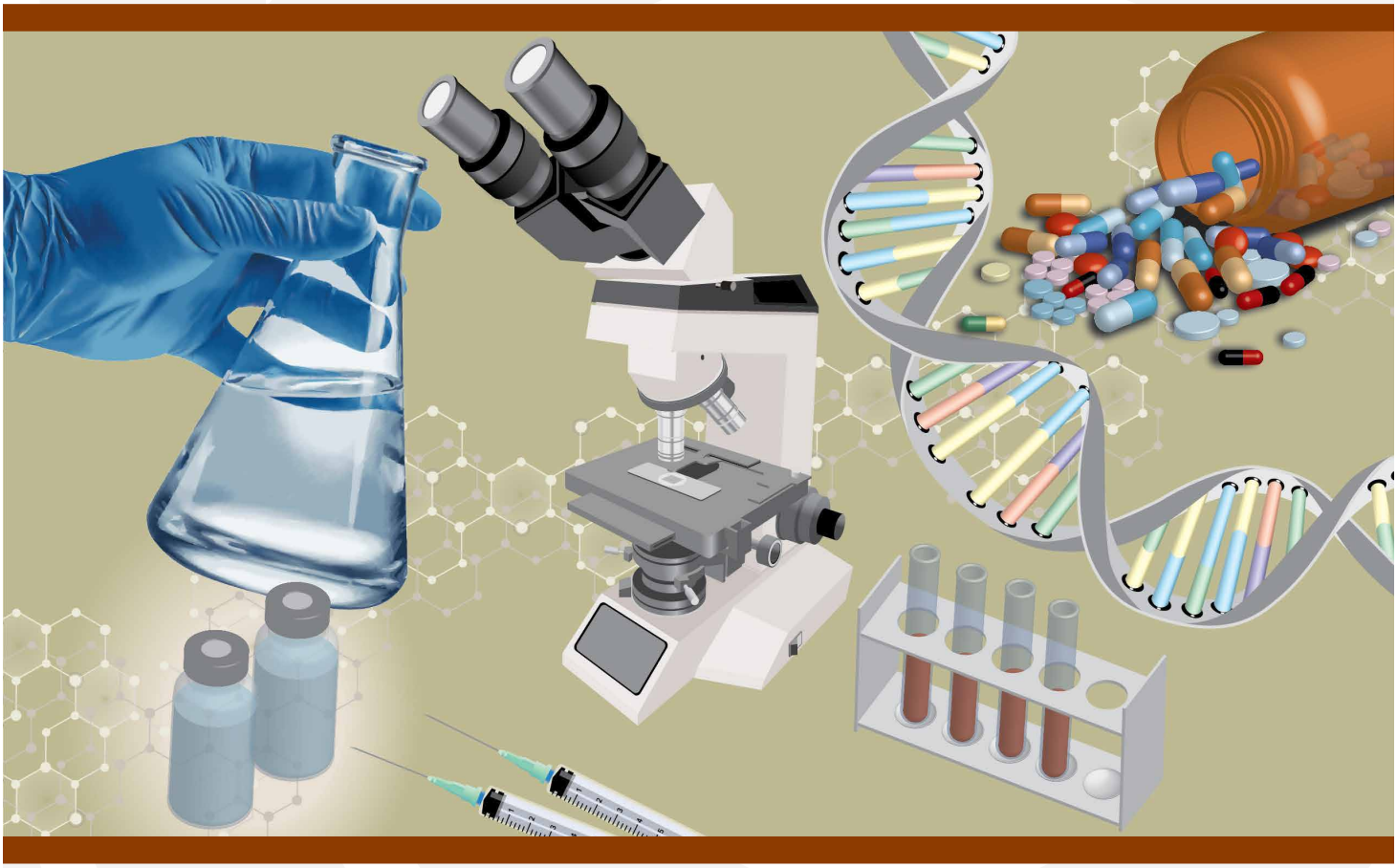
Congressional Budget Office
Nonpartisan Analysis for the U.S. Congress

Research and Development in the Pharmaceutical Industry



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At a Glance

This report examines research and development (R&D) by the pharmaceutical industry.

Spending on R&D and Its Results. Spending on R&D and the introduction of new drugs have both increased in the past two decades.

- In 2019, the pharmaceutical industry spent $83 billion dollars on R&D. Adjusted for inflation, that amount is about 10 times what the industry spent per year in the 1980s.
- Between 2010 and 2019, the number of new drugs approved for sale increased by 60 percent compared with the previous decade, with a peak of 59 new drugs approved in 2018.

Factors Influencing R&D Spending. The amount of money that drug companies devote to R&D is determined by the amount of revenue they expect to earn from a new drug, the expected cost of developing that drug, and policies that influence the supply of and demand for drugs.

- The expected lifetime global revenues of a new drug depends on the prices that companies expect to charge for the drug in different markets around the world, the volume of sales they anticipate at those prices, and the likelihood the drug-development effort will succeed.
- The expected cost to develop a new drug—including capital costs and expenditures on drugs that fail to reach the market—has been estimated to range from less than $1 billion to more than $2 billion.
- The federal government influences the amount of private spending on R&D through programs (such as Medicare) that increase the demand for prescription drugs, through policies (such as spending for basic research and regulations on what must be demonstrated in clinical trials) that affect the supply of new drugs, and through policies (such as recommendations for vaccines) that affect both supply and demand.

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To remove the effects of inflation, the Congressional Budget Office adjusted dollar amounts with the gross domestic product price index from the Bureau of Economic Analysis. Amounts are expressed in 2019 dollars.

Research and Development in the Pharmaceutical Industry

Summary

Every year, the U.S. pharmaceutical industry develops a variety of new drugs that provide valuable medical benefits. Many of those drugs are expensive and contribute to rising health care costs for the private sector and the federal government. Policymakers have considered policies that would lower drug prices and reduce federal drug expenditures. Such policies would probably reduce the industry's incentive to develop new drugs.

In this report, the Congressional Budget Office assesses trends in spending for drug research and development (R&D) and the introduction of new drugs. CBO also examines factors that determine how much drug companies spend on R&D: expected global revenues from a new drug; cost to develop a new drug; and federal policies that affect the demand for drug therapies, the supply of new drugs, or both.

What Are Recent Trends in Pharmaceutical R&D and New Drug Approvals?

The pharmaceutical industry devoted $83 billion to R&D expenditures in 2019. Those expenditures covered a variety of activities, including discovering and testing new drugs, developing incremental innovations such as product extensions, and clinical testing for safety-monitoring or marketing purposes. That amount is about 10 times what the industry spent per year in the 1980s, after adjusting for the effects of inflation. The share of revenues that drug companies devote to R&D has also grown: On average, pharmaceutical companies spent about one-quarter of their revenues (net of expenses and buyer rebates) on R&D expenses in 2019, which is almost twice as large a share of revenues as they spent in 2000. That revenue share is larger than that for other knowledge-based industries, such as semiconductors, technology hardware, and software.

The number of new drugs approved each year has also grown over the past decade. On average, the Food and Drug Administration (FDA) approved 38 new drugs per year from 2010 through 2019 (with a peak of 59 in 2018), which is 60 percent more than the yearly average over the previous decade.

Many of the drugs that have been approved in recent years are "specialty drugs." Specialty drugs generally treat chronic, complex, or rare conditions, and they may also require special handling or monitoring of patients. Many specialty drugs are biologics (large-molecule drugs based on living cell lines), which are costly to develop, hard to imitate, and frequently have high prices. Previously, most drugs were small-molecule drugs based on chemical compounds. Even while they were under patent, those drugs had lower prices than recent specialty drugs have. Information about the kinds of drugs in current clinical trials indicates that much of the industry's innovative activity is focused on specialty drugs that would provide new cancer therapies and treatments for nervous-system disorders, such as Alzheimer's disease and Parkinson's disease.

What Factors Influence Spending for R&D?

Drug companies' R&D spending decisions depend on three main factors:

- Anticipated lifetime global revenues from a new drug,
- Expected costs to develop a new drug, and
- Policies and programs that influence the supply of and demand for prescription drugs.

Various considerations inform companies' expectations about a drug's revenue stream, including the anticipated prices it could command in different markets around the world and the expected global sales volume at those prices (given the number of people who might use the drug). The prices and sales volumes of existing drugs provide information about consumers' and insurance plans' willingness to pay for drug treatments. Importantly, when drug companies set the prices of a new drug, they do so to maximize *future* revenues net of manufacturing and distribution costs. A drug's sunk R&D costs—that

is, the costs already incurred in developing that drug—do not influence its price.

Developing new drugs is a costly and uncertain process, and many potential drugs never make it to market. Only about 12 percent of drugs entering clinical trials are ultimately approved for introduction by the FDA. In recent studies, estimates of the average R&D cost per new drug range from less than $1 billion to more than $2 billion per drug. Those estimates include the costs of both laboratory research and clinical trials of successful new drugs as well as expenditures on drugs that do not make it past the laboratory-development stage, that enter clinical trials but fail in those trials or are withdrawn by the drugmaker for business reasons, or that are not approved by the FDA. Those estimates also include the company's capital costs—the value of other forgone investments—incurred during the R&D process. Such costs can make up a substantial share of the average total cost of developing a new drug. The development process often takes a decade or more, and during that time the company does not receive a financial return on its investment in developing that drug.

The federal government affects R&D decisions in three ways. First, it increases *demand* for prescription drugs, which encourages new drug development, by fully or partially subsidizing the purchase of prescription drugs through a variety of federal programs (including Medicare and Medicaid) and by providing tax preferences for employment-based health insurance.

Second, the federal government increases the *supply* of new drugs. It funds basic biomedical research that provides a scientific foundation for the development of new drugs by private industry. Additionally, tax credits—both those available to all types of companies and those available to drug companies for developing treatments of uncommon diseases—provide incentives to invest in R&D. Similarly, deductions for R&D investment can be used to reduce tax liabilities immediately rather than over the life of that investment. Finally, the patent system and certain statutory provisions that delay FDA approval of generic drugs provide pharmaceutical companies with a period of market exclusivity, when competition is legally restricted. During that time, they can maintain higher prices on a patented product than they otherwise could, which makes new drugs more profitable and thereby increases drug companies' incentives to invest in R&D.

Third, some federal policies affect the number of new drugs by influencing both *demand and supply*. For example, federal recommendations for specific vaccines increase the demand for those vaccines and provide an incentive for drug companies to develop new ones. Additionally, federal regulatory policies that influence returns on drug R&D can bring about increases or decreases in both the supply of and demand for new drugs.

Trends in R&D Spending and New Drug Development

Private spending on pharmaceutical R&D and the approval of new drugs have both increased markedly in recent years, resuming a decades-long trend that was interrupted in 2008 as generic versions of some top-selling drugs became available and as the 2007–2009 recession occurred. In particular, spending on drug R&D increased by nearly 50 percent between 2015 and 2019. Many of the drugs approved in recent years are high-priced specialty drugs for relatively small numbers of potential patients. By contrast, the top-selling drugs of the 1990s were lower-cost drugs with large patient populations.

R&D Spending

R&D spending in the pharmaceutical industry covers a variety of activities, including the following:

- **Invention**, or research and discovery of new drugs;
- **Development**, or clinical testing, preparation and submission of applications for FDA approval, and design of production processes for new drugs;
- **Incremental innovation**, including the development of new dosages and delivery mechanisms for existing drugs and the testing of those drugs for additional indications;
- **Product differentiation**, or the clinical testing of a new drug against an existing rival drug to show that the new drug is superior; and
- **Safety monitoring**, or clinical trials (conducted after a drug has reached the market) that the FDA may require to detect side effects that may not have been observed in shorter trials when the drug was in development.

In real terms, private investment in drug R&D among member firms of the Pharmaceutical Research and

Manufacturers of America (PhRMA), an industry trade association, was about $83 billion in 2019, up from about $5 billion in 1980 and $38 billion in 2000.[1] Although those spending totals do not include spending by many smaller drug companies that do not belong to PhRMA, the trend is broadly representative of R&D spending by the industry as a whole.[2] A survey of all U.S. pharmaceutical R&D spending (including that of smaller firms) by the National Science Foundation (NSF) reveals similar trends.[3]

Although total R&D spending by all drug companies has trended upward, small and large firms generally focus on different R&D activities. Small companies not in PhRMA devote a greater share of their research to developing and testing new drugs, many of which are ultimately sold to larger firms (see Box 1). By contrast, a greater portion of the R&D spending of larger drug companies (including those in PhRMA) is devoted to conducting clinical trials, developing incremental "line extension" improvements (such as new dosages or delivery systems, or new combinations of two or more existing drugs), and conducting postapproval testing for safety-monitoring or marketing purposes.

CBO relied on the PhRMA data because before 2008, the NSF survey did not include domestic firms' R&D spending outside of the United States. (Both the NSF and PhRMA estimates reflect worldwide R&D spending by pharmaceutical companies with operations in the United States.) NSF's estimates of R&D spending since 2008 suggest that PhRMA members' worldwide R&D spending constitutes about 75 percent to 85 percent of the industry total, depending on the year.

In recent years, the pharmaceutical industry's R&D spending as a share of net revenues (sales less expenses and rebates) has increased: Consumer spending on brand-name prescription drugs has risen, but R&D spending has risen more quickly. In the early 2000s, when drug industry revenues were rising sharply, the industry's R&D intensity—that is, its R&D spending as a share of net revenues—averaged about 13 percent each year. Over the decade from 2005 to 2014, the industry's R&D intensity averaged 18 percent to 20 percent each year. That ratio has been trending upward since 2012, and it exceeded 25 percent in 2018 and 2019, the highest R&D intensities recorded by the pharmaceutical industry as a whole since at least 2000. Data are limited for earlier years, but among PhRMA member companies, annual R&D intensities averaged 18 percent from 1980 through 2010 and never exceeded 22 percent.[4] Since then, R&D intensity has increased among PhRMA firms just as it has for the industry as a whole, reaching 25 percent in 2017 before decreasing slightly in 2018. By comparison, average R&D intensity across all industries typically ranges between 2 percent and 3 percent.[5] R&D intensity in the software and semiconductor industries, which are generally comparable to the drug industry in their reliance on research and development, has remained below 18 percent (see Figure 1).

There are several possible explanations for the increase in the industry's R&D intensity over the past eight years. It could reflect the increased role of small drug companies, which have little revenue and, therefore, high ratios of R&D spending to net revenues. It could also indicate that the expected returns from investments in R&D have increased (if market conditions have changed) or that opportunities to develop new drugs have increased (if recent advances in science and technology have been particularly productive). Finally, it could reflect rising costs of R&D inputs, such as capital equipment and skilled labor. CBO has not evaluated the relative importance of those possibilities.

1. See Pharmaceutical Research and Manufacturers of America, *2020 PhRMA Annual Membership Survey* (PhRMA, 2020), https://tinyurl.com/ydh6p64t, and *2019 PhRMA Annual Membership Survey* (PhRMA, 2019), https://tinyurl.com/ycvneve7 (PDF, 2.15 MB).

2. The total includes only research funded by PhRMA member firms, including any contract research funded by those firms and performed on their behalf by universities or other contract-research laboratories. In particular, the PhRMA total does not include expenditures to acquire the R&D assets (such as drugs in development) of another firm.

3. See National Science Foundation, "Business Enterprise Research and Development Survey" (accessed February 25, 2021), www.nsf.gov/statistics/srvyberd/.

4. See Pharmaceutical Research and Manufacturers of America, *2019 PhRMA Annual Membership Survey* (PhRMA, 2019), Table 2, https://tinyurl.com/ycvneve7 (PDF, 2.15 MB).

5. That range applies to average R&D intensity for the approximately 4,000 firms in the Standard & Poor's (S&P) Total Market Index, a combination of the S&P 500 Index and the S&P Completion Index (an index of the total U.S. stock market, excluding firms in the S&P 500). CBO chose the Total Market Index as a basis of comparison because of its breadth.

Box 1.

Large and Small Drug Companies and the "Make or Buy" Decision

Small drug companies (those with annual revenues of less than $500 million) now account for more than 70 percent of the nearly 3,000 drugs in phase III clinical trials.[1] They are also responsible for a growing share of drugs already on the market: Since 2009, about one-third of the new drugs approved by the Food and Drug Administration have been developed by pharmaceutical firms with annual revenues of less than $100 million.[2] Large drug companies (those with annual revenues of $1 billion or more) still account for more than half of new drugs approved since 2009 and an even greater share of revenues, but they have only initiated about 20 percent of drugs currently in phase III clinical trials.[3]

For a large drug company, one option for increasing the number of drugs it expects to introduce is to acquire a smaller firm that is developing new drugs. Over the past three decades, about one-fifth of drugs in development—or the companies developing them—have been acquired by another pharmaceutical company.[4]

When a large company acquires a small drug company or the rights to one of its drugs, it can use its specialized knowledge to increase the value of its acquisition or to diversify its risk of a decline in revenues (from a drug's loss of patent protection, for instance). In making that acquisition, a large company might bring a drug to market more quickly than the small company could have or might distribute it more widely. With the rise of generic drugs, the loss in sales revenues that occurs when a drug's patent expires can leave firms with excess capacity in production. Acquiring a smaller company can help quickly fill that capacity.

The acquisition of a small company by a larger one can create efficiencies that might increase the combined value of the firms by allowing drug companies of different sizes—in terms of the number of researchers, administrative employees, and financial and physical assets—to specialize in activities in which they have a comparative advantage. Small companies—with relatively fewer administrative staff, less expertise in conducting clinical trials, and less physical and financial capital to manage—can concentrate primarily on research. For their part, large drug companies are much better capitalized and can more easily finance and manage clinical trials. They also have readier access to markets through established drug distribution networks and relationships with buyers.

Researchers have found some evidence that such acquisitions by larger drug firms are sometimes motivated by large firms' desire to limit competition. According to a recent study of acquisitions in the pharmaceutical industry, for example, a company was about 5 percent to 7 percent less likely to complete the development of drugs in its acquired company's pipeline if those drugs would compete with the acquirer's existing drugs than it would be otherwise.[5] In a 2017 study of competition and research and development (R&D), the Government Accountability Office cited several retrospective studies of mergers in the drug industry that found such transactions reduced R&D spending and patenting for several years.[6] The reverse was also true: Increases in pharmaceutical industry competition have been found to increase firms' R&D spending.[7]

1. See IQVIA Institute for Human Data Science, *The Changing Landscape of Research and Development* (April 2019), p. 15, https://tinyurl.com/1cm3g2fs.

2. See Ulrich Geilinger and Chandra Leo, *HBM New Drug Approval Report* (HBM Partners, January 2019), p. 16. https://tinyurl.com/yyzze476, (PDF, 1.14 MB). HBM Partners is a Swiss health care investment company.

3. The 30 largest companies have developed 53 percent of drugs approved since 2009, and in 2014, the 25 largest drug companies received more than 70 percent of industry revenues. See IQVIA Institute for Human Data Science, *The Changing Landscape of Research and Development* (April 2019), p. 16, https://tinyurl.com/y2kpxve8; and Government Accountability Office, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals*, GAO-18-40 (November 2017), p. 16, www.gao.gov/products/GAO-18-40.

4. See Colleen Cunningham, Florian Ederer, and Song Ma, "Killer Acquisitions," *Journal of Political Economy*, vol. 129, no. 3 (March 2021), p. 670, http://dx.doi.org/10.1086/712506.

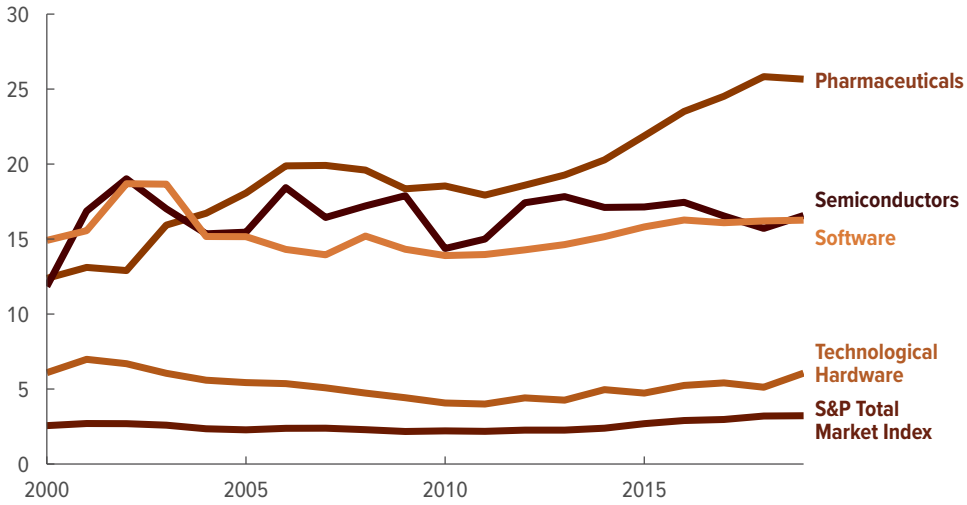
5. Ibid., pp. 649–702.

6. See Government Accountability Office, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals*, GAO-18-40 (November 2017), p. 16, www.gao.gov/products/GAO-18-40. For the individual studies, see Carmine Ornaghi, "Mergers and Innovation in Big Pharma," *International Journal of Industrial Organization*, vol. 27, no. 1 (January 2009), pp. 70–79, https://doi.org/10.1016/j.ijindorg.2008.04.003; and Patricia M. Danzon, Andrew Epstein, and Sean Nicholson, "Mergers and Acquisitions in the Pharmaceutical and Biotech Industries," *Managerial and Decision Economics*, vol. 28, no. 4/5 (June–August 2007), pp. 307–328, www.jstor.org/stable/25151520.

7. See Richard T. Thakor and Andrew W. Lo, "Competition and R&D Financing: Evidence From the Biopharmaceutical Industry," *Journal of Financial and Quantitative Analysis* (forthcoming), http://dx.doi.org/10.2139/ssrn.3754494.

Figure 1.

Average R&D Intensities for Publicly Traded U.S. Companies, by Industry



Pharmaceutical companies have devoted a growing share of their net revenues to R&D activities, averaging about 19 percent over the past two decades. By comparison, other research-intensive industries, like software and semiconductors, averaged about 15 percent.

Data source: Congressional Budget Office, using data from Bloomberg, limited to U.S. firms as identified by Aswath Damodaran, "Data: Breakdown" (accessed January 13, 2020), https://tinyurl.com/yd5hq4t6. See www.cbo.gov/publication/57025#data.

R&D intensity is research and development spending as a share of net revenues (sales less expenses and rebates).

R&D = research and development; S&P = Standard and Poor's.

New Drug Development

Over the past decade, the pharmaceutical industry has introduced growing numbers of new drugs annually (see Figure 2). Between 2010 and 2019, 38 new drugs were approved each year, on average. That is about a 60 percent increase compared with the previous decade. Drug approvals reached a new peak in 2018, surpassing the record number of approvals of the late 1990s. (Counts of new drug approvals are a readily available but imperfect measure of output from the drug industry's R&D spending. The measure does not reflect differences in the effectiveness of the new drugs relative to alternative treatments, or the number of people who might benefit from the new drugs.)

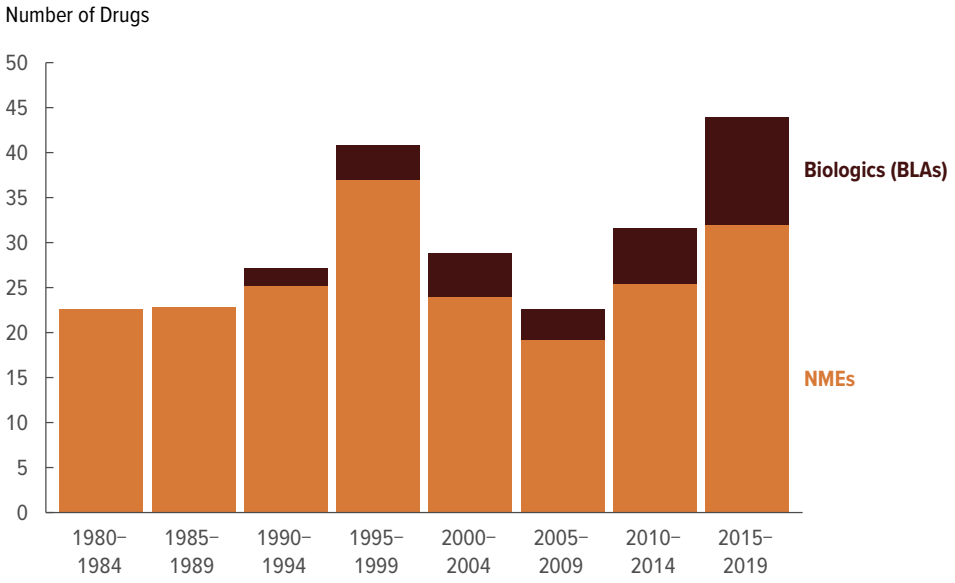
Information about the *kinds* of new drugs the pharmaceutical industry has introduced can be inferred from changes in retail spending across different therapeutic classes of drugs. When ranked by retail spending, therapeutic classes in which many expensive specialty drugs have been introduced over the past decade top the ranking, whereas classes in which the best-selling drugs are now available in generic form rank lower now than they did a decade ago.[6] Information about the kinds of new drugs the pharmaceutical industry may introduce in the future can be inferred from clinical trials under way.

Approval of New Drugs. Over the past five years, both R&D spending and drug approvals have increased substantially. The relationship between them is complex and variable (see Figure 3). Because it can take a decade or more of R&D spending to develop a new drug and successfully shepherd it through clinical trials, drug approvals lag behind the underlying R&D spending. That lag makes it difficult to interpret the relationship between R&D spending and new drug approvals. For instance, drug approvals declined over the 2000s despite steadily rising R&D spending over the preceding years, provoking concerns about a decline in the industry's R&D productivity. Those concerns proved temporary, however. Despite flat R&D spending from 2008 through 2014, drug approvals began to increase around 2012.

6. See Congressional Budget Office, *Prices for and Spending on Specialty Drugs in Medicare Part D and Medicaid* (March 2019), www.cbo.gov/publication/54964.

Figure 2.

Average Annual Approvals of New Drugs by the FDA



From 2015 to 2019, the FDA approved about twice as many new drugs as it did a decade earlier. Biologic drugs make up a growing share of FDA approvals.

Data source: Congressional Budget Office, using data from the FDA's Center for Drug Evaluation and Research and the FDA's Center for Biologics Evaluation and Research. See www.cbo.gov/publication/57025#data.

Until the 1990s, the FDA did not count biologics as a separate category; they were counted with NMEs.

BLA = biologic license application; FDA = Food and Drug Administration; NME = new molecular entity.

That increase in drug approvals does not, by itself, indicate the extent to which the new drugs are particularly innovative (for instance, targeting illnesses in new ways) as opposed to improving only incrementally upon existing drugs. Furthermore, the recent trend of sharply rising R&D spending does not necessarily portend a continued high rate of drug introductions. A decline in clinical trials success rates, for example, could slow the rate of new drug introductions even while R&D spending continued to increase. Additionally, not all R&D spending is directed toward development of new drugs. Drug companies devote some R&D resources to finding effective new combinations of existing drugs, as with newer HIV treatments and preventatives, or to new drug-delivery mechanisms, such as insulin pumps.

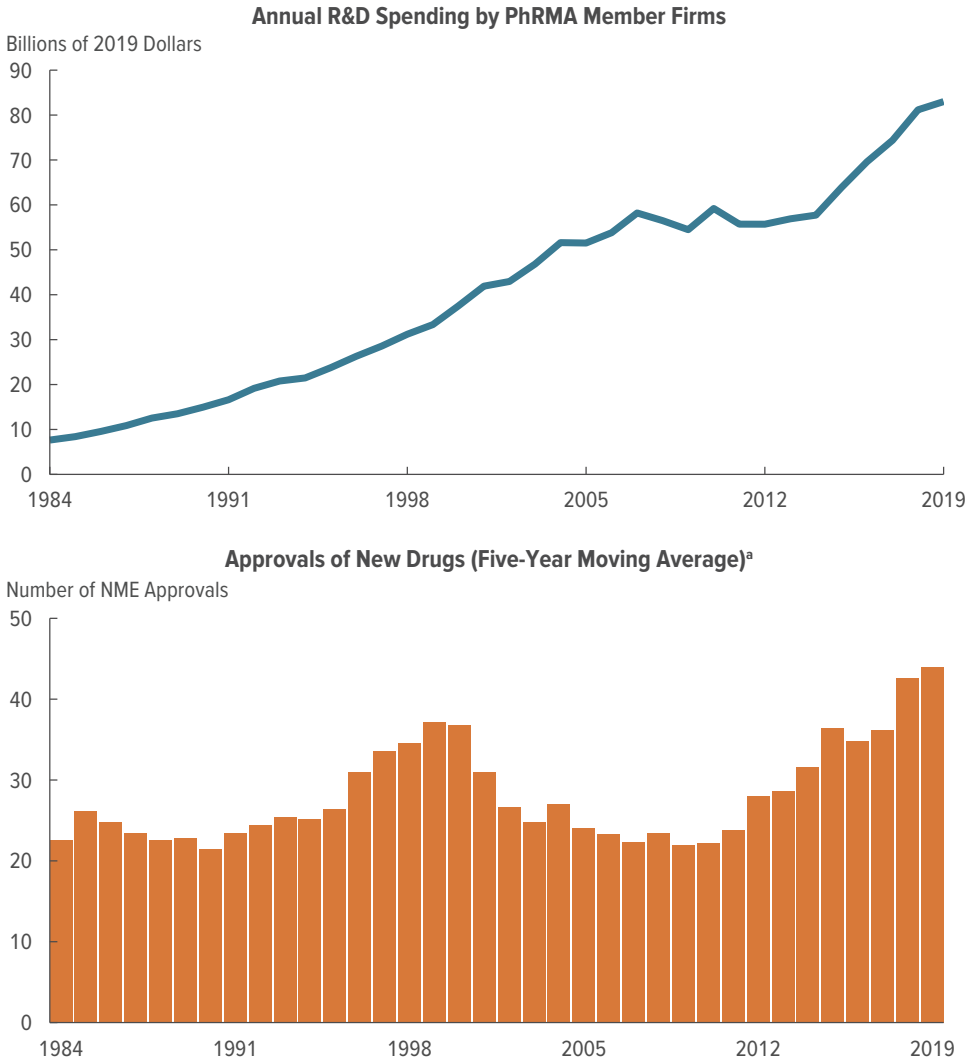
Finally, the rise in the industry's R&D spending does not provide information about the kinds of drugs that may be introduced in coming years. To some degree, that information can be inferred from descriptions of clinical trials currently in progress. But it cannot be known with any certainty which of those drugs will eventually make it to market.

Trends in Recent Drug Spending by Therapeutic Class. New or improved specialty drugs for diabetes, various cancers, autoimmune disorders (such as rheumatoid arthritis or multiple sclerosis), and HIV have propelled large retail-spending increases in the therapeutic classes for those illnesses (see Figure 4). Many of the new specialty drugs are biologics, based on living cell lines rather than chemical active ingredients. For HIV, the new antiretroviral therapies have been combinations of specialty drugs that simplify treatment.

Some of the therapeutic classes that have experienced large spending increases feature new drugs with relatively large populations of patients or new treatments for chronic conditions that can be therapeutically managed but require continued treatment. (As a result, drugs for chronic conditions typically sell in steady quantities.) Other such classes include new drugs with relatively small numbers of potential patients or shorter treatment durations but that have high prices per unit of treatment. High prices may reflect demand that is relatively insensitive to price because of the serious nature of the illness

Figure 3.

R&D Spending and New Drug Approvals



Sustained increases in pharmaceutical R&D spending do not necessarily lead to rising numbers of new drugs. R&D spending also reflects rising costs of labor (skilled researchers) and capital (laboratory technologies).

Data source: Congressional Budget Office, using data from the FDA's Center for Drug Evaluation and Research and PhRMA annual reports (various years). See www.cbo.gov/publication/57025#data.

Data for 1980–1983 are not shown because the five-year moving average cannot be calculated for the first four years of data.

FDA = Food and Drug Administration; NME = new molecular entity; PhRMA = Pharmaceutical Research Manufacturers of America; R&D = research and development.

a. A five-year moving average replaces the value for each year in an annual data series with an average over five consecutive years. (Here the arithmetic mean of each annual value and the preceding four is used.) A moving average is smoother than the underlying data series and is useful for reducing year-to-year changes unrelated to overall trends in the data.

and coverage of those drugs by insurance plans. For example, prices for oncology drugs tend to be high.

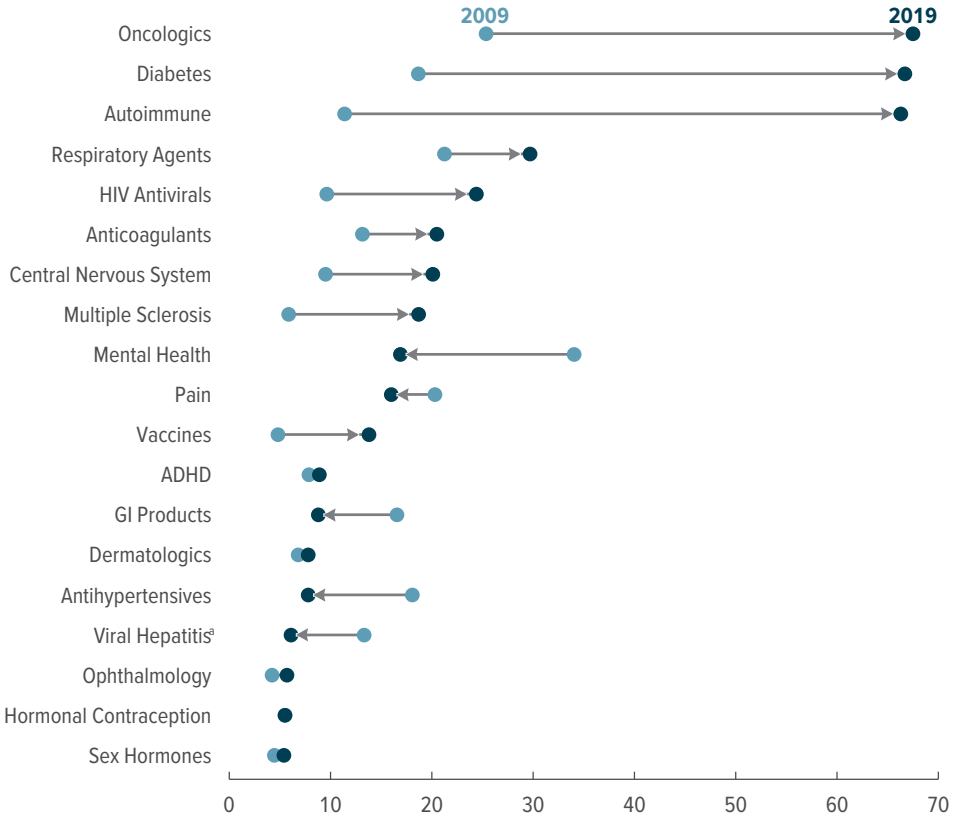
In some cases, observed increases in retail spending overstate increases in net revenues to the manufacturer because they do not account for unobserved rebates.[7] Rebates tend to be higher for drugs for which several

7. Unobserved rebates are paid by manufacturers to insurers or buyers and are considered proprietary information.

Figure 4.

Total U.S. Retail Drug Spending by Therapeutic Class, 2009 and 2019

Billions of 2019 dollars



New drugs can lead to large increases in retail spending because they have higher prices, they are in high demand, or both. Spending decreases can result when patent protection expires on leading drugs and low-cost generic versions are introduced.

Data source: Congressional Budget Office, using data from IQVIA Institute for Human Data Science, *Medicine Spending and Affordability in the United States: Understanding Patients' Costs for Medicines* (August 2020), Exhibit 24, https://tinyurl.com/5655tnoc; IMS Institute for Healthcare Informatics, *Medicines Use and Spending Shifts: A Review of the Use of Medicines in the U.S. in 2014* (April 2015), p. 40, https://tinyurl.com/3bk9oufn, and *Medicine Use and Shifting Costs of Healthcare: A Review of the Use of Medicines in the United States in 2013* (April 2014), Appendix 8, https://go.usa.gov/xsaFR. See www.cbo.gov/publication/57025#data.

Therapeutic classes in the figure are ranked in order of 2019 spending. The figure excludes "other cardiovasculars" (ranked 12th in 2019, with total spending of $10.1 billion) because 2009 data for that class could not be found.

Retail spending overstates actual spending and revenues received by manufacturers, because it does not include rebates paid by those manufacturers.

ADHD = attention deficit hyperactivity disorder; GI = gastrointestinal.

a. Viral hepatitis entered the list of the top 20 therapeutic classes by retail spending in 2014; therefore, spending levels for that year have been substituted for 2009 levels.

competing therapies are available. (Larger rebates correspond with lower net prices.) Thus, rebates on diabetes drugs tend to be considerably higher—as a percentage of the retail price—than they do for oncology drugs, which are not highly substitutable.

Several therapeutic classes that contain top-selling drugs developed in the 1990s experienced decreases in retail spending from 2009 to 2019 as they faced competition from generic versions. Those blockbuster small-molecule drugs include atypical antipsychotics, ACE inhibitors, and proton pump inhibitors. The therapeutic classes containing those drugs—mental health, antihypertensives, and gastrointestinal products, respectively—experienced large declines in retail spending. One therapeutic class, lipid regulators (the class that includes statins), experienced such a decrease that it no longer appears among the top 20, ranked by retail spending. Those declines

reflect widespread use of the new generic versions of those drugs.

One therapeutic class has experienced a decline in retail spending for a different reason. Viral hepatitis only entered the top 20 in 2014, coinciding with the introduction of several highly effective—and high-priced—new treatments for hepatitis C. In contrast to the spending declines described above, the decline in retail spending on viral hepatitis drugs is attributable to a combination of factors. First, newer, lower-priced drugs have since been introduced, lowering the average price in that class as they have gained market share. Second, the number of prescriptions has declined: As the treatments have been administered, the number of potential patients has fallen. That is because the new drugs successfully treat about 95 percent of patients with chronic hepatitis C infection.[8] By contrast, older, less expensive therapies were successful in far fewer patients and had severe side effects in many cases.

Types of New Drugs in Development. Information about the kinds of drugs that may be approved in coming years can be gleaned from data on recent clinical trials. That information suggests that drug companies are emphasizing treatments for cancer and nervous system disorders like Alzheimer's disease and Parkinson's disease. Among human clinical trials in progress as of 2018, drugs in those two therapeutic classes accounted for more than twice as many trials as did drugs in the next three classes combined (vaccines; pain, including arthritis therapies; and dermatologics.)[9]

The 2020–2021 coronavirus pandemic has spurred the development of vaccines to halt the spread of COVID-19, the disease caused by the coronavirus. In addition to R&D spending by the private sector, the federal government has provided support to the private sector to develop vaccines to address the pandemic (see Box 2).

Factors That Influence R&D Spending

Pharmaceutical companies invest in R&D in anticipation of future profits. For each drug that a company considers pursuing, anticipated returns depend on three main factors: the expected lifetime global revenue from the drug (minus its manufacturing and marketing costs), the new drug's likely R&D costs, and policies that affect the supply of and demand for prescription drugs. When the anticipation of future profits is higher, companies invest more in R&D and produce more new drugs, CBO estimates. Similarly, if expectations about prices and profits were lower, companies would invest in less R&D, and fewer drugs would be developed (see Box 3 on page 12).

Anticipated Revenues

A company's expectations about the revenues it could earn from a drug depend on the prices that the company anticipates the drug could command in various markets around the world and the quantities that the company anticipates might be purchased at those prices. Those expectations are informed by the prices and sales volumes observed for existing drugs in various markets. For established drug companies, current revenue streams from existing products also provide an important source of financing for their R&D projects.

How Revenue Expectations are Formulated. A company develops its expectations about a potential drug's lifetime future revenues based on the drug's potential market size, which depends on the prices it might command in sales to different patient groups and in negotiations with payers, domestically and abroad. In that sense, the prices of existing drugs—including variations in prices to different patient populations—help determine R&D spending on future drugs. (The converse is not true: In CBO's assessment, current R&D spending does not influence the future prices of the drugs that result from that spending.)

Revenues generated by existing drugs provide information about the potential market size for new drugs by indicating consumers' and insurance plans' willingness to pay for drug treatments. The number of prescriptions for those drugs support inferences about the number of potential patients, their propensity to use drug therapies at the observed prices, and the popularity of competing therapies.

Sales revenues from other unrelated drugs also help companies form expectations about market size. They reveal information about the magnitude of drug-treatment costs that the market currently tolerates, both in general and for various conditions that will have more or less in common—with regard to duration, severity, or effects on

8. See Department of Veterans Affairs, "Hepatitis C Medications: An Overview for Patients" (accessed March 16, 2021), https://go.usa.gov/xs7qe.

9. See IQVIA Institute for Human Data Science, *Medicine Use and Spending in the U.S.* (April 2018), p. 37, https://tinyurl.com/yd5cnvrl.

Box 2.

Federal Funding to Support the Development of a COVID-19 Vaccine

The federal government can directly support private vaccine development in two primary ways, either by covering the costs of research and development (R&D), or by committing in advance to purchasing a successful vaccine contingent upon a firm achieving specified development goals. Under the first method, the government would supply R&D funding that would ordinarily come from the pharmaceutical firms themselves, from venture capital investments, or from other sources outside the firm. That method might be better suited to cases in which the R&D effort had a relatively high risk of failure and an expected return that would be too low to attract private investment. The rationale for government funding in such cases would depend on whether the expected value to society—rather than to private investors—exceeded the cost of the funding. However, a drawback of such funding is that the outside funder—including the government, in this case—cannot observe the innovator's private costs and may pay more than necessary for developing the vaccine.

Under the second method—that is, agreeing to a future purchase of a specified number of vaccine doses at a specific price—the government would become the source of demand that ordinarily comes from the market. Such an advance-purchase agreement might be preferable in cases in which the government planned to purchase the new product in large quantities regardless of the amount of financial support it provided for R&D. It might also be preferable in cases in which a variety of approaches to developing the product are available, but with much uncertainty about which approach is best. An advance-purchase agreement would also ensure the developer a certain amount of revenues in cases in which the government was supporting the development of multiple, competing products simultaneously. By offering advance purchase contracts to vaccine manufacturers—the promise of future payment conditional on a successful vaccine being developed—the government can provide greater certainty to pharmaceutical firms undertaking risky investments in R&D for vaccines.

In May 2020, the Department of Health and Human Services initiated "Operation Warp Speed," a collaborative effort involving the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the National Institutes of Health, and the Department of Defense, with funding provided through the Biomedical Advanced Research and Development Authority (BARDA). Through Operation Warp Speed, the federal government has provided more than $19 billion in assistance to seven private pharmaceutical manufacturers to develop and produce a vaccine or treatment for COVID-19, the disease caused by the coronavirus (see the table below).[1] As of March 2, 2021, five of those seven companies accepted up-front funding for research and clinical trials. Five of the seven companies accepted advance funding aimed at helping manufacturers ramp up their production capabilities while their potential vaccines were still in development; a sixth accepted funding to develop the capacity to manufacture another firm's vaccine after it received emergency use authorization. Finally, six of the seven manufacturers signed advance-purchase agreements. Two of the companies with vaccines that have received emergency use authorizations have received additional funding for selling more doses than were guaranteed by advance-purchase agreements.

The parallel execution of several stages of development that would usually be conducted in sequence, such as combining phase I and phase II clinical trials or building manufacturing capacity while the trials are still under way, has allowed pharmaceutical manufacturers to advance much more quickly through the development process than is typical for vaccines.[2] One year after the first case of COVID-19 was diagnosed in the United States, three of the vaccines supported by BARDA funding had received emergency use authorizations from the FDA, and two other vaccines were in phase III clinical trials. (It ordinarily takes several years of research and testing before a candidate vaccine enters phase III clinical trials.[3] Seasonal influenza vaccines take much less time to develop and approve because their technologies, and the regulatory and licensing procedures for those vaccines, have been used before.) According to the World Health Organization, more than 200 candidate COVID-19 vaccines were in development in February 2021.[4]

1. Most of the manufacturers have also received research support from or signed advance-purchase agreements with the European Union, several national governments, and two global partnerships supported by foundations and other donors (Coalition for Epidemic Preparedness Innovations and Gavi, the Vaccine Alliance). See, for example, Christopher M. Snyder and others, "Designing Pull Funding for a COVID-19 Vaccine," *Health Affairs*, vol. 39, no. 9 (September 2020), pp. 1633–1642, https://doi.org/10.1377/hlthaff.2020.00646.

2. See Nicole Lurie and others, "Developing Covid-19 Vaccines at Pandemic Speed," *New England Journal of Medicine,* vol. 382 (May 21, 2020), pp. 1969-1973, https://doi.org/10.1056/NEJMp2005630.

3. See Wellcome Trust, "The 5 Stages of Vaccine Development" (accessed January 15, 2021), https://tinyurl.com/y6rxbbuf.

4. See World Health Organization, "COVID-19 Vaccines" (accessed March 24, 2021), https://tinyurl.com/fpdcc777.

Continued

Patent Owner Actelion, EX2014, p. 10
Actelion Pharmaceuticals Ltd.
IPR2025-01139

Box 2. Continued

Federal Funding to Support the Development of a COVID-19 Vaccine

BARDA Funding for COVID-19 Vaccines as of March 2, 2021

Sponsor	BARDA Funding (Millions of dollars)	Funding for Research and Clinical Trials?	Funding for Manufacturing?	Funding to Purchase Vaccine?	Type of Vaccine	Date Entered Phase I Clinical Trials	Date Entered Phase II Clinical Trials	Date Entered Phase III Clinical Trials	Date Received EUA	Doses to be Purchased (Millions)
Pfizer and BioNTech	5,973	No	No	Yes	mRNA	4/29/20[a]		7/27/20	12/11/20	300
Moderna and NIAID	5,896	Yes	Yes	Yes	mRNA	3/16/20	5/29/20	7/27/20	12/18/20	300
Sanofi Pasteur and GlaxoSmithKline	2,073	Yes	Yes	Yes[b]	Spike Protein	9/3/20[a]		*	*	100
Johnson & Johnson (Janssen subsidiary)	1,998	Yes	Yes	Yes	Viral Vector	7/15/20[a]		9/7/20	2/27/21	100
Novavax	1,600	No	Yes	Yes[b]	Protein Subunit	5/25/20[a]		12/22/20[c]	*	100
AstraZeneca and Oxford University	1,600	Yes	Yes	Yes[b]	Viral Vector	4/23/20[a]		8/28/20[d]	*	300
Merck and IAVI	143	Yes	Yes[e]	No	Viral Vector	8/27/20[a]		Discontinued 1/25/21		

Data source: Congressional Budget Office, using data from the Department of Health and Human Services. See www.cbo.gov/publication/57025#data.

BARDA = Biomedical Advanced Research and Development Authority; EUA = emergency use authorization; IAVI = International AIDS Vaccine Initiative; mRNA = messenger ribonucleic acid; NIAID = National Institute of Allergy and Infectious Diseases; * = The vaccine has not yet reached this stage.

a. Phase I and phase II clinical trials combined.

b. Contingent upon receiving emergency use authorization.

c. Phase III trials with South African participants began on August 17, 2020; trials with U.K. participants began on September 28, 2020.

d. Phase III trials with U.K. participants began on June 2, 2020.

e. Funding to manufacture the Johnson & Johnson vaccine.

quality or length of life—with the conditions the new drug would treat.

Expected revenues also depend on anticipated unit sales in different markets around the world. Those quantities are determined by the number of potential patients for the drug in those markets, the shares of those populations that might buy the drug at the prices the manufacturer envisions for those markets (taking into account any substitute drugs that might be available), and the number of prescriptions a course of treatment would require.

Once a new drug has been approved, CBO expects that its developer would set its price in a forward-looking fashion, meaning the price is set to maximize the net revenues from the drug without regard to how much it cost to develop.

Real (inflation-adjusted) pharmaceutical revenues increased sharply from the mid-1990s until around the mid-2000s, when patents on a number of blockbuster drugs expired and lower-cost generic equivalents were introduced. Revenues then declined slightly from the mid-2000s through the mid-2010s, a result of those patent expirations and the 2007–2009 recession. Revenue

Box 3.

Effects of Changes in Expected Profitability on the Introduction of New Drugs

If expected profitability of new drugs declined—because of a change in federal policy, a shift in demand or supply, a revision in the balance of power between drug companies and drug buyers, or for any other reason—the expected returns on drug R&D would decline as well. Lower expected returns would probably mean fewer new drugs, because there would be less incentive for companies to spend on R&D. (If expected profitability were to rise, the opposite effects would occur.) Expectations about returns on R&D partly depend on expectations of prices that future drugs could command—which, in turn, partly depend on current drug prices and influences on those prices.

The Congressional Budget Office's analysis of H.R. 3 in the 116th Congress illustrates those effects. That bill would have required the Secretary of Health and Human Services to negotiate prices for drugs—primarily those for which spending was highest—and to subject manufacturers who did not participate in negotiations to an excise tax. In that analysis, CBO concluded that the bill would reduce drug companies' expectations about future revenues because of the new negotiating leverage of the Secretary. The prospect of such lower revenues would make investments in R&D less attractive to pharmaceutical companies. CBO estimated that under the bill, approximately 8 fewer drugs would be introduced to the U.S. market over the 2020–2029 period and about 30 fewer drugs over the subsequent 10 years.[1] Those estimates were in the middle of the distribution of possible outcomes, in CBO's assessment, and were uncertain. CBO's analysis is in line with a broader literature that has found a positive relationship between drug prices and R&D efforts.[2]

1. See Congressional Budget Office, letter to the Honorable Frank Pallone Jr. regarding the budgetary effects of H.R. 3, the Elijah Cummings Lower Drug Costs Now Act (December 10, 2019), www.cbo.gov/publication/55936.

2. See Margaret E. Blume-Kohout and Neeraj Sood, "Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development," *Journal of Public Economics,* vol. 97 (January 2013), pp. 327–336, https://doi.org/10.1016/j.jpubeco.2012.10.003; Daron Acemoglu and Joshua Linn, "Market Size in Innovation: Theory and Evidence From the Pharmaceutical Industry," *Quarterly Journal of Economics,* vol. 119, no. 3 (August 2004), pp. 1049–1090, https://doi.org/10.1162/0033553041502144; and Pierre Dubois and others, "Market Size and Pharmaceutical Innovation," *RAND Journal of Economics,* vol. 46, no. 4 (Winter 2015), pp. 844–871, https://doi.org/10.1111/1756-2171.12113.

growth returned with the introduction of some expensive new drugs (see Figure 5).

Revenues as Source of Funding for R&D. In the pharmaceutical industry, revenues have traditionally been an important source of R&D financing for established companies with brand-name drugs to sell. Brand-name drugs can generate large volumes of cash because their manufacturing and distribution costs are typically very low relative to their sales revenues. Established companies appear to prefer to finance their R&D with current revenues whenever possible rather than to rely on outside funding sources such as venture capital.[10] Outside financing involves transactions costs as well as other implicit costs, such as compensation for risks borne by outside investors who cannot perfectly monitor a firm's efforts and skills.[11]

The share of R&D funded directly by revenues has declined in recent years because an increasing amount of R&D is now conducted by research-oriented drug companies with few or no products on the market. Over the past decade, small or emerging drug companies have developed a rising share of new drugs. Those companies have relatively little revenue (some have none at all), and most of them must seek outside financing, such as venture capital, and collaborative agreements with larger drug companies. Although venture capital still only finances a small share of the drug industry's R&D spending in total,

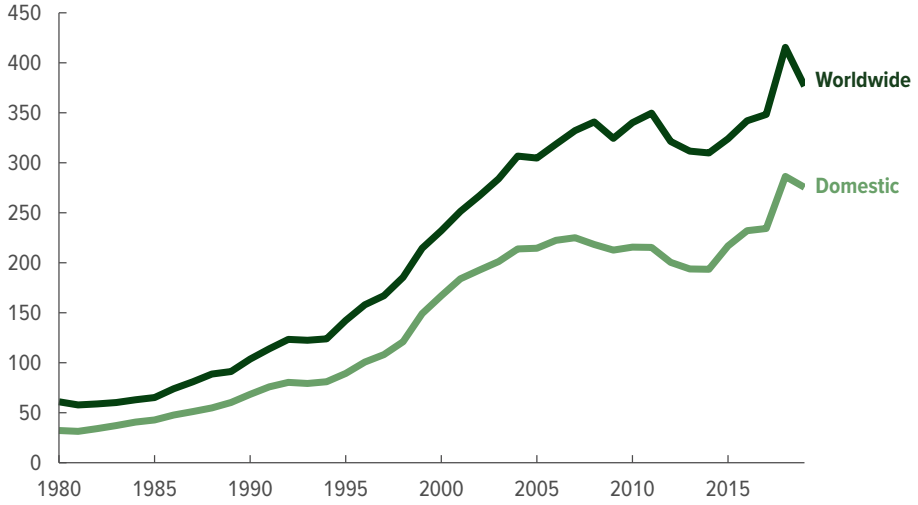
10. See Qi Sun and Mindy Z. Xiaolan, "Financing Intangible Capital," *Journal of Financial Economics,* vol. 133, no. 3 (September 2019), pp. 564-588, https://doi.org/10.1016/j.jfineco.2019.04.003; Bronwyn Hall and Josh Lerner, "The Financing of R&D and Innovation," in Bronwyn H. Hall and Nathan Rosenberg, eds., *Handbook of the Economics of Innovation*, vol. 1 (North Holland, 2010), pp. 609–639; and Thomas W. Bates, Kathleen M. Kahle, and René M. Stulz, "Why Do U.S. Firms Hold So Much More Cash Than They Used To?" *The Journal of Finance,* vol. 64, no. 5 (October 2009), pp. 1985–2021, https://doi.org/10.1111/j.1540-6261.2009.01492.x.

11. See R. Glenn Hubbard, "Capital-Market Imperfections and Investment," *Journal of Economic Literature,* vol. 36, no. 1 (March 1998), pp. 193–225, www.jstor.org/stable/2564955.

Figure 5.

Worldwide and Domestic Revenues of PhRMA Member Firms

Billions of 2019 Dollars



Revenues from drug sales have grown substantially since 1980, although that growth was interrupted by patent expirations of some widely used drugs and by the 2007–2009 recession. Revenue growth has since resumed, in part due to expensive new drugs.

Data source: Congressional Budget Office, using data from PhRMA, *2019 PhRMA Annual Membership Survey*, Table 4 (PhRMA, 2019), https://tinyurl.com/ycvneve7 (PDF, 2.15 MB). See www.cbo.gov/publication/57025#data.

PhRMA revenue data reflect payments received by manufacturers, excluding cash discounts, Medicaid rebates, returns, and allowances for marketing expenses.

PhRMA = Pharmaceutical Research and Manufacturers of America.

it supports a much larger share of the R&D spending of smaller firms than of large established companies.

Drug development also occurs in university research labs. In addition to grants funded by the National Institutes of Health (NIH) that many universities receive for performing basic biomedical research, universities may collaborate with (and be funded by) private drug companies to perform applied research toward the development of new drugs.[12] The funding for that R&D may come predominantly from revenues, as the collaborations typically involve established pharmaceutical companies.[13]

R&D Costs of a New Drug

R&D spending is also influenced by the expected costs of developing a new drug, including those incurred in the preclinical research phase and in clinical trials. In addition to those out-of-pocket expenses, drug companies incur capital costs that result from tying up funds in the drug-development process for years before they generate earnings from those investments. Those capital costs reflect the returns that the funds could have earned if they had been invested in other ways.

Development of a drug that will eventually reach the market often entails a decade or more of R&D expenditures. Each successive phase of clinical trials requires increasing amounts of spending. Drug developers can reassess their commitment at each stage, and a drug's expected value may change as more is learned in clinical trials or as market conditions change—that is, there is an option value to continuing. Companies will not necessarily cancel a drug project even if its likely future costs exceed its likely value when that assessment is made, because the expected value might rise with additional information about the drug or its market.

Pharmaceutical research is inherently risky and canceled or failed projects are a normal part of any drug development program. Companies initiate drug projects knowing that most of them will not yield a marketable drug. Some drugs developed in the preclinical phase never enter clinical trials, and of those that do, only about

12. See Government Accountability Office, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals*, GAO-18-40 (November 2017), p. 36, www.gao.gov/products/GAO-18-40.

13. Ibid., p. 37.

12 percent reach the market (recent estimates range from 10 percent to 14 percent).[14]

Estimates, from multiple sources, of average R&D expenditures per new drug range from less than $1 billion to more than $2 billion. Those estimates all include capital costs as well as expenditures on drugs that did not make it to market. The different estimates are averages over different samples of companies and drugs—that is, they depend on analytical and sampling choices made by the researchers producing those estimates and are best interpreted as illustrative of the general conclusion that developing new drugs is expensive and subject to high rates of failure.

Preclinical Phase. Although drugs spend much less time in preclinical development than they do in clinical trials, a company's total preclinical R&D expenditures typically constitute a considerable share of its total R&D spending. That is because companies typically develop many potential drugs in the preclinical phase that never enter or complete clinical trials. According to one estimate using data provided by large pharmaceutical firms, preclinical development accounted for an average of 31 percent of a company's total expenditures on drug R&D, or $474 million per approved new drug.[15]

When capital costs were taken into account, the share of R&D spending in the preclinical phase rose to 43 percent. Any return on R&D spending on early, preclinical drug development must await successful completion of both the preclinical phase and the clinical trials that follow. As a result, the lag between investment and return is longer for R&D spending that occurs in the preclinical phase than for spending in clinical trials. (For drugs that do not reach the market, no return is realized, although lessons learned from those efforts may aid the development of other drugs.) According to one study, the preclinical phase takes an average of about 31 months, followed by around 95 months, on average, for clinical trials—or about 10.5 years from start to finish.[16] Other estimates differ; in a sample of 10 cancer drugs, for example, one study found that the median time from discovery to approval was 7.3 years.[17] Those numbers are measures of central tendency: Some drugs are brought to market in less time.[18]

Clinical-Trials Phase. The costs to conduct clinical trials on a drug are higher than those to conduct the preclinical phase because trials involve the contributions of many more people for a longer time. Clinical trials occur in several phases:

- Phase I trials (also known as human-safety trials) test a potential new drug at different dosage levels, generally in a small group of healthy volunteers in order to assess its safety in humans. For drugs with high levels of expected toxicity, phase I trial subjects are people with the targeted illness.
- Phase II trials are larger and include only people with the medical condition the drug is intended to treat. Phase II trials assess the drug's biological activity and identify and characterize any side effects.
- Phase III trials are larger still and assess a drug's clinical effectiveness. They can take years to complete. The smaller a drug's expected therapeutic effect relative to a placebo, the larger the number of patients that are needed in the drug's phase III trials so that the drug's true effect (if any) can be distinguished from random variation in patient outcomes.

14. A company can, within limits, influence its own success rate because that rate depends on the kinds of drugs the company chooses to pursue and to advance into clinical trials and on how the company manages its research process. For estimated success rates, see Chi Heem Wong, Kien Wei Siah, Andrew W Lo, "Estimation of clinical trial success rates and related parameters," *Biostatistics*, vol. 20, no. 2 (April 2019), pp. 273–286, https://doi.org/10.1093/biostatistics/kxx069; David Thomas and others, *Clinical Development Success Rates 2006–2015* (Biotechnology Innovation Organization, Amplion, and Biomedtracker, 2016), https://tinyurl.com/y2n8rnzb (PDF, 4.02 MB); and Michael Hay and others, "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology*, vol. 32, no. 1 (2014), pp. 40–51, https://doi.org/10.1038/nbt.2786.

15. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics,* vol. 47 (May 2016), p. 25, https://doi.org/10.1016/j.jhealeco.2016.01.012. The estimate reported in that study is $430 million in 2013 dollars.

16. Ibid., p. 23.

17. See Vinay Prasad and Sham Mailankody, "Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval," *JAMA Internal Medicine,* vol. 177, no. 11 (November 2017), pp. 1569–1575, https://doi.org/10.1001/jamainternmed.2017.3601.

18. See Barbara Bolten, "Fastest Drug Developers and Their Practices," *The CenterWatch Monthly,* vol. 24, no. 8 (August 1, 2017), www.centerwatch.com/articles/13284%20.

- Phase IV trials (also known as pharmacovigilance trials) may be conducted after a new drug has reached the market. They look for side effects not seen in earlier trials and measure a drug's efficacy over longer periods of use than were studied in earlier trials.

Generally, only drugs that have successfully navigated the first three phases can be considered for FDA approval, although regulators sometimes approve new drugs without a phase III trial. (Of the 59 drugs approved in 2018, 7 did not undergo phase III trials before approval.)[19] In some cases the FDA may require a phase IV trial after the drug is approved to detect adverse reactions that might not be observed until a drug is in wider use. Drug companies also might choose to conduct phase IV trials to show (for marketing purposes) the superiority of their product over other available drug therapies.

Few of the drugs that enter clinical trials are ultimately approved; some fail in clinical trials, and others are set aside when a company decides to focus on more promising drugs. In a few cases, drugs submitted for approval are rejected by the FDA. In one sample of drugs in clinical trials, researchers found that for every 100 drugs entering phase I trials, around 60 advanced to phase II trials, just over 20 entered phase III trials, and only about 12 gained FDA approval.[20] Such winnowing is reflected in the average R&D cost per approved drug, which includes all of the R&D spending on drugs that do not reach the market.

Costs tend to rise in each successive phase of development. In the sample just described, companies spent an average of about $1,065 million in clinical trials per approved new drug (more than twice the amount spent in the preclinical research phase). Spending averaged $28 million in phase I, $65 million in phase II, and $282 million in phase III.[21] For each drug that completed the first three phases of clinical trials, the average total cost of those trials was about $375 million.

The remaining $690 million (of the $1,065 million in average total spending on clinical trials) reflects companies' contemporaneous spending on drugs that failed in clinical trials or were otherwise set aside.

Capital Costs of R&D. In addition to the cost of preclinical research and clinical trials, drug companies incur costs by forgoing other opportunities for investment with money spent on clinical trials. Because drug companies' R&D spending on a drug occurs over many years, those capital costs are substantial and can approach the value of actual R&D expenditures to develop a new drug.

Estimates of Total R&D Costs. Three recent studies have estimated the average R&D cost per new drug. They all measure R&D costs the same way: They add up all of the R&D spending by each company in their sample—not only its spending on the sampled new drug but the company's spending on other drugs that were being developed at the same time but that did not reach the market. The studies also all apply a cost-of-capital adjustment to each company's R&D spending to reflect the lag between investment and return on investment.[22] Despite their methodological similarities, the studies' estimates range from $0.8 billion to $2.3 billion of R&D spending per new drug.

Differences in sample selection and data sources appear to be important sources of variation in those estimates. The largest estimate, $2.3 billion (from a 2016 study, expressed here in 2019 dollars), includes around $900 million in preclinical research spending and $1.4 billion for clinical trials.[23] Those estimates are based

19. See IQVIA Institute for Human Data Science, *The Changing Landscape of Research and Development* (April 2019), p. 7, https://tinyurl.com/y2kpxve8.

20. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (May 2016), pp. 23–24, https://doi.org/10.1016/j.jhealeco.2016.01.012.

21. Ibid., pp. 24–25. The corresponding values in the study, reported in millions of 2013 dollars, are $965, $25.3, $58.6, and $255.4, respectively.

22. The values reported here all use a 7 percent cost of capital, as each study includes calculations that use that rate. (In its analysis of the budgetary effects of H.R. 3 for the 116th Congress, CBO used an 8.1 percent cost of capital for drug R&D because that is CBO's assessment of the cost; using a higher rate tends to slightly increase estimates of R&D costs.) See Congressional Budget Office, letter to the Honorable Frank Pallone Jr. regarding the budgetary effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act (December 10, 2019), www.cbo.gov/publication/55936. CBO has converted the values reported here to 2019 dollars.

23. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (May 2016), p. 26–27, https://doi.org/10.1016/j.jhealeco.2016.01.012. The values reported in the 2016 DiMasi study, in millions of 2013 dollars and using their central discount rate value of 10.5 percent, are $2,558, $1,098, and $1,460, respectively.

on a sample of 106 randomly selected drugs from 10 large pharmaceutical firms, 5 of which are ranked among the industry's top 10 by sales revenues, with an additional 3 ranked in the top 50 but outside the top 25.[24] That widely cited study is the latest in a series of similar studies the authors have published over the past three decades. Because the R&D expenditures reported by the sampled firms are not publicly available, it is difficult to evaluate the extent to which the results of those studies are affected by the selection of the sample and other aspects of the method of collecting data.[25] An independent effort to replicate an earlier iteration of the study found similar results, however.[26]

The second study, which was conducted in part to provide an alternative to those 2016 estimates, found an average R&D cost of $1.2 billion (expressed here in 2019 dollars), with expenditures for individual drugs ranging from $137 million to $5.8 billion.[27] That upper bound, based on one outlier drug accounting for $2.2 billion in actual R&D outlays and $3.6 billion in capital costs, skews the average estimate upward. The *median* R&D cost, unaffected by the outlier, is $0.9 billion.

The sample in that study consisted of 63 drugs (developed by 47 different companies) out of the 355 drugs that the FDA approved between 2009 and 2018. R&D expenditure data for those 63 drugs are publicly available (unlike the data used in the 2016 study). The sample skews toward smaller firms—although the same is now true of drug development generally—and the authors caution that their sample may overrepresent drugs approved between 2014 and 2018 and those in certain therapeutic areas, first-in-class drugs, orphan drugs, and therapeutic agents that received accelerated approval. The R&D data include the companies' spending on drugs that did not reach the market.

In the third study, researchers limited their sample to new cancer drugs from companies with no previously approved products. They found an average cost of $0.9 billion per approved drug (expressed here in 2019 dollars).[28] Notably, that study excluded R&D spending by firms that had not developed any approved drugs, and thus the study underestimates R&D spending on failed drugs and, by extension, expected costs per new drug. Median observed R&D costs in that sample were about $0.8 billion per new drug, with estimates for individual drugs ranging from about $212 million to $2.7 billion including capital costs. Those estimates include the developers' total R&D spending while the approved drugs were under development, including that on failed drugs.

Trends in R&D Costs. R&D costs have increased by about 8.5 percent per year over roughly the past decade.[29] The increase in average R&D costs might reflect changes in the kinds of drugs being developed or in the number of drugs in costly clinical trials. If success rates for new biologic drugs were lower than for traditional, small-molecule drugs, or if R&D spending on failed drugs was higher for biologics, that would also contribute to higher average R&D costs.

Some evidence suggests that average success rates may indeed have declined. The 2016 study found that fewer

24. Ibid., p. 20.

25. For a critical review of the 2016 study by DiMasi and others, see Sammy Almashat, "Pharmaceutical Research Costs: The Myth of the $2.6 Billion Pill" (Public Citizen, September 2017), https://tinyurl.com/y4kb4xoq.

26. See Christopher P. Adams and Van V. Brantner, "Estimating the Cost of New Drug Development: Is It Really $802 Million?" *Health Affairs*, vol. 25, no. 2 (March/April 2006), pp. 420–428, https://doi.org/10.1377/hlthaff.25.2.420.

27. See Olivier J. Wouters, Martin McKee, and Jeroen Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018," *Journal of the American Medical Association,* vol. 323, no. 9 (2020), pp. 844–853, https://doi.org/10.1001/jama.2020.1166. The study's central published values differ from those reported above: they are expressed in 2018 dollars and use a 10.5 percent cost of capital. The authors also estimated R&D costs using a 7 percent discount rate.

28. See Vinay Prasad and Sham Mailankody, "Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval," *JAMA Internal Medicine,* vol. 177, no. 11 (November 2017), pp. 1569–1575, https://doi.org/10.1001/jamainternmed.2017.3601. The estimates reported in the study are in 2017 dollars.

29. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (May 2016), p. 20, https://doi.org/10.1016/j.jhealeco.2016.01.012. The estimate is based on the authors' comparison of their 2016 findings with an estimate they published in 2007 ($1.2 billion, in 2005 dollars) using the same methods. See Joseph A. DiMasi and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, vol. 28, no. 4-5 (June–August 2007), pp. 469–479, https://doi.org/10.1002/mde.1360.

than 12 percent of the drugs entering phase I clinical trials ultimately reached the market, but it reported success rates in excess of 20 percent for drugs developed in the 1980s and 1990s.[30] However, other evidence suggests that the overall success rate of clinical trials has not declined.[31]

Another possible factor in rising R&D costs is that it has become harder to recruit candidate patients into some kinds of clinical trials.[32] For example, prospective patients might be less interested in taking a chance on untested treatments in clinical trials when approved treatment options are relatively effective already. And, in some therapeutic classes, it has become more difficult to demonstrate that a new drug would improve on the existing standard of care. For example, advances in oncology treatments have extended cancer patients' expected lifespans. As a result, clinical trials on potential cancer drugs have had to be expanded or extended so that the treatment effect on the lifespans of patients can be estimated with suitable precision. That is, because oncology treatments have become more effective, it now takes longer, on average, to observe a given number of deaths in a clinical trial.[33]

Public Policy

Federal policy influences pharmaceutical companies' R&D spending, both in magnitude and direction. (Policies in other countries and at other levels of government can also affect such spending. Those policies are outside the scope of this report.)

Policies around federal health care programs and subsidies most directly affect the *demand* for new drugs. Other policies affect the *supply* of new drugs (federal support for basic research, tax treatment of R&D spending, and those policies that affect market exclusivity). Still other areas of federal policymaking affect both *supply and demand* (vaccine policies and regulatory policies).

Changes in policy that increased the demand for pharmaceuticals or encouraged their supply would tend to make R&D activity a more attractive investment. Policy changes in the opposite direction could make it a less appealing one.

Federal Health Care Programs and Subsidies. A variety of federal health care programs and subsidies increase demand for health care services and products, including prescription drugs. Such initiatives indirectly stimulate spending on drug R&D. In particular, the federal government—through Medicare, Medicaid, TRICARE, the Veterans Health Administration, the Children's Health Insurance Program, and health insurance marketplaces established by the Affordable Care Act—purchases or subsidizes the purchase of a substantial number of prescription drugs on behalf of retirees, veterans, persons with disabilities, and low-income households. Taken together, federal and state expenditures on prescription drugs accounted for about 40 percent of total U.S. retail expenditures on prescription drugs in 2019.[34]

Changes to those programs would influence R&D spending. For instance, when Medicare Part D (Medicare's prescription drug benefit) was implemented in 2006, sales of prescription drugs to enrollees increased considerably. In addition, for Medicare enrollees with full Medicaid benefits, coverage of prescription drugs shifted from Medicaid to Medicare Part D, increasing the average prices paid for those enrollees' brand-name drugs. Those increases in current and anticipated revenues encouraged the industry to develop new drugs for the Medicare population. Between 2003 and 2010, the number of drugs entering phase I clinical trials increased by roughly 50 percent in therapeutic classes with

30. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (May 2016), Table 1, https://doi.org/10.1016/j.jhealeco.2016.01.012.

31. See Chi Heem Wong, Kien Wei Siah, and Andrew W. Lo, "Estimation of Clinical Trial Success Rates and Related Parameters," *Biostatistics*, vol. 20, no. 2 (April 2019), pp. 273–286. https://doi.org/10.1093/biostatistics/kxx069; and Jorge Mestre-Ferrandiz, Jon Sussex, and Adrian Towse, *The R&D Cost of a New Medicine* (Office of Health Economics, United Kingdom, 2012).

32. See Anup Malani and Tomas J. Philipson, *Can Medical Progress Be Sustained? Implications of the Link Between Development and Output Markets*, Working Paper 17011 (National Bureau of Economic Research, September 2012), www.nber.org/papers/w17011.

33. See Darius N. Lakdawalla, "Economics of the Pharmaceutical Industry," *Journal of Economic Literature,* vol. 56, no. 2 (June 2018), p. 401, https://doi.org/10.1257/jel.20161327.

34. See Centers for Medicare & Medicaid Services, National Health Expenditures Data, "NHE Tables" (accessed December 16, 2020), Table 16, https://go.usa.gov/xASdV. In the table, the sum of expenditures by Medicare, Medicaid, and "Other Health Insurance Programs" (primarily the Veterans Health Administration, TRICARE, and the Children's Health Insurance Program) accounts for 40 percent of total retail expenditures on prescription drugs in 2019.

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relatively high sales to Medicare enrollees. That increased development activity eventually led to increases in the number of drugs in those classes.[35]

The federal government also increases demand for prescription drugs by subsidizing employment-based health insurance: An employer's contribution toward the cost of that coverage is excluded from an employee's taxable income, effectively reducing its price to the employee. As a result, many people select more generous health insurance coverage than they otherwise would, which increases their spending on health care (including prescription drugs) and indirectly stimulates pharmaceutical R&D. That stimulus would disappear if the tax subsidy on employment-based health insurance was eliminated. The size of the effect that would have on R&D spending would depend on how the elimination of the subsidy would affect individuals' choices of health insurance coverage.[36]

Support for Basic Research. The federal government is the primary funder of basic research in biomedical sciences. That research ultimately increases the supply of new drugs because drug companies rely on the findings from that research—for example, the identification of disease targets toward which new drug therapies can be aimed. That basic research creates knowledge that, in effect, reduces private companies' R&D costs and stimulates private investment in R&D, because it expands the set of potentially profitable drug development opportunities. In particular, increases in basic health-related research at the NIH or other federal research agencies have been found to increase private drug R&D in therapeutic classes related to that basic research.[37]

The rationale for public investment in basic biomedical research is that private firms' incentives to invest in it are muted. Basic research generates knowledge (such as the identification of a disease target) that is not readily embodied in a marketable product (such as a drug). The more of that information a company could keep to itself, the greater its value to the company—and the stronger the company's incentive would be to invest in that research. But because information can be communicated at low cost, it can be difficult to contain within a firm. Private companies tend to be reluctant to conduct basic research such as identifying a new disease target, because it would be difficult to keep much of the value of that discovery for themselves. For example, once a disease target is known, multiple companies (not just the company that identified it) might be able to develop drugs aimed at that target. That weakens private incentives to invest in basic research and, as a result, private firms do too little of it from the perspective of society as a whole (meaning that the social benefit if they performed additional basic research would be greater than the cost).

The Role of NIH-Funded Research. In the past two decades, federal funding for NIH has totaled over $700 billion.[38] Much of that funding has supported basic research (in genomics, molecular biology, and other life sciences) that has identified new disease mechanisms. Federal support for NIH nearly doubled between 1995 and 2003, rising from $18 billion to about $37 billion (see Figure 6). Federal funding for NIH declined (in inflation-adjusted dollars) each year from 2003 to 2015, when that funding was about $33 billion. With real annual increases over the subsequent five years, funding for NIH reached $41 billion in 2020.

Between 2010 and 2016, every drug approved by the FDA was in some way based on biomedical research funded by NIH.[39] In many cases, new drugs targeted a

35. See Margaret E. Blume-Kohout and Neeraj Sood, "Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development," *Journal of Public Economics,* vol. 97 (January 2013), pp. 327–336, https://doi.org/10.1016/j.jpubeco.2012.10.003; and David Dranove, Craig Garthwaite, and Manuel I. Harmosilla, *Expected Profits and the Scientific Novelty of Innovation*, Working Paper 27093 (National Bureau of Economic Research, May 2020), www.nber.org/papers/w27093.

36. For an analysis of likely effects of such a policy change on individuals' decisions about health insurance and consumption of health-care services in general, see Congressional Budget Office, *Options for Reducing the Deficit: 2019 to 2028* (December 2018), pp. 235–236, www.cbo.gov/publication/54667.

37. See Margaret E. Blume-Kohout, "Does Targeted, Disease-Specific Public Research Funding Influence Pharmaceutical Innovation?" *Journal of Policy Analysis and Management*, vol. 31, no. 3 (Summer 2012), pp. 641–660, https://doi.org/10.1002/pam.21640; and Michael R. Ward and David Dranove, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry,* vol. 33, no. 1 (January 1995), pp. 70–87, https://tinyurl.com/z7huxuxv.

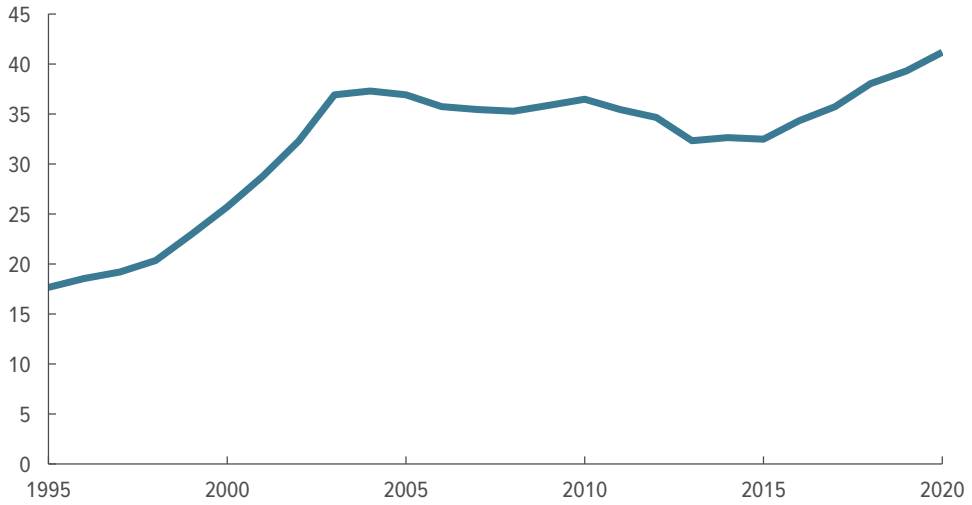
38. See Kavya Sekar, *National Institutes of Health (NIH) Funding, FY1995–FY2021,* Report R43341, version 39 (Congressional Research Service, May 12, 2020), https://go.usa.gov/xshZu. Nominal funding levels have been adjusted for inflation by CBO using the gross domestic price index.

39. Ekaterina Galkina Cleary and others, "Contribution of NIH Funding to New Drug Approvals 2010–2016," *Proceedings of the National Academy of Sciences*, vol. 115, no. 10 (March 6, 2018), pp. 2329–2334. https://doi.org/10.1073/pnas.1715368115.

Figure 6.

Federal Funding for the National Institutes of Health, Fiscal Years 1995 to 2020

Billions of 2019 Dollars



Large increases in funding for NIH—the locus of much of the federal government's basic biomedical research support—in the late 1990s and early 2000s preceded a decade of declining funding. Since 2016, NIH funding has increased annually.

Data source: Congressional Budget Office, using data from National Institutes of Health, Office of Budget. See www.cbo.gov/publication/57025#data.

NIH = National Institutes of Health.

disease mechanism that had been identified by advances in basic science resulting from that funding. Indeed, most of the important new drugs introduced by the pharmaceutical industry over the past 60 years were developed with the aid of research conducted in the public sector.[40] Publicly funded basic science thus provided the foundation upon which complementary work on the applied science of drug development could be undertaken by the private sector.

How NIH-Funded Research Affects Private R&D. Empirical studies find that public-sector research tends to increase private R&D rather than to decrease it—that is, they are complements, not substitutes.[41] Several recent studies have associated increases in NIH-funded basic research with increased private R&D efforts.[42] One study found that in the decade following an increase in NIH funding, private R&D spending grew by about eight times as much as the increase in that funding.[43] Another study found that for every two NIH research grants, about one new private-sector patent was awarded.[44]

The complementary relationship between public and private R&D spending arises mainly because NIH funding focuses on basic research that leads to the discovery of new drugs, whereas private spending focuses on applications of such research. Private R&D spending on clinical

40. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Report to Congress: Prescription Drug Pricing* (May 20, 2020), https://go.usa.gov/xAVns (PDF, 2.04 MB).

41. See Paul A. David, Bronwyn H. Hall, and Andrew A. Toole, "Is Public R&D a Complement or Substitute for Private R&D? A Review of the Econometric Evidence," *Research Policy*, vol. 29, no. 4–5 (April 2000), pp. 497–529, https://doi.org/10.1016/S0048-7333(99)00087-6; and Bettina Becker, "Public R&D Policies and Private R&D Investment: A Survey of the Empirical Evidence," *Journal of Economic Surveys*, vol. 29, no. 5 (December 2015), pp. 917–942, https://doi.org/10.1111/joes.12074.

42. For additional information, see Wendy H. Schacht, *Federal R&D, Drug Discovery, and Pricing: Insights From the NIH-University-Industry Relationship*, Report RL32324 (Congressional Research Service, November 30, 2012).

43. See Andrew A. Toole, "Does Public Scientific Research Complement Private Investment in R&D in the Pharmaceutical Industry?" *Journal of Law & Economics*, vol. 50, no. 1 (February 2007), pp. 81–104, https://doi.org/10.1086/508314.

44. See Pierre Azoulay and others, "Public R&D Investments and Private-Sector Patenting: Evidence From NIH Funding Rules," *Review of Economic Studies*, vol. 86, no. 1 (January 2019), pp. 117–15, https://doi.org/10.1093/restud/rdy034.

testing, incremental innovation, product differentiation, and safety all follows from basic research.

That relationship is complicated by two factors. First, the distinction between basic and applied research is not well defined, and the likelihood that federal research spending crowds out private R&D spending varies by type of research. The risk of crowding out is greater when the government funds research whose potential commercial applications are obvious and valuable, as was the case when federal and private research labs raced to map the human genome. Second, federal research spending can also indirectly crowd out private spending by increasing the demand for skilled researchers. That could cause an increase in research labor costs in the private sector as well as in the public sector.[45]

Tax Treatment of R&D Spending. The tax code increases the supply of new drugs in two ways: First, it provides tax credits for certain R&D expenditures (including credits available to all types of companies and credits specifically for developing drug treatments for uncommon diseases). Second, it allows all types of companies to deduct expenditures that are not eligible for the credits as business expenses in the year they are made. Both incentives encourage R&D spending by reducing its cost to the company.

Tax Incentives. The research and experimentation tax credit, available to all types of companies for certain qualifying R&D expenditures, directly reduces the amount of income tax a company owes.[46] That tax credit has been modified over time and was made permanent by the Consolidated Appropriations Act, 2016 (Public Law 114-113).[47] Some of the increase in R&D spending by pharmaceutical industries over the past several decades might have been a response to changes in that credit. In addition, the Orphan Drug Act (P.L. 97-414), enacted in 1983, created a tax credit to encourage the development of drugs to treat relatively uncommon diseases. Companies can also choose to deduct the cost of R&D investments immediately rather than over the life of the investment. Many companies use both tax credits and the ability to accelerate their deductions for investments in R&D, although only one tax preference may be used for any particular investment expense.

Effects of the 2017 Tax Act. The net effect of P.L. 115-97 (originally called the Tax Cuts and Jobs Act and called the 2017 tax act in this report) on R&D investment is uncertain. Investment in R&D is encouraged by the reduction in the top corporate tax rate from 35 percent to 21 percent because earnings on new drugs would be taxed at a lower rate.

Investment is discouraged by changes in how deductions for R&D expenditures can be taken. The act is expected to reduce the value of tax deductions for R&D when they take effect. Beginning in 2022, companies will deduct their annual R&D costs over a five-year period rather than receiving the full tax deduction in the year the expenses are incurred. That discourages investment in R&D because the value of that deduction will decline. The reduction in the top corporate tax rate will further reduce the value of the tax deduction.

The 2017 tax act also reduced the tax credit created by the Orphan Drug Act from 50 percent to 25 percent of the cost of clinical trials.[48] When combined with the lower tax rate, that change will reduce the first-year tax benefits for R&D spending on orphan drugs by about 40 percent. (Costs applied to the tax credit for orphan drugs cannot also be applied to the research and experimentation credit, nor can they be deducted as expenses.) That change will also discourage investment in drug R&D.

Policies Affecting Market Exclusivity. The federal government has adopted a variety of policies that grant periods of market exclusivity to manufacturers in order to increase the supply of new drugs. During those periods, the average prices for those new drugs are higher than they will be later, once lower-priced, generic versions are allowed to enter the market. The return on R&D spending provided by those higher prices encourages

45. See Austan Goolsbee, "Does Government R&D Policy Mainly Benefit Scientists and Engineers?" *American Economic Review*, vol. 88, no. 2 (May 1998), pp. 298–302, www.jstor.org/stable/116937.

46. For example, only spending on research deemed to be "technological in nature" qualifies for the credit. See Congressional Budget Office, *How Taxes Affect the Incentive to Invest in New Intangible Assets* (November 2018), www.cbo.gov/publication/54648.

47. For a history and description of the credit, see Gary Guenther, *Research Tax Credit: Current Law and Policy Issues for the 114th Congress,* Report RL31181, version 70 (Congressional Research Service, June 18, 2016), https://go.usa.gov/xshBx.

48. See Congressional Budget Office, *How Taxes Affect the Incentive to Invest in New Intangible Assets* (November 2018), www.cbo.gov/publication/54648.

companies to develop new drugs. That incentive is not unlimited: A manufacturer only receives market exclusivity over its own drug. There may be competing drugs in the same therapeutic market, and companies may introduce other new drugs into that market, providing they do not infringe the existing drugs' patents.

The primary way that the federal government grants innovators temporary market exclusivity is through the U.S. patent system. Most patents expire 20 years after the date on which the patent application was filed, but pharmaceutical companies can receive several additional years of patent protection in recognition that patented drugs cannot be sold until they complete clinical trials. (Drug patent applications are often filed before the drug enters clinical trials, because disclosures from those trials could be considered "prior art" that might invalidate a patent if its application were filed after those disclosures occurred.) In recognition that a drug might spend several years of its market exclusivity in clinical trials, earning no revenue, the Hatch-Waxman Act (P.L. 98-417) allows pharmaceutical companies to seek up to five years of additional patent protection.

Pharmaceutical companies can also receive additional exclusivity—distinct from that afforded by patents—for drugs that treat relatively uncommon diseases. The Orphan Drug Act, enacted in 1983, offers seven years of market exclusivity (for the designated orphan use, irrespective of remaining patent life) for drugs that either treat conditions affecting fewer than 200,000 persons in the United States or that, in the FDA's judgment, face market conditions making it unlikely that an innovator could recover its R&D costs. The Orphan Drug Act appears to have led to an increase in the number of new drugs for rare diseases.[49]

Policies Affecting Generic Drugs. In addition to extending the period of market exclusivity on brand-name drugs, the Hatch-Waxman Act (enacted in 1984) also supports the development of generic drugs. It extends drug patents by up to five years but encourages competition from generic drugs once the patents on a pioneering drug have expired.

The legislation allows the FDA to approve most generic drugs without clinical trials. Instead, a manufacturer must show that its drug is pharmaceutically equivalent to the brand-name drug it copies, with the same active ingredients and no significant differences in the rate and extent of absorption at the site of drug action in the body.

The legislation also allows the FDA to extend by three years a brand-name drug's market exclusivity for incremental changes, such as new indications, dosing regimens, or patient populations. (The FDA only grants that additional exclusivity when the manufacturer has conducted clinical trials that the agency judges were essential.)[50]

Thus, the act strengthened incentives to develop new drugs by extending drug patent life, and it made it easier for lower-cost generic versions to be introduced when the drugs enter the public domain by allowing the FDA to approve most generics based on pharmaceutical equivalence rather than clinical trials.

Policies Affecting Biosimilar Drugs. Congress has sought to provide inducement to the development of biosimilar drugs—the analog, for biologic drugs, of the generic copies of small-molecule drugs. The Patient Protection and Affordable Care Act (P.L. 111-148) created an abbreviated pathway for FDA approval of biosimilar drugs. The manufacturer of a proposed biosimilar drug must demonstrate that the drug is "highly similar to and has no clinically meaningful differences from" the pioneering biologic drug.[51] In addition, biosimilar manufacturers do not need to conduct as many clinical trials as were conducted for the pioneering drug because they can cite the FDA's safety and effectiveness determinations for the original biologic drug.

So far, that legislation has resulted in relatively few approved biosimilar drugs compared to the effect that the Hatch-Waxman Act had on the development of generic drugs. As of December 2020, the FDA had approved only 29 biosimilar drugs, and not all of them have been introduced.[52] Of the $125 billion in reported domestic retail spending on biologic drugs in 2017 (expressed here in 2019 dollars), $11 billion

49. Wesley Yin, "Market Incentives and Pharmaceutical Innovation," *Journal of Health Economics,* vol. 27, no. 4 (2008), pp. 1060–1077. https://doi.org/10.1016/j.jhealeco.2008.01.002.

50. See New Drug Product Exclusivity, 21 C.F.R. § 314.108 (2020).

51. See Food and Drug Administration, "Biosimilar Development, Review, and Approval" (October 20, 2017), https://go.usa.gov/xASPs.

52. See Food and Drug Administration, "Biosimilar Product Information" (December 17, 2020), https://go.usa.gov/xAVna.

was spent on biologics for which biosimilar versions are available, and only $0.9 billion was spent on those biosimilars.[53]

The relative lack of competition for pioneering biologic drugs might contribute to the shift in new-drug development toward biologic drugs instead of small-molecule drugs. In part, that shift might simply reflect advances in the underlying science. But biologic drugs are also attractive targets of research because they are harder to copy. The patent system does not require the original innovator to share the original cell line. Manufacturers seeking to make a biosimilar drug must develop their own living cell line to use as the basis for the new drug. By contrast, the primary challenge in making a generic copy of a small-molecule drug is to replicate the original drug's active molecule, which is publicly disclosed in the patent. In addition, even under the abbreviated pathway specified by the FDA, biosimilar drugs must still be put through some clinical trials; unlike generic drugs, biosimilar drugs cannot avoid them altogether.[54]

Biologic drugs may face less competition than small-molecule drugs. Independent of (but concurrent with) patent protection, the FDA grants pioneering biologic drugs 12 years of guaranteed exclusivity in contrast to 5 years of exclusivity for small-molecule drugs.[55] In addition, where biologic drugs are concerned, consumers may not as readily accept a biosimilar substitute as they do a generic drug, because a biosimilar is not identical to the drug it imitates.[56] Consumer acceptance may be increasing with greater availability and familiarity with biosimilars. However, certain federal payment policies and private contractual agreements may discourage the use of biosimilars.[57] With the possibility of facing less competition even beyond the period of market exclusivity, makers of biologic drugs would anticipate greater lifetime sales of those drugs as well.

Vaccine Policies. Several federal policies increase the demand for vaccines and therefore R&D spending to develop them. The federal Vaccines for Children program provides vaccines at no cost to children who might otherwise go unvaccinated because of their family's inability to pay. Additionally, the Centers for Disease Control and Prevention publishes a schedule of recommended childhood and adult vaccinations, including specific recommendations for various groups, such as health care providers, travelers, expectant mothers, racial and ethnic populations, and people with certain underlying health conditions. Those recommendations induce individuals to have themselves and their children vaccinated, and federal subsidies lower the costs to consumers of those vaccinations. A study that analyzed the effects of such policies found that the recommendation in 1991 that infants be vaccinated against hepatitis B and the expansion of Medicare coverage to include the cost of influenza vaccination in 1993 were both associated with subsequent increases in the development of new vaccines.[58] Those findings suggest that manufacturers expected demand for vaccines to increase as a result of the new recommendations.

Federal policies also affect the supply of vaccines. The same study considered the federal Vaccine Injury Compensation Fund, which was established in 1986 to encourage manufacturers to develop and supply new vaccines by indemnifying the manufacturers against lawsuits arising from adverse reactions to childhood vaccines. The study found that the fund's introduction was associated with increased development of new vaccines.

53. See IQVIA Institute for Human Data Science, *Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022* (April 2018), p. 11. https://tinyurl.com/y36l4bqt.

54. See Food and Drug Administration, "Generic Drugs Undergo Rigorous FDA Scrutiny" (October 8, 2014), https://go.usa.gov/xAVRg, and "Biosimilar Development, Review, and Approval" (October 20, 2017), https://go.usa.gov/xAVR4.

55. For biologics, see 42 U.S.C. § 262(k)(7)(A) (2018); for orphan drugs, see 21 U.S.C. § 360cc (2018); for small-molecule drugs, see § 355(j)(5)(F)(ii) (2018). Companies can receive an additional six months of exclusivity (beyond its patent exclusivity) if a drug—in any of its formulations, dosages, or approved indications—is designed for pediatric patients. See Food and Drug Administration, "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity" (November 30, 2016), https://go.usa.gov/xAVRP.

56. See Darius N. Lakdawalla, "Economics of the Pharmaceutical Industry," *Journal of Economic Literature,* vol. 56, no. 2 (June 2018), pp. 403–404, https://doi.org/10.1257/jel.20161327.

57. See Revisions to Payment Policies under the Physician Fee Schedule and Other Revisions to Part B for CY 2018, 82 Fed. Reg. 52976, 53181 (November 15, 2017), www.govinfo.gov/app/details/FR-2017-11-15; and Tony Hagen, "Remove the Disincentives and Biosimilars Will Flourish," The Center for Biosimilars (July 7, 2020), https://tinyurl.com/acq5f5t3.

58. See Amy Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence From the Vaccine Industry," *Quarterly Journal of Economics,* vol. 119, no. 2 (May 2004), pp. 527–564, https://doi.org/10.1162/0033553041382166.

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In 2020, the federal government invested directly in the development of vaccines by providing more than $19 billion in funding to support the private development of vaccines to prevent COVID-19 through its Biomedical Advanced Research and Development Authority (see Box 2 on page 10).

Regulatory Policies. Federal regulatory policies that affect either drug supply or drug demand can influence drug companies' returns on R&D spending, which would in turn affect the amount they were willing to spend on R&D. Proposed regulation of some drug prices would affect the sales volumes of existing drugs and, as a result, expected returns on R&D on future drugs; in turn, lower expected returns would result in fewer new drugs. Changes to regulation of clinical trials would also affect the supply of new drugs.

Drug Prices. U.S. markets are subject to less price regulation than are the markets in many other countries. Drug companies can mostly set their own prices, although some federal agencies purchase drugs at prices subject to a statutory cap, impose statutory limits on how quickly a manufacturer can raise its prices, or receive rebates from manufacturers that are specified in statute.[59]

In 2019, the House of Representatives passed H.R. 3, which would have required the Secretary of Health and Human Services to negotiate with drug manufacturers over the domestic prices of certain high-priced, single-source drugs to ensure that they were no more than 20 percent higher than the average prices for those drugs in specific other countries. Under H.R. 3, drug manufacturers that did not agree to participate in negotiations or that failed to agree to a negotiated price would have been subject to an excise tax. The combination of income taxes and excise taxes on a drug's sales might have caused the manufacturer to lose money if the drug were sold in the United States. Those taxes would have had the same effect as if the drug had not been approved for sale or as if there were a formulary—that is, a national list of drugs that insurers could cover—from which the drug was excluded. Therefore, the potential use of the excise tax would have served as a source of pressure on drug manufacturers in negotiations and would have lowered drug prices and federal spending, CBO estimated.[60]

(For a discussion of the effects of lower prices on the introduction of new drugs, see Box 3 on page 12.)

More generally, state laws mandating or encouraging substitution of generic drugs for their brand-name equivalents help lower drug prices.[61] In addition, most Medicare Part D plans encourage the substitution of generic drugs for their brand-name equivalents.[62] And although the existence of generic drugs is enabled by the patent system's disclosure requirement (compelling drugmakers to disclose the molecular structure of a drug's active ingredient), several federal regulatory decisions hasten the introduction of those drugs.[63] Under the Hatch-Waxman Act, generic drugs shown to contain the same active ingredient as the pioneering drug do not need to be tested in clinical trials, as described above. The act also provides legal protections from claims of patent infringement to manufacturers who try to develop generic versions of a pioneering drug before its patents have expired and from liability for adverse events not listed on the label of the pioneering drug.[64]

That competition from generic drugs—which can also reduce the demand for new drugs entering those

59. See Congressional Budget Office, *A Comparison of Brand-Name Drug Prices Among Selected Federal Programs* (February 2021), www.cbo.gov/publication/56978.

60. See Congressional Budget Office, letter to the Honorable Frank Pallone Jr. regarding the budgetary effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act (December 10, 2019), www.cbo.gov/publication/55936; Christopher Adams and Evan Herrnstadt, *CBO's Model of Drug Price Negotiations Under the Elijah E. Cummings Lower Drug Costs Now Act*, Working Paper 2021-01 (Congressional Budget Office, February 2021), www.cbo.gov/publication/56905.

61. See Yan Song and Douglas Barthold, "The Effects of State-Level Pharmacist Regulations on Generic Substitution of Prescription Drugs," *Health Ecoomics,* vol. 27, no. 11 (November 2018), pp. 1717-1737. https://doi.org/10.1002/hec.3796.

62. See Stacie B. Dusetzina and others, "Medicare Part D Plans Rarely Cover Brand-Name Drugs When Generics Are Available," *Health Affairs,* vol. 39, no. 8 (August 2020), pp. 1326–1333, https://doi.org/10.1377/hlthaff.2019.01694.

63. The patent system enables imitation of innovation (such as generic copies of pioneering drugs) by requiring the innovator, in exchange for a patent on a pioneering drug, to disclose sufficient details about the invention to allow "a person having ordinary skill in the art" to replicate it when the patent expires. See 35 U.S.C. § 103 (2018).

64. For legal protection against adverse-event liability, see Aaron S. Kesselheim, Jerry Avorn, and Jeremy A. Greene, "Risk, Responsibility, and Generic Drugs," *New England Journal of Medicine,* vol. 367, no. 18 (November 1, 2012), pp. 1679–1681, https://doi.org/10.1056/NEJMp1208781. In the Hatch-Waxman Act, those provisions are balanced by the provision of stronger patent protections to drug innovators, including extension of the statutory period of patent protection by a portion of the time the drug is under FDA review, and five years of ensured market exclusivity before the FDA may approve the first generic copy of a pioneering drug.

markets—has tended to discourage investment in drug R&D.[65] Several studies have found that a real 10 percent decrease in the growth of drug prices would be associated with about a 6 percent decrease in pharmaceutical R&D spending as a share of net revenues.[66]

Clinical Trials. A substantial R&D expense that can account for more than half of R&D spending (excluding capital costs), clinical trials are conducted in accordance with federal requirements. As a result, changes to federal policy regarding clinical trials can meaningfully affect private R&D spending. In particular, policymakers have made several changes to federal regulations governing clinical trials in an effort to reduce the time they take and therefore lower their cost.

For example, FDA's guidance, described above, on how drug companies can establish bioequivalence between a biosimilar drug and the pioneering biologic drug is intended to minimize the expenses of clinical trials associated with developing biosimilar drugs.[67] The Prescription Drug User Fee Act, enacted in 1992, provided the FDA with additional resources to hasten the drug approval process, which reduced both the time to market and the capital costs of new-drug development.

More recently, federal policymakers have allowed the use of "surrogate endpoints" in drug trials for certain illnesses, including HIV infection and some cancers, to shorten some clinical trials. Surrogate endpoints include indirect, predictive indicators (such as blood pressure, cholesterol level, tumor size, T-cell counts, or other physical signs of disease), along with other test results and laboratory measures.[68] The FDA can approve certain kinds of drug for sale in the U.S. based on clinical-trials results that rely on such surrogate measures rather than on direct measures of a drug's clinical benefit.

The use of surrogate endpoints has helped neutralize a tendency in privately funded research to emphasize treatments that can be commercialized more quickly, which can result in too little investment in clinically valuable treatments that would take longer to develop.[69] Speedier clinical trials can also benefit patients by hastening the introduction of life-extending therapies like the HIV antiretroviral treatments developed in the 1990s.[70] However, relying on surrogate endpoints means that consumers might spend money on some drugs that would turn out to have little clinically meaningful effect.[71]

65. See Joseph P. Cook, Graeme Hunter, and John A. Vernon, *Generic Utilization Rates, Real Pharmaceutical Prices, and Research and Development Expenditures*, Working Paper 15723 (National Bureau of Economic Research, February 2010), www.nber.org/papers/w15723.

66. See Carmelo Giaccotto, Rexford E. Santerre, and John A. Vernon, "Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry," *Journal of Law and Economics*, vol. 48, no. 1 (April 2005), pp. 194–214, https://doi.org/10.1086/426882; and F. M. Scherer, *Industry Structure, Strategy, and Public Policy* (Harper Collins, 1996).

67. See Food and Drug Administration, "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations" (March 2014), https://go.usa.gov/xAV5f.

68. For a comprehensive list of surrogate endpoints used, see Food and Drug Administration, "Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure" (March 30, 2021), https://go.usa.gov/xASyF.

69. See Eric Budish, Benjamin N. Roin, and Heidi Williams, "Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials," *American Economic Review,* vol. 105, no. 7 (July 2015), pp. 2044–2085. https://doi.org/10.1257/aer.20131176.

70. See Mark G. Duggan and William N. Evans, "Estimating the Impact of Medical Innovation: A Case Study of HIV Antiretroviral Treatments," *Forum for Health Economics and Policy,* vol. 11, no. 2 (January 2008), pp. 1–37, https://doi.org/10.2202/1558-9544.1102.

71. See Bishal Gyawali, Spencer Phillips Hey, and Aaron S. Kesselheim, "Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval," *JAMA Internal Medicine,* vol. 179, no. 7 (May 28, 2019), pp. 906–913, https://doi.org/10.1001/jamainternmed.2019.0462.

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About This Document

This Congressional Budget Office report was prepared at the request of the Chairman of the Senate Committee on Finance. In accordance with CBO's mandate to provide objective, impartial analysis, the report makes no recommendations.

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CBO continually seeks feedback to make its work as useful as possible. Please send any comments to communications@cbo.gov.

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