Our current system can lead to underinvestment in drugs with substantial public health benefits, such as vaccines, and under-deployment of such drugs when they are developed, as we have seen with therapies that cure hepatitis C. By contrast, the current system creates powerful incentives to invest in research and development of drugs for people with good health insurance even when the incremental value relative to existing therapies is limited.

Direct government funding and purchasing can cure some of the distortions in investment and deployment. Yet, public resources are limited and it is more efficient to harness the power of the market to achieve these social goals. A recent National Academies of Sciences, Engineering, and Medicine study explored alternative public purchasing models for hepatitis C drugs with the goals of increased access and affordability.[1]

The committee appropriately recommends exploration of alternative payment models. Yet, once again the committee's general language downplays what is at stake. Robust value assessments, which include consideration of patient-defined outcomes and public health consequences, should be used when establishing or negotiating drug prices. Such an approach would build in market incentives for actions that guide investment in innovation and the deployment of developed drugs toward improving population health.

CONCLUSION

We reiterate our support for the committee's recommendations. However, we believe the committee could and should have gone further in strengthening and expanding our recommendations to achieve the goals set out in our charge. A more patient-centric biopharmaceutical sector that provides access to affordable drugs is within the nation's reach.

[1] NASEM. 2017. *A national strategy for the elimination of hepatitis B and C: Phase two report*. Washington, DC: The National Academies Press.

C

Glossary

actual acquisition cost (AAC)—The net cost of a drug paid by a pharmacy. A drug's actual acquisition cost includes discounts, rebates, chargebacks, and other adjustments to the price of the drug, but excludes the pharmacy's dispensing fees.

average manufacture price (AMP)—The average price paid to a manufacturer by wholesalers for drugs distributed to retail pharmacies.

average sales price (ASP)—The average sales price is derived from the sales from manufacturers to all purchasers and includes practically all discounts, but is limited in that it is only available for Medicare Part B–covered drugs.

average wholesale price (AWP)—A national average of price paid by pharmacies to purchase drug products from wholesalers in the supply chain.

beta blocker—A drug used to treat high blood pressure, irregular heartbeats, shaking (tremors), and other conditions.

biological products (biologics)*—A category of products regulated by the U.S. Food and Drug Administration, including vaccines, blood and blood components, allergenic compounds, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

* This definition is from the Glossary included in the 2016 National Academies of Sciences, Engineering, and Medicine report *Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine*. Washington, DC: The National Academies Press.

biomarker*—A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic sequences, or pharmacologic responses to an intervention.

catastrophic coverage phase—For example, in 2017 this phase begins when Medicare prescription drug plans and Medicare Advantage prescription drug plans beneficiaries' out-of-pocket costs reach $4,950. During this phase, beneficiaries pay a small coinsurance or copayment for covered prescription drugs for the remainder of the year.

chemotherapy*—Treatment with drugs that kill cancer cells.

clinical endpoint*—A characteristic or variable that reflects how a patient feels, functions, or survives in response to an intervention.

clinical trial*—A formal study carried out according to a prospectively defined protocol that is intended to discover or verify the safety and the effectiveness of procedures or interventions in humans.

coinsurance—The percentage of costs of a covered health care service beneficiary will pay after a deductible has been met.

companion diagnostic*—The U.S. Food and Drug Administration designation for a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. Co-development of a drug and companion diagnostic ensures faster access to promising new treatments for patients.

conflict of interest*—A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.

copays—A fixed amount that a beneficiary will pay for a covered health care service after the deductible has been met.

cost sharing—The share of costs covered by a beneficiary's insurance that he or she will pay out of pocket. This term generally includes deductibles, coinsurance, and copayments, or similar charges, but it does not include premiums, balance billing amounts for non-network providers, or the cost of non-covered services.

deductible—The amount a beneficiary will pay for covered health care services before the insurance plan starts to pay.

discount—A reduction of price granted to specified purchasers under specific conditions prior to purchase.

dispense as written—Written on a prescription by a clinician, indicates that the clinician wants the pharmacy to dispense the brand medication that is written on the prescription pad.

drug take-up—The acceptance of a drug therapy.

FDA approval*—The U.S. Food and Drug Administration (FDA) can approve a device after reviewing a sponsor's premarket approval (PMA) application that has been submitted to the FDA. To acquire approval of a device through a PMA application, the applicant must provide reasonable assurance of the device's safety and effectiveness.

FDA clearance*—The U.S. Food and Drug Administration (FDA) can clear a device after reviewing a sponsor's premarket notification, also known as a 510(k) submission (named for a section in the Food, Drug, and Cosmetic Act), that has been filed with the FDA. To acquire clearance to market a device using the 510(k) pathway, the 510(k) applicant must show that the medical device is "substantially equivalent" to a device that is already legally marketed for the same use.

formulary—An approved list of medications that may be prescribed for a particular hospital, health system, health insurance policy, or pharmacy benefit.

generic substitution—A practice of substituting higher-cost brand drugs with lower-cost generics containing the same active ingredient(s).

health insurance risk pool—Special health insurance coverage programs for individuals whose health status limits their access to coverage in the private individual health insurance market often due to a pre-existing condition.

launch price—The price set by the manufacturer for a new drug when it is first available on the market.

list price—The prices that purchasers display as those at which they are prepared to sell their products and/or the prices regulated by legislation.

march-in rights—Allow the government, in specified circumstances, to require the contractor or successors in title to the patent to grant a

"nonexclusive, partially exclusive, or exclusive license" to a "responsible applicant or applicants."

Medicaid—Medicaid provides health coverage to millions of Americans, including eligible low-income adults, children, pregnant women, elderly adults, and people with disabilities. Medicaid is administered by states, according to federal requirements.

Medicare—Medicare is the federal health insurance program for people who are 65 years or older, certain younger people with disabilities, and people with end-stage renal disease (permanent kidney failure requiring dialysis or a transplant, sometimes called ESRD).

new brands—Products on the market fewer than 24 months during the year reported.

out-of-pocket spending—The expenses for medical care that are not reimbursed by insurance and are the responsibility of the beneficiary to pay. Out-of-pocket costs include deductibles, coinsurance, and copayments for covered services plus all costs for services that are not covered.

patient management*—Decisions about the care and treatment of individual patients, based on information about their disease status and history.

pharmacy benefit managers (PBMs)—Develop and administer drug-benefit plans for employers and health insurers.

phase I clinical trial*—Clinical trial in a small number of patients in which the toxicity and the dosing of an intervention are assessed.

phase II clinical trial*—Clinical trial in which the safety and the preliminary efficacy of an intervention are assessed in patients.

phase III clinical trial*—Large-scale clinical trial in which the safety and the efficacy of an intervention are assessed in a large number of patients. The U.S. Food and Drug Administration generally requires new drugs to be tested in phase III trials before they can be put on the market.

premarket approval (PMA)*—U.S. Food and Drug Administration approval for a new test or device that enables it to be marketed for clinical use. To receive this approval, the manufacturer of the product must submit the clinical data showing the product is safe and effective for its intended use.

premarket notification or 510(k)*—A U.S. Food and Drug Administration review process that enables a new test or device to be marketed for clinical use. This review process requires a manufacturer to submit data showing the accuracy and precision of its product and, in some cases, its analytical sensitivity and specificity. The manufacturer also has to provide documentation supporting the claim that its product is substantially equivalent to one already on the market. This review does not typically consider the clinical safety and effectiveness of the product. (See also FDA clearance.)

protected brands—Products that are no longer "new" and have yet to reach patent expiry.

quality-adjusted life-year (QALY) index*—An index that combines measures of quality of life with length of life.

rebate—A payment made to the purchaser after the transaction has occurred.

safety net—Provision of health care services regardless of the means to pay by the patient. The patient population served includes a large proportion of uninsured, Medicaid, and other vulnerable patients with limited or no access to care.

section 340B—Section 340B of the 1990 U.S. Public Health Service Act provides discounts to qualifying hospital systems for the purpose of subsidizing accessible and affordable medical care among low-income and vulnerable patients.

specialty drugs—General term for medications that feature one or more of the following characteristics: highly expensive, complex molecularly (often derived from living cells), non-standard administration process such as via injection or infusion, limited availability or having a specialized distribution network, or indicated for a rare or complex syndrome.

tier—Prescription drug plans are often organized into different drug tiers. The tier in which a medication is placed determines a patient's proportion of the drug cost.

wholesalers—Drug distribution companies that purchase drugs from the manufacturers and then sell them to pharmacies at negotiated prices.

D

Stakeholder Input

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E

Biographical Information

COMMITTEE MEMBERS

Norman Augustine, M.S.E. (*Chair*), is a retired chairman and chief executive officer of Lockheed Martin Corporation. He has served as an assistant secretary, undersecretary, and subsequently, acting secretary of the U.S. Army. He has been on the faculty of Princeton University and has served as chairman and principal officer of the American Red Cross and as chairman of the Defense Science Board. He has served as a member of the boards of directors of ConocoPhillips, Black & Decker, Proctor & Gamble, and Lockheed Martin. He is a regent of the University System of Maryland and has been a trustee of Princeton University, Massachusetts Institute of Technology, and Johns Hopkins University. He has served for 16 years on the President's Council of Advisors on Science and Technology under both Republican and Democratic presidents. He was also the founding chair of the National Institutes of Health Scientific Management Review Board and chair of the Henry M. Jackson Foundation for the Advancement of Military Medicine. He is a member of the American Philosophical Society and the Council on Foreign Relations and a fellow of the American Academy of Arts and Sciences. He received the U.S. National Medal of Technology, Joint Chiefs of Staff Distinguished Public Service Award, and for five times the U.S. Department of Defense's highest civilian decoration, the Distinguished Service Medal. He is a member of the National Academy of Sciences and a member and former chairman of the National Academy of Engineering. He holds 35 honorary degrees.

Jeff Bingaman, J.D., is a former U.S. senator from New Mexico, serving from 1983 to 2013. He held several committee assignments during his tenure in the U.S. Senate including the Committee on Energy and Natural Resources, Committee on Finance, Joint Economic Committee, Committee on Armed Services, and the Committee on Health, Education, Labor, and Pensions. On the Senate Energy Committee, he has contributed to every major piece of energy policy legislation in the past two decades. Earlier, he worked as a private practice attorney. He served as counsel to the New Mexico Constitutional Convention and was attorney general of New Mexico. He earned his B.A. from Harvard University and his J.D. from Stanford University.

Rena Conti, Ph.D., is an associate professor in the Department of Pediatrics and the Department of Public Health Sciences at The University of Chicago. Her research focuses on financing, regulation, and organization of medical care with an emphasis on biopharmaceutical markets. She serves as an ad hoc advisor to the U.S. Senate's Committee on Finance and the U.S. House of Representatives' Committee on Oversight and Government Reform and has provided congressional testimony on prescription drug shortages. She is an elected member of the Conference on Research in Income and Wealth. She received her Ph.D. in health policy from Harvard University.

Stacie Dusetzina, Ph.D., is an assistant professor at the University of North Carolina (UNC) Eshelman School of Pharmacy's Division of Pharmaceutical Outcomes and Policy. She also has a faculty appointment at the UNC Gillings School of Global Public Health in the Department of Health Policy and Management and is a member of the Lineberger Comprehensive Cancer Center, the Cecil G. Sheps Center for Health Services Research, and the Carolina Health Informatics Program. Earlier, she was an assistant professor in the Division of General Medicine and Clinical Epidemiology in the UNC School of Medicine. Her primary research focus is on assessing the role of health system policies, drug safety warnings, and costs on prescription drug use and the subsequent health outcomes for patients, particularly among individuals with cancer or mental illness. She received her Ph.D. from the UNC Eshelman School of Pharmacy and completed her postdoctoral work in health care policy at Harvard Medical School.

Martha Gaines, J.D., L.L.M., is the founder and director of the Center for Patient Partnerships and a distinguished clinical professor at the University of Wisconsin schools of law, medicine, nursing, and pharmacy. Her work focuses on consumer engagement and empowerment in all aspects of health care, including its reform. She served on the steering committee of National Academy of Medicine's Vital Directions Task Force and the

National Cancer Research Advocates of the National Cancer Institute. She also serves on the board of the American Academy on Communication in Healthcare and has led patient partnership and related initiatives for diverse organizations including the Josiah Macy, Jr. Foundation, National Patient Advocacy Foundation, the Institute of Medicine, and the American Board of Internal Medicine Foundation. She has received numerous awards for her work, including the National American Cancer Society Lane Adams Quality of Life Award, the Chancellor's Hilldale Award for Excellence in Teaching, the Robert Heidman Award for Excellence in Public Service, and the inaugural Health Law Attorney of the Year Award from the Wisconsin State Bar Association. She earned her A.B. at Vassar College and her J.D. and L.L.M. from the University of Wisconsin Law School. She is a long-term survivor of metastatic ovarian cancer.

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Michael Rosenblatt, M.D., is the chief medical officer of Flagship Pioneering. Recently, he served as the executive vice president and chief medical officer at Merck & Co., Inc. Previously, he served as dean of Tufts University School of Medicine and held the appointments of George R. Minot Professor of Medicine at Harvard Medical School, president of Beth Israel Deaconess Medical Center, and director of the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology. Earlier, he was the senior vice president for research at Merck Sharp & Dohme Research Laboratories, where he co-led the worldwide development team for alendronate (Fosamax), Merck's bisphosphonate for osteoporosis and bone disorders. In addition, he directed drug discovery efforts in molecular biology, bone biology, virology, cancer research, lipid metabolism, and cardiovascular research in the United States, Japan, and Italy. He also headed Merck Research's worldwide University and Industry Relations Department. He is the recipient of the Fuller Albright Award for his work on parathyroid hormone, the Vincent du Vigneaud Award in peptide chemistry and biology, and the Chairman's Award from Merck. He has served on the board of directors and scientific advisory boards of several biotech companies. He was a scientific founder of ProScript, the company that discovered bortezomib (Velcade), now Takeda Millennium Pharmaceutical's drug for multiple myeloma and other malignancies. He has served as a founding scientist, scientific advisory board member, or director of more than a dozen biopharmaceutical companies, including ProScript, Millennium, Human Genome Sciences, and Radius Pharmaceuticals. He currently serves on the board of directors of the Flagship company

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Sharyl Nass, Ph.D., serves as director of the Board on Health Care Services and director of the National Cancer Policy Forum at the National Academies of Sciences, Engineering, and Medicine. To enable the best possible care for all patients, the work of the board entails independent, scholarly analysis of the organization, financing, effectiveness, workforce, and delivery of health care, with emphasis on quality, cost, and accessibility. The National Cancer Policy Forum examines policy issues pertaining to the entire continuum of cancer research and care. For 18 years, she has

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Disclosure of Conflicts of Interest

The conflict-of-interest policy of the National Academies of Sciences, Engineering, and Medicine (www.nationalacademies.org/coi) prohibits the appointment of an individual to a committee like the one that authored this Consensus Study Report if the individual has a conflict of interest that is relevant to the task to be performed. An exception to this prohibition is permitted only if the National Academies determine that the conflict is unavoidable and the conflict is promptly and publicly disclosed.

When the committee that authored this report was established a determination of whether there was a conflict of interest was made for each committee member given the individual's circumstances and the task being undertaken by the committee. A determination that an individual has a conflict of interest is not an assessment of that individual's actual behavior or character or ability to act objectively despite the conflicting interest.

Dr. Michael Rosenblatt was determined to have a conflict of interest because he is the chief medical officer for Flagship Pioneering and is a shareholder of Radius (of which he is a founder) and Merck & Co., Inc.

Mr. Henri Termeer was determined to have a conflict of interest because he was former chairman, president, and chief executive officer of Genzyme Corporation and also served on the boards of directors for several pharmaceutical and biotech companies.

Dr. Reed Tuckson was determined to have a conflict of interest because he is a former executive vice president and chief of medical affairs for the UnitedHealth Group.

In each case, the National Academies determined that the experience and expertise of the individual was needed for the committee to accom-

plish the task for which it was established. The National Academies could not find another available individual with the equivalent experience and expertise who did not have a conflict of interest. Therefore, the National Academies concluded that the conflict was unavoidable and publicly disclosed it through the National Academies Current Projects System (www.nationalacademies.org/cp).