



November 2017

DRUG INDUSTRY

Profits, Research and Development Spending, and Merger and Acquisition Deals

GAO Highlights

Highlights of [GAO-18-40](#), a report to congressional requesters

Why GAO Did This Study

Retail prescription drug expenditures were estimated to account for about 12 percent of total personal health care service spending in the United States in 2015, up from about 7 percent through the 1990s. Much of this growth was driven by use of expensive brand-name drugs, but price increases have been reported for some generic drugs as well. Prior GAO reports have identified multiple reasons for drug price increases, including limited competition. Experts have questioned whether consolidation among drug companies could reduce competition and R&D investment in new drugs.

GAO was asked to examine changes in the drug industry. This report describes: (1) how the financial performance and structure of the industry have changed over time, (2) how reported R&D spending and new drug approvals have changed, and (3) what is known about the potential effects of consolidation on drug prices and new drug development. GAO analyzed Bloomberg drug industry financial data for 2006 through 2015, and examined select publicly available estimates of company market shares for 2014 and market shares for certain therapeutic classes for 2016. GAO also analyzed estimates of company self-reported R&D spending and federal funding for biomedical R&D data, aggregate tax credit claims data, and drug approval data for the same approximate time period. All data were the most current available. In addition, GAO also reviewed published research and interviewed federal agency officials, economists, and representatives from industry and advocacy groups.

View [GAO-18-40](#). For more information, contact John Dicken at (202) 512-7114 or dickenj@gao.gov, or Oliver Richard at (202) 512-8424 or richardo@gao.gov.

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What GAO Found

GAO's analysis of revenue, profit margin, and merger and acquisition deals within the worldwide drug industry from 2006 through 2015 identified key trends:

- Estimated pharmaceutical and biotechnology sales revenue increased from \$534 billion to \$775 billion in 2015 dollars.
- About 67 percent of all drug companies saw an increase in their annual average profit margins from 2006 to 2015. Among the largest 25 companies, annual average profit margin fluctuated between 15 and 20 percent. For comparison, the annual average profit margin across non-drug companies among the largest 500 globally fluctuated between 4 and 9 percent.
- The number of reported mergers and acquisitions generally held steady during this period, but the median disclosed deal value increased.

The largest 10 companies had about 38 percent of the drug industry's sales revenue in 2014. However, concentration was higher for narrower markets, such as for certain drugs in the same therapeutic class. In addition, experts noted that market pressures such as rising research and development (R&D) costs, fewer drugs in development, and competition from generic drugs, have driven structural changes in the industry such as increased use of acquisition by large drug companies to obtain access to new research.

From 2008 through 2014, worldwide company-reported R&D spending, most of which went to drug development (rather than research), increased slightly from \$82 billion to \$89 billion in 2015 dollars. During the same period, federal spending, which funded a greater amount of basic research relative to industry, remained stable at around \$28 billion. In addition to grants, several federal tax provisions provided incentives for industry R&D spending, including the orphan drug credit, available for companies developing drugs intended to treat rare diseases, which increased more than five-fold from 2005 through 2014. Pertaining to drug approvals, the total number of new drugs approved for marketing in the United States fluctuated between 2005 and 2016, ranging from 179 to 263 drug approvals annually. Novel drugs—innovative products that serve previously unmet medical need or help advance patient care—accounted for about 13 percent of all approvals each year. Biologics—drugs derived from living rather than chemical sources—and orphan drugs accounted for growing shares of drug approvals, reflecting market and policy incentives to invest in these areas, according to experts GAO interviewed.

Research GAO reviewed indicates that fewer competitors in the drug industry are associated with higher prices, particularly for generic drugs. Research also suggests that drug company mergers can have varied impacts on innovation as measured by R&D spending, patent approvals, and drug approvals. Certain merger retrospective studies have found a negative impact on innovation.

The Department of Health and Human Services, Federal Trade Commission, Internal Revenue Service, and National Science Foundation provided technical comments on a draft of this report, which we incorporated as appropriate.

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Abbreviations

ANDA	abbreviated new drug application
BICS	Bloomberg Industry Classification System
BLA	biologic license application
DOJ	Department of Justice
FDA	Food and Drug Administration
FTC	Federal Trade Commission
IRS	Internal Revenue Service
NAICS	North American Industry Classification System
NDA	new drug application
NIH	National Institutes of Health
NSF	National Science Foundation
PBM	pharmacy benefit manager
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	research and development

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November 17, 2017

The Honorable Elijah E. Cummings
Ranking Member
Committee on Oversight and Government Reform
House of Representatives

The Honorable Bernard Sanders
Ranking Member
Subcommittee on Primary Health and Retirement Security
Committee on Health, Education, Labor, and Pensions
United States Senate

In 2015, expenditures for prescription drugs sold through retail pharmacies were estimated to account for nearly 12 percent of total personal health care services spending in the United States, up from approximately 7 percent of such spending through the 1990s.¹ Use of expensive brand-name drugs accounted for much of the growth in recent years, but price increases have been reported for some generic drugs as well.² Recent concerns about drug prices have sparked interest in drug company profitability and competition in the industry.³ Limited competition for particular drugs due to market exclusivity—granted by law after the

¹Data are from the 2015 National Health Expenditure Accounts, National Health Expenditures by type of service and source of funds, CY 1960-2015. The National Health Expenditure Accounts are the official estimates of total health care spending in the United States.

In addition to retail prescription drug sales to consumers, drugs may also be administered by providers such as hospitals and physicians. According to estimates by the Office of the Assistant Secretary for Planning and Evaluation, retail and provider-administered drugs combined represented about 17 percent of personal health care expenditures in 2015. See, Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Observations on Trends in Prescription Drug Spending* (March 8, 2016).

²See IMS Institute for Health Informatics, *Medicines Use and Spending in the U.S.: A Review of 2015 and Outlook to 2020* (April 2016).

³Drugs are a global industry that encompasses a variety of companies, including large multinational pharmaceutical corporations that traditionally focus on developing chemical and biologic drugs; makers of generic versions of such drugs; and small, research-oriented biotechnology companies. For the purposes of this review, we refer to pharmaceutical and biotechnology companies collectively as drug companies, unless otherwise noted.

Food and Drug Administration (FDA) approves certain drugs—is one factor that often has been noted as influencing drug prices. Prior GAO reports have identified multiple reasons for drug price increases, including limited competition. Further, some drug companies have undergone mergers and acquisitions, leading to concerns about reduced competition and higher drug prices. Economists have expressed apprehension that reduced competition may also decrease the amount of industry research and development (R&D) invested into new drugs, which could result in fewer drug choices for consumers and fewer treatment options for providers.

Amid these questions, you asked us to provide an overview of the drug industry and the potential effects of consolidation on drug prices and new drug development. This report describes:

1. how the financial performance and structure of the drug industry have changed over time;
2. how reported research and development spending and new drug approvals have changed over time; and
3. what is known about the potential effects of consolidation on drug prices and new drug development.

To describe how the financial performance and structure of the drug industry have changed over time, we:

- analyzed Bloomberg data on revenues, profit margins, and mergers and acquisitions for drug companies and, for comparison, software companies and the largest 500 companies by worldwide revenue from 2006 through 2015;⁴ and
- examined overall industry concentration using data from QuintilesIMS from 2007 through 2014, and reports from EvaluatePharma to discuss concentration across smaller markets. All data were the most current available.⁵

To describe how reported research and development spending and new drug approvals have changed, we:

⁴Bloomberg data were obtained through the Bloomberg Terminal, which is a commercial database containing data from company financial disclosure statements and other documents.

⁵QuintilesIMS and EvaluatePharma collect health care data and offer analytic services.

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- analyzed data from the National Science Foundation's (NSF) National Center for Science and Engineering Statistics' Business Research, Development, and Innovation Survey on company-reported R&D expenditures and sales data for drug companies for years 2008 through 2014 and, for comparison, select other industries for 2013 and 2014;
 - analyzed data from NSF's National Center for Science and Engineering Statistics' Federal Funds for Research Survey on federal obligations for research in biomedical related fields made by agencies identified as funding drug-related research from fiscal year 2008 through 2014;
 - analyzed aggregate tax return data from the Internal Revenue Service (IRS) for income tax credits and deductions for research investment for relevant industries for years 2005 through 2014;⁶ and
 - analyzed data from FDA on drugs approved by its Center for Drug Evaluation and Research between 2005 and 2016. All data were the most current available.⁷

To describe what is known about the potential effects of consolidation on drug prices and new drug development, we reviewed studies obtained from a literature search of scholarly peer reviewed studies, government reports, select working papers, and policy research organization publications published from 2005 through August 2017 that examined the impact of consolidation or competition on drug price and drug development.

In addition, for all objectives, we interviewed industry experts, including representatives from industry groups, advocacy organization, economists, and federal agencies. For all of the data analyzed, we took steps to assure their reliability, including interviewing knowledgeable officials, conducting data checks, and comparing to published information when available. After taking these steps, we determined that the data were sufficiently reliable for the purposes of our reporting objectives. Appendix I provides additional details on our scope and methodology, including

⁶Specifically, we analyzed claims for the orphan drug credit, research credit, and deductions for qualified research expenses by pharmaceutical companies, all industries, and certain additional industries.

⁷Data from NSF's Federal Funds for Research Survey were limited to fiscal years 2008 through 2014 to be consistent with the years analyzed using NSF's Business Research, Development, and Innovation Survey data.

limitations of our analyses and steps we took to assure the reliability of the data we analyzed.

We conducted this performance audit from April 2016 to November 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings based on our audit objectives.

Background

The drug industry encompasses a variety of companies involved in the research, development, distribution, and payment for chemically synthesized and biologic drugs. For the purpose of our review, the drug industry includes pharmaceutical companies that traditionally concentrate on developing or manufacturing drugs derived from chemicals and biotechnology companies that develop or manufacture biologics—more complex drugs derived from living cells.

The federal government plays a role in various aspects of the drug supply chain as well. To market drugs in the United States, drug companies must apply and receive approval from the FDA that their drugs are safe and effective. The federal government also supports R&D for new drugs, such as through grants by the National Institutes of Health (NIH), NSF, and other agencies, and through tax incentives administered by the IRS. In addition, mergers and acquisitions affecting the drug industry are subject to review by the federal government to ensure compliance with applicable antitrust laws.

Drug Research, Discovery, Development, and Approval Process

The process of bringing a new drug to the market is long and costly and involves multiple public and private entities that fund and perform R&D. (See fig. 1.) For a new drug, the entire drug discovery, development, and

review process can take up to 15 years, often accompanied by high costs.⁸ The process consists of several main stages:

- **Basic research:** This is research aimed at acquiring new knowledge or understanding without immediate commercial application or use. Basic research is often federally funded and conducted to better understand the workings of disease, which increases the potential of discovering and developing innovative drugs.
- **Drug discovery:** This is undertaken by numerous researchers from drug companies, academia, and government searching for and identifying promising chemical entities, or chemical and biological compounds, capable of curing or treating diseases.
- **Preclinical testing:** During preclinical testing, compounds are tested in laboratories and in animals to predict whether a drug is likely to be safe and effective in humans. If the compound is found to be promising, a drug company may decide to test it as a new drug on humans and it proceeds to the clinical trials stage. Before doing so, the company must submit to FDA and have in effect an investigational new drug application that summarizes the data that have been collected on the compound and outlines plans for the clinical trials.
- **Clinical trials:** Clinical trials test potential drugs in human volunteers to determine if they should be approved for wider use in the general population. An investigational new drug typically goes through three phases of clinical trials before it is submitted to FDA for marketing approval. Clinical trials proceed through Phases I, II, and III, beginning with testing in a small group of healthy volunteers and then moving on to testing in larger groups of patients whom the drug is intended to treat to assess the compound's effectiveness, rate of adverse events, and uses in combination with other drugs.
- **FDA Review and Approval:** To market a drug in the United States, drug companies submit their research in a new drug application

⁸For example, one study estimated average cost per new molecular compound that received FDA approval between 2005 and 2013 to be \$1.4 billion. See J. A. DiMasi, H. G. Grabowski, and R. W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (2016). Other studies suggest lower development costs. For example, another study estimated a median cost to develop cancer drugs of \$0.6 billion. See V. Prasad and S. Mailankody, "Research and Development Spending to Bring Single Cancer Drug to Market and Revenues After Approval," *JAMA Internal Medicine*, Published online September 11, 2017, accessed October 31, 2017, <https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2653012>.

(NDA) or biologic license application (BLA) to FDA, which then reviews and approves the drug for marketing if it is shown to be safe and effective for its intended use. An NDA is an application to market a new chemically synthesized drug—either an innovative drug or a variation of a previously marketed drug. A BLA is an application for a license to market a new biological product (complex drugs derived from living organisms).⁹ Companies may also submit a supplement to an already approved NDA or BLA—known as an efficacy supplement—to propose changes to the way an approved drug is marketed or used, such as adding or modifying an indication or claim, revising the dose or dose regimen, providing a new route of administration, or changing the marketing status from prescription to over-the-counter use.

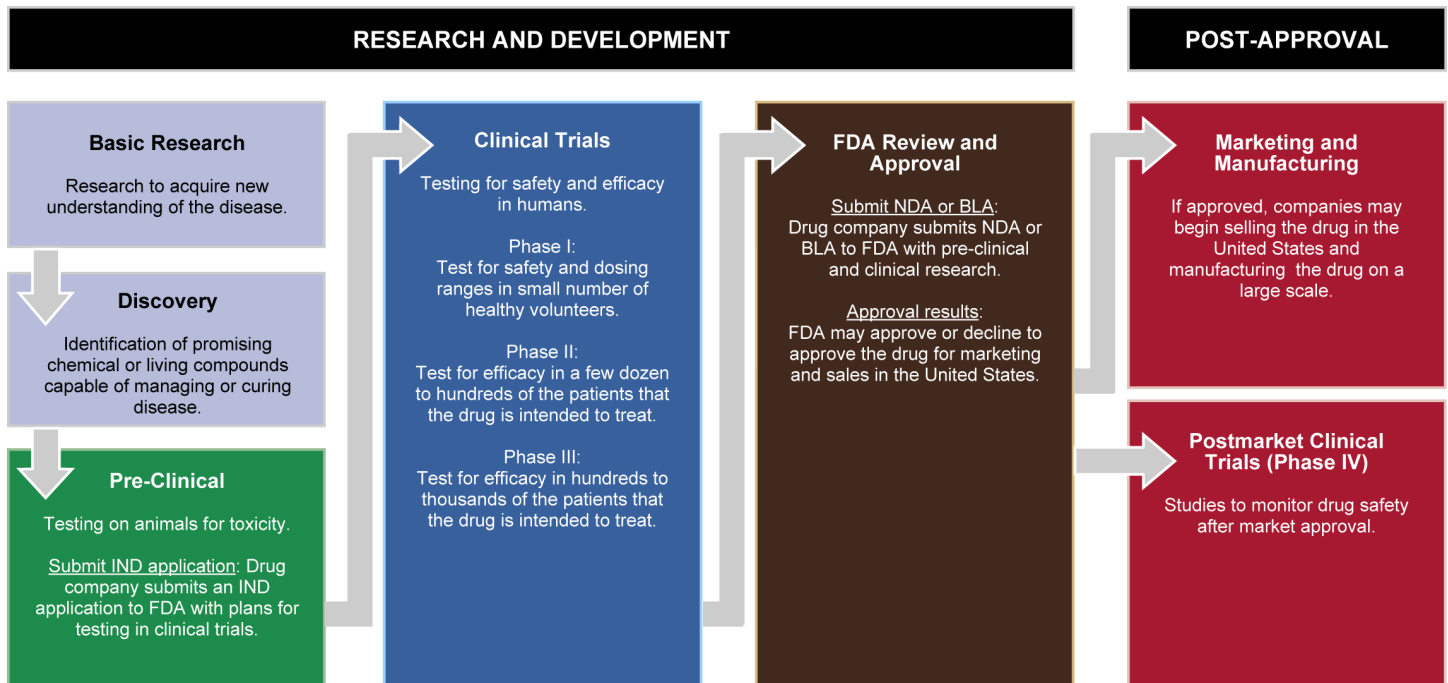
For the purposes of its review, FDA classifies certain NDAs as new molecular entities—products that contain active chemical substances that have not been approved by FDA previously—and certain BLAs as new therapeutic biologics. FDA generally considers drugs approved either as new molecular entities or new therapeutic biologics to be “novel” drugs—products that are often innovative and serve previously unmet medical needs or otherwise significantly help to advance patient care and public health.¹⁰

- **Post-approval:** After FDA has approved a drug for marketing, the drug company may begin marketing and large-scale manufacturing of the drug. FDA also continuously monitors the safety of the drug which includes, amongst other activities, oversight of postmarket clinical studies that it can require or request companies to complete (known as phase IV clinical trials). Drug companies may also undertake these studies independently to identify modifications to the drug such as new delivery mechanisms or additional indications for use. The company may then submit a new application or supplement application with new clinical data to FDA to market the modification as a new drug, or market it for the new use.

⁹Biologics are more complex than chemically synthesized drugs, can provide more targeted treatments for conditions like cancers and autoimmune diseases, are typically injectable or infusible, and are usually not self-administered. For simplicity, in this report the term “drugs” refers to both chemically synthesized and biologic products.

¹⁰FDA’s Center for Drug Evaluation and Research annually publishes a summary of novel product approvals. See for example, Department of Health and Human Services, U.S. Food and Drug Administration, *2016 Novel Drugs Summary* (Silver Spring, MD: January 2017).

Figure 1: Stages in the Typical Brand-Name Drug Development Process



Legend: BLA = biologic license application; FDA = Food and Drug Administration; IND = investigational new drug; NDA = new drug application

Source: GAO analysis of Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America information. | GAO-18-40

Patent and Market Exclusivity and Other Incentives for Drug Development

Patents and market exclusivity periods are two ways brand-name drug companies may recoup their R&D investments by limiting competition for specified periods of time. Typically, early in the R&D process, companies developing a new brand-name drug apply for a patent on the active ingredient and may additionally apply for patents on other aspects of the drug, such as the method of use, from the U.S. Patent and Trademark Office.¹¹ Once a patent is granted, other drug companies are excluded from making, using, or selling the patented aspect of the drug during the term of the patent, which generally expires after 20 years from filing.¹² In addition, federal law authorizes certain periods of exclusive marketing

¹¹See 35 U.S.C. §§ 111, 154.

¹²Since new drugs must be approved before marketing, the useful patent life can be shorter than this amount, according to FDA. In some cases, patents can be extended to compensate for time lost because of the U.S. regulatory review of a drug prior to approval.

rights, or market exclusivity, for new FDA-approved drugs, during which time FDA generally cannot approve a similar competing version of the drug for marketing. These exclusivities are independent of the rights granted under patent and can relate to chemical entities never approved before by FDA (5 years of exclusivity); new biologics (12 years); approval of a supplement for a new condition or use or other change to a previously approved chemically synthesized drug based on new clinical studies (3 years); and orphan drugs—drugs designated to treat rare diseases or conditions (7 years); among others.¹³ Patent protection and market exclusivity are independent of one another and can run concurrently or not.

When brand-name drug products' patents expire and exclusivity periods end, similar versions of the drug product that have been approved by FDA may enter the market. These are referred to as generics for chemically synthesized drugs and biosimilars for biologics. The Drug Price Competition and Patent Term Restoration Act of 1984—commonly known as the Hatch-Waxman Amendments—facilitated earlier, and less costly, market entry of generic drugs. A generic drug must generally be demonstrated to be equivalent to the brand-name drug product in active ingredient, dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.¹⁴ For biologics, the Biologics Price Competition and Innovation Act of 2009 provided an abbreviated pathway for companies to obtain approval of “biosimilar” and “interchangeable” biological products. A biosimilar must be demonstrated to be highly similar to an already approved biological product and to have no clinically meaningful differences in terms of safety and effectiveness

¹³Chemical entities never before approved by FDA: 21 U.S.C. § 355(c)(3)(E)(ii). The exclusivity period runs from the time of NDA approval. New biologics: 42 U.S.C. § 262(k)(7)(A). The exclusivity period runs from the time of BLA approval. Supplement to an application for a previously approved drug: 21 U.S.C. § 355(c)(3)(E)(iv). The exclusivity period runs from the time of approval of the supplement. Orphan drugs: 21 U.S.C. § 360cc. Drug companies must apply for orphan designation from FDA prior to a drug's approval. Orphan drugs may receive 7 instead of 5 years of exclusivity for a new molecular entity.

¹⁴Drug companies submit an abbreviated new drug application (ANDA) to FDA to market a generic drug. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified in pertinent part as amended at 21 U.S.C. § 355(j)).

from the reference product.¹⁵ See table 1 for a description of drug application types.

Table 1: Selected Food and Drug Administration Drug (FDA) Application Types

Drug Type	Description	Typical application for regulatory approval
Brand-name chemically synthesized drug	Drugs synthesized through a chemical process. These often have patent protection and market exclusivity at the time of FDA approval.	New Drug Application (NDA)
Brand-name biologic	Drugs synthesized from living organisms or tissues. Biologics are more complex than chemically synthesized drugs and are often injectable or infusible. These often have patent protection and market exclusivity at the time of FDA approval.	Biologic License Application (BLA)
Generic	Chemically synthesized drugs equivalent to an approved brand-name drug in active ingredient, dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.	Abbreviated New Drug Application (ANDA)
Biosimilar	A biological product that is highly similar to an FDA-approved biological product and has no clinically meaningful differences in terms of safety and effectiveness.	BLA

Source: GAO summary of FDA information. | GAO-18-40

In addition to incentivizing drug development through patent and market exclusivity, the federal government supports new drug research both directly, through grants from—and intramural research by—agencies such as NIH and indirectly through tax incentives for companies that develop new drugs. Specifically, the Internal Revenue Code includes incentives for research-related spending in three ways: through two income tax credits—the credit for clinical testing expenses for certain drugs for rare diseases (known as the orphan drug credit) and the credit for increasing research activities (known as the research credit)—and through special methods for treatment and reporting of research and experimental expenditures, including current-year deduction to arrive at net income. In general, the credit incentives are available to companies with qualified research spending in the United States. Companies include businesses organized as corporations or non-corporate businesses such as partnerships. These provisions are described below:

- **Orphan drug credit:** Companies may claim the orphan drug credit for half the “qualified clinical testing expenses” for drugs intended to treat

¹⁵Pub. L. No. 111-148, tit. VII, subtit. A, 124 Stat. 119, 804 (2010) (codified in pertinent part as amended at 42 U.S.C. § 262(k), (l)). Only minor differences in clinically inactive components are allowable in biosimilar products.

rare diseases.¹⁶ Expenditures that give rise to the orphan drug credit may include expenses related to testing outside the United States. A company may claim foreign clinical testing expenses if there is an insufficient testing population in the United States to test the safety and efficacy of the drug.¹⁷ The orphan drug credit is nonrefundable; that is, while the credit can be used to reduce a company's income tax liability generally, the credit cannot be used to generate a refund if the business has no tax liability or fully used if the credit would reduce tax liability below zero. The credit is also a component of and subject to the limitations of the general business credit.¹⁸

- **Research credit:** Companies may claim a research credit for qualified research expenditures they undertake in a given year that exceed a threshold or base amount.¹⁹ This incremental design of the credit is intended to create an incentive for companies to do more research than they otherwise would. Qualified research expenses are certain expenses for qualified research incurred by the taxpayer during the taxable year in carrying on a trade or business. Qualified research is research that is undertaken for the purpose of discovering information that is technological in nature and the application of which is intended to be useful in the development of a new or improved business component of the taxpayer. In general, substantially all the activities that constitute a process of experimentation relating to new or improved functions, performance, or reliability or quality are qualified research. The rate of credit can be 14 or 20 percent. Like the orphan drug credit, the research credit is nonrefundable and is a

¹⁶“Qualified Clinical Testing Expenses” are expenses defined under 26 U.S.C. § 45C(b).

¹⁷The testing population in the United States is insufficient if there are not within the United States the number of available and appropriate human subjects needed to produce reliable data from the clinical investigation. 26 C.F.R. § 1.28-1(d)(3)(ii)(B).

¹⁸The general business credit is generally nonrefundable and may not exceed the taxpayer's net regular income tax less the greater of its tentative minimum tax liability or 25 percent of the net regular tax liability over \$25,000. If the taxpayer does not have a sufficient pre-credit tax liability against which to use the credit in the current tax year, the taxpayer can carry back some or all of the unused credit to the preceding tax year (if it had a tax liability that year), or carry the credit forward for use in a future tax year for up to 20 years. The orphan drug credit can be carried back for 3 years and carried forward for 15 years.

¹⁹“Qualified Research Expenditures” are specific expenses defined under 26 U.S.C. § 41(b) which are associated with research activities defined under 26 U.S.C. § 41(d).

component of, and subject to, the limitations of the general business credit.

- **Deductions of qualified research expenses:** If elected, the tax code allows businesses to currently deduct “research or experimental expenditures” from gross income in the tax year they are incurred rather than depreciate (or amortize) the assets the R&D created over time.²⁰ Research and experimental expenditures include all costs incident to research, including research conducted outside the United States. Since “qualified research expenses” and “qualified clinical testing expenses” are a particular subset of research and experimental expenditures, expenditures that can give rise to either the research or orphan drug tax credits can be deducted in the year that they occur. However, these deductions must be reduced by the amount of tax credits claimed in order to prevent expenses from both generating a tax credit and being deducted from income.

Drug Distribution, Payment, and Pricing

The distribution of, and payment for, prescription drugs involve interactions and negotiated transactions among multiple commercial entities along the supply chain from the drug manufacturer to the consumer (see fig. 2). Brand-name and generic drug manufacturers typically sell their drugs to drug wholesalers, who in turn sell the drugs to retail pharmacies or to health care providers (such as hospitals, clinics, and physicians). Pharmacies or providers dispense or administer prescription drugs to consumers.²¹ Most consumers purchasing drugs pay a portion of the drug’s price in the form of a copayment or coinsurance, with the specifics of this cost sharing dictated by the consumers’ insurance plan.²² Insurance plans often use pharmacy benefit managers (PBMs) to help them manage their prescription drug benefits, including negotiating prices with manufacturers, processing claims, and negotiating with retail pharmacies to assemble networks where the beneficiaries can fill prescriptions. PBMs negotiate with manufacturers for rebates on behalf of the insurance plan based on market share, volume, and formulary placement. PBMs also contract with pharmacies; contract terms and

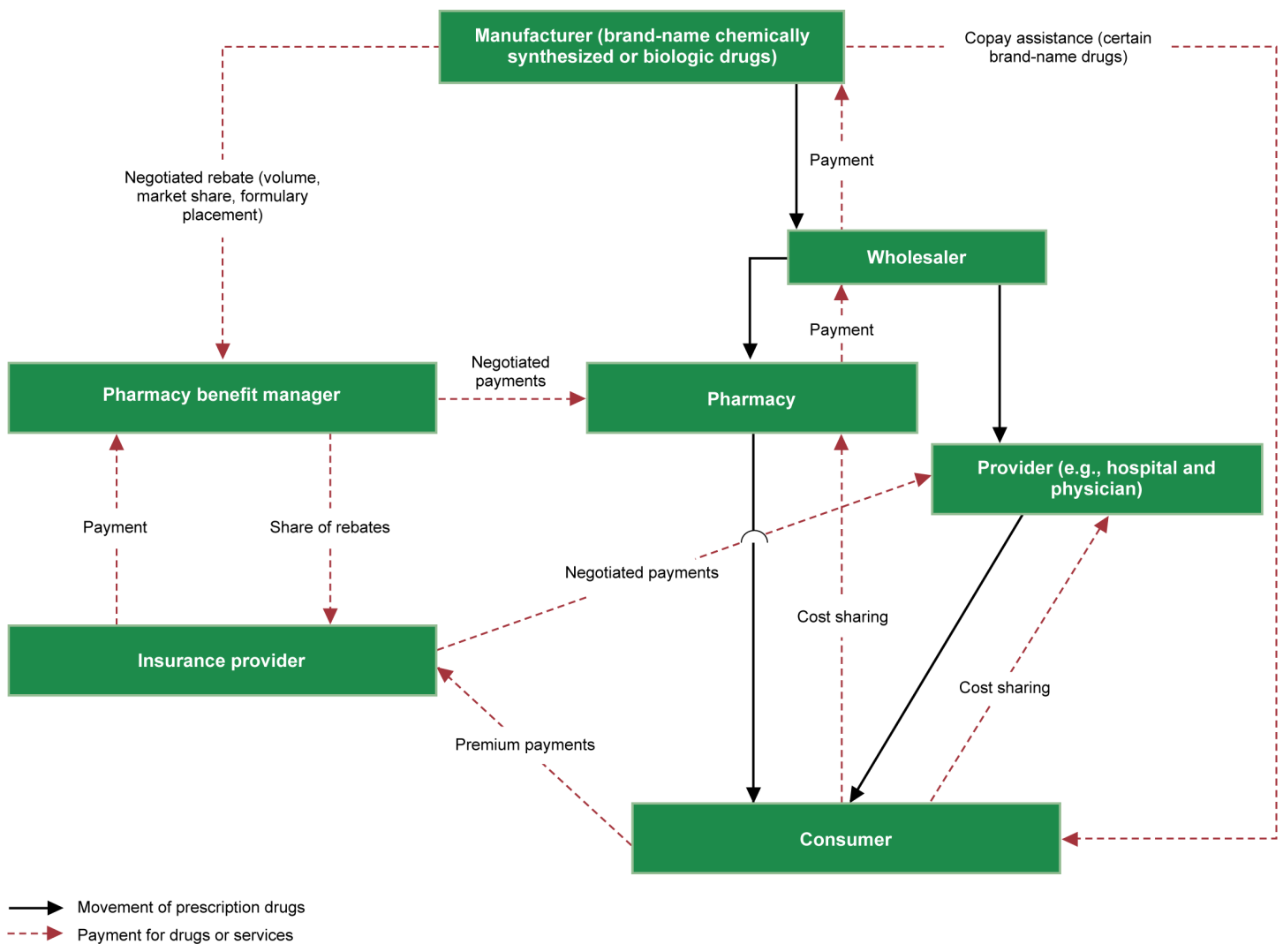
²⁰“Research and Experimental Expenditures” are expenses defined under 26 U.S.C. § 174 and Treasury Regulation 1.174-2.

²¹Some drugs cannot be self-administered by patients, such as chemotherapy drugs and inhalation solutions, and these are typically administered by nonretail providers (e.g., doctors and other hospital staff).

²²A copayment is usually a fixed dollar amount paid by the beneficiary, while coinsurance is a percentage of the cost.

conditions may include specifics about negotiated reimbursement rates (how much the pharmacy will be paid for dispensed drugs) and payment terms. Health care providers may also negotiate with insurers for the drugs they administer. The price that payers, PBMs, and ultimately consumers pay for prescription drugs depends in part on the amount of competition and the purchasers' negotiating power. The negotiating power is influenced by the ability to choose from competing drugs and the volume of drug purchased.

Figure 2: Example Interactions and Stakeholders in the Distribution of and Payment for Brand-Name Drugs



Source: GAO. | GAO-18-40

Note: Figure is illustrative of interactions for brand-name drugs and not exhaustive of all potential financial and distribution arrangements.

According to economic experts, the usual mechanisms that enforce market discipline may not work in the same way in the health care market as they do in other markets. In most markets—automobiles, for example—consumers are expected to be conscious of the price of goods. If a company raises the price of its goods, consumers would likely purchase fewer goods, causing the company’s revenues to decline. However, in the health care market, the purchase of goods and services is largely influenced by health care providers, who may not be well-informed about, or incentivized to consider, the prices involved. In the case of drugs, some experts argue that marketing and advertising may further distort provider decision making. In addition, if the patients’ medical bills are largely paid by insurance plans (other than copayment or coinsurance costs), then patients’ demand may not be significantly influenced by changes in price to the extent that it might be in other markets where the consumers see and pay the bill themselves.

Certain payment policies may also limit the negotiating power of insurers. For example, Medicare Part D is required to cover all drugs in six protected classes, which some experts argue reduces the negotiating power of its contractors (known as plan sponsors).²³ In addition, some brand-name drug companies are providing coupons to consumers to mitigate patient drug costs when a company’s drugs are not covered by payer formularies or require higher patient costs than preferred drugs. Some research and experts we interviewed have noted that this practice erodes the negotiating power of insurers and the cost management utility of formularies, which may result in lower prices for the patient using the coupon but higher prices overall.²⁴ In addition, patients and providers in

²³ See 42 U.S.C. § 1395w-104(b)(3)(G)(iv); 42 C.F.R. § 423.120(b)(2)(v) (2016). Part D sponsor formularies must include all or substantially all drugs in the following six classes of clinical concern: immunosuppressant (for prophylaxis of organ transplant rejection), antidepressant, antipsychotic, anticonvulsant, antiretroviral, and antineoplastic. Examples of other therapeutic classes include analgesics, blood glucose regulators, cardiovascular agents, dermatological agents, respiratory tract agents, and sedatives..

²⁴ We have previously reported on the use of coupons with respect to drugs typically administered by a physician or under a physician’s supervision and the implications of coupon programs on Medicare Part B spending. See GAO, *Medicare Part B: Data on Coupon Discounts Needed to Evaluate Methodology for Setting Drug Payment Rates*, GAO-16-643 (Washington, D.C.: Jul. 27, 2016).

many cases may not have clear information about the benefit relative to cost of one drug over another drug or treatment.

Consolidation and the Antitrust Review Process

Experts have said that consolidation as a result of mergers and acquisitions is one of multiple factors that could influence competition.²⁵ Fewer companies producing and marketing drugs can lead to greater market dominance by certain companies and less competition.

The Federal Trade Commission (FTC) and the U.S. Department of Justice (DOJ) enforce federal antitrust laws that prohibit activities, such as price fixing and mergers and acquisitions where the effect may be substantially to lessen competition or tend to create a monopoly.²⁶ Drug companies are subject to these antitrust laws. Companies are required to notify FTC and DOJ of certain pending mergers, also known as the premerger notification program.²⁷ As part of its premerger review process, these agencies can approve mergers contingent on company divestiture of assets, including those related to products in development—a process known as a negotiated merger remedy. These agreements are subject to public notice and comment and result in an enforceable order. The goal of a merger remedy is to preserve or restore competition in the relevant

²⁵A merger involves either the sale of all or part of the stock or assets of one company to another. FTC generally uses the term “merger” to refer to the purchase of all the stock of one company by another company. FTC generally uses the term “asset acquisition” or “partial stock acquisition” to describe types of transactions beyond mergers.

²⁶See 15 U.S.C. §§ 1, 18, 45. In addition, private parties and states may enforce state and federal antitrust laws by bringing suit for violations of these laws. See 15 U.S.C. §§ 15, 15c.

²⁷See 15 U.S.C. § 18a. Companies involved in transactions that do not meet certain criteria are not required to notify the FTC and DOJ, but these transactions may be subject to post-consummation review if they violate federal antitrust law.

markets.²⁸ Although FTC and DOJ each have authority and responsibilities under the antitrust laws, FTC typically examines proposed drug industry mergers. In addition, FTC has authority to investigate and take action against unfair methods of competition in or affecting commerce, as well as mergers and acquisitions that may substantially lessen competition or tend to create a monopoly, including in the drug industry.²⁹

Drug Industry Profit Margins and Merger and Acquisition Deal Values Increased, and the Industry Underwent Structural Changes

Among the worldwide drug companies included in the data we reviewed, reported pharmaceutical and biotechnology revenues and profit margins for most companies grew from 2006 through 2015. The number of mergers and acquisitions among companies in the industry generally held steady from 2006 through 2015, but merger and acquisition deal values increased. Market concentration varied by the specific market level considered. Industry experts we interviewed noted that market pressures have driven structural changes in the industry.

²⁸In 2017, FTC issued a retrospective study of agency-ordered merger remedies, including remedies ordered for 24 pharmaceutical mergers between 2006 and 2012. The study considered a remedy for on-market drugs—those marketed by both merging companies—successful if the company to which the product was divested subsequently sold the product in the market. Of the 60 on-market products for which FTC required divestitures to maintain competition, three-quarters were successful. The study also examined divestiture relating to pipeline products—products in development by one or both of the merging parties—and considered these successful if all assets relating to those products were transferred to a new firm with the same ability and incentive to bring the pipeline product to market. During the study period, FTC required asset divestitures to preserve competition for 32 pharmaceutical products in development; all of these asset transfers were successful. The study did not examine post-merger concentration or prices. See Federal Trade Commission, *The FTC's Merger Remedies 2006-2012: A Report of the Bureaus of Competition and Economics* (January 2017).

²⁹See 15 U.S.C. § 45.

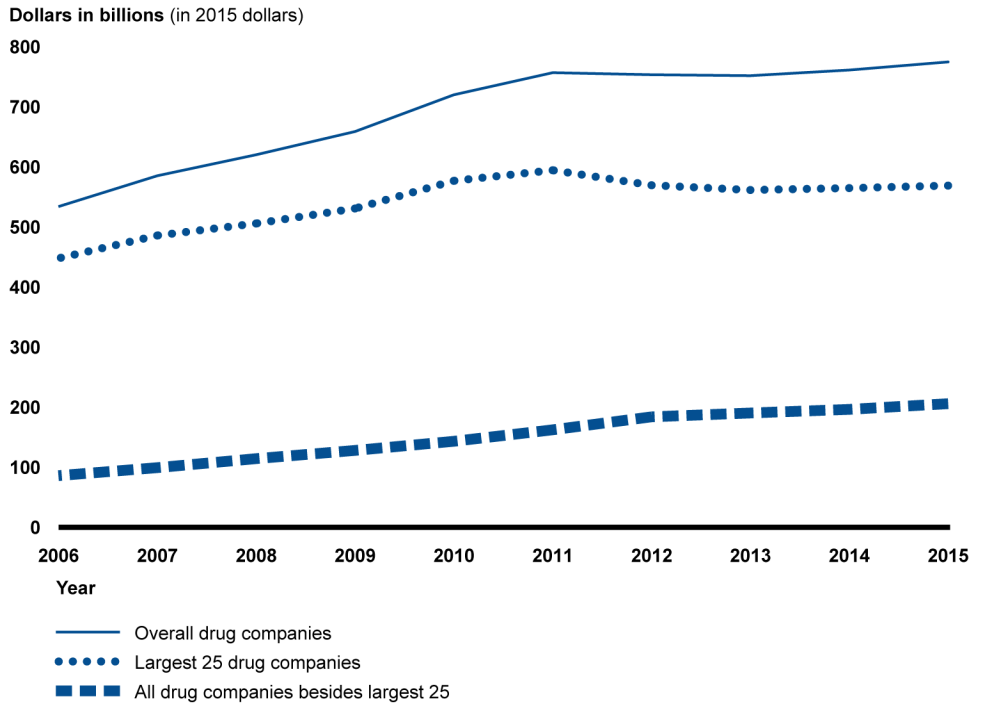
Company-Reported Revenues and Profit Margins Grew from 2006 through 2015

According to the data we reviewed, between 2006 and 2015 estimated aggregate worldwide pharmaceutical and biotechnology sales revenue for drug companies grew from \$534 billion to \$775 billion in real 2015 dollars (about 45 percent), with most of the growth occurring between 2006 and 2011.³⁰ The largest 25 of these companies (by 2015 pharmaceutical and biotechnology revenue) saw their aggregate sales revenue increase from \$448 billion in 2006 to \$569 billion in 2015, or about 27 percent. Aggregate sales revenue for all other drug companies in our data grew more sharply, from \$86 billion in 2006 to \$206 billion in 2015—an increase of about 140 percent (see fig. 3).³¹

³⁰Estimate is based on an analysis of 503 worldwide drug companies (i.e., pharmaceutical and biotechnology companies) in the market continuously from 2006 through 2015 and includes only worldwide pharmaceutical and biotechnology sales revenues. Total sales revenue for these companies not limited to pharmaceutical and biotechnology revenue followed a similar trend.

³¹Among the companies we examined, the largest 25 companies accounted for about 73 percent of 2015 pharmaceutical and biotechnology revenues. About 27 percent of pharmaceutical and biotechnology revenue in 2015 was held by the 5 largest companies.

Figure 3: Aggregate Worldwide Pharmaceutical and Biotechnology Sales Revenue for Drug Companies, Overall, Largest 25, and All Others, 2006-2015



Source: GAO analysis of Bloomberg data. | GAO-18-40

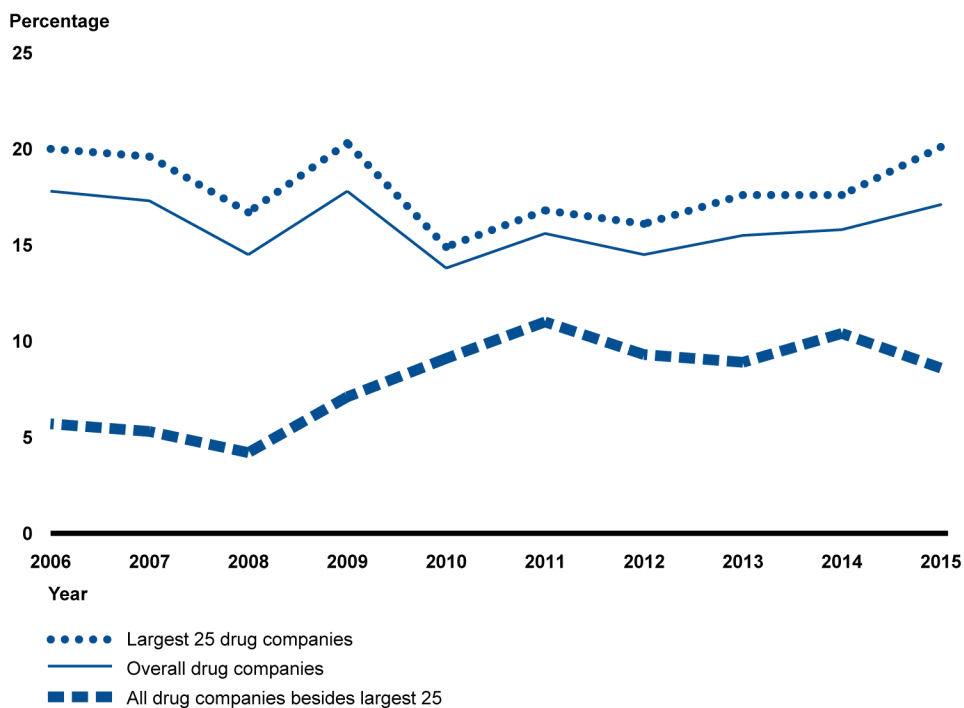
Note: The largest 25 drug companies consist of those with the highest pharmaceutical and biotechnology sales revenue in 2015. Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

Drug companies' average profit margins also grew from 2006 to 2015, though the trends differed for the largest 25 companies compared to the remaining companies in our data.³² Overall, about 67 percent of companies saw their profit margins increase between 2006 and 2015. While there was some fluctuation over time, the average profit margin was 17.1 percent in 2015 for all drug companies; profit margins were

³²Estimate is based on an analysis of 403 companies in the market continuously from 2006 through 2015. Profit margins were weighted by companies' reported pharmaceutical and biotechnology sales revenue for each year. Bloomberg calculates profit margin as (net income/revenue)*100. This ratio is computed on a post-tax basis.

higher for the largest 25 companies (20.1 percent in 2015) than for all others (8.6 percent in 2015; see fig. 4).³³

Figure 4: Average Profit Margin for Drug Companies, Overall, Largest 25, and All Others, 2006-2015



Source: GAO analysis of Bloomberg data. | GAO-18-40

Note: Largest 25 drug companies consist of those with the highest pharmaceutical and biotechnology sales revenue in 2015. Profit margins are weighted by drug companies' pharmaceutical and biotechnology sales revenue for each year. Bloomberg calculates profit margin as (net income/revenue)*100. This ratio is computed on a post-tax basis.

To better place large drug companies' profit margins into context, we conducted a similar examination of profit margins for large companies in other industries, specifically software companies and the largest 500 companies (by 2015 total worldwide revenue as reported in Bloomberg)

³³As alternative measures of profitability, we additionally examined the average sales-weighted return on assets and the average sales-weighted return on equity. Trends were similar to the average sales-weighted profit margin trend presented here.

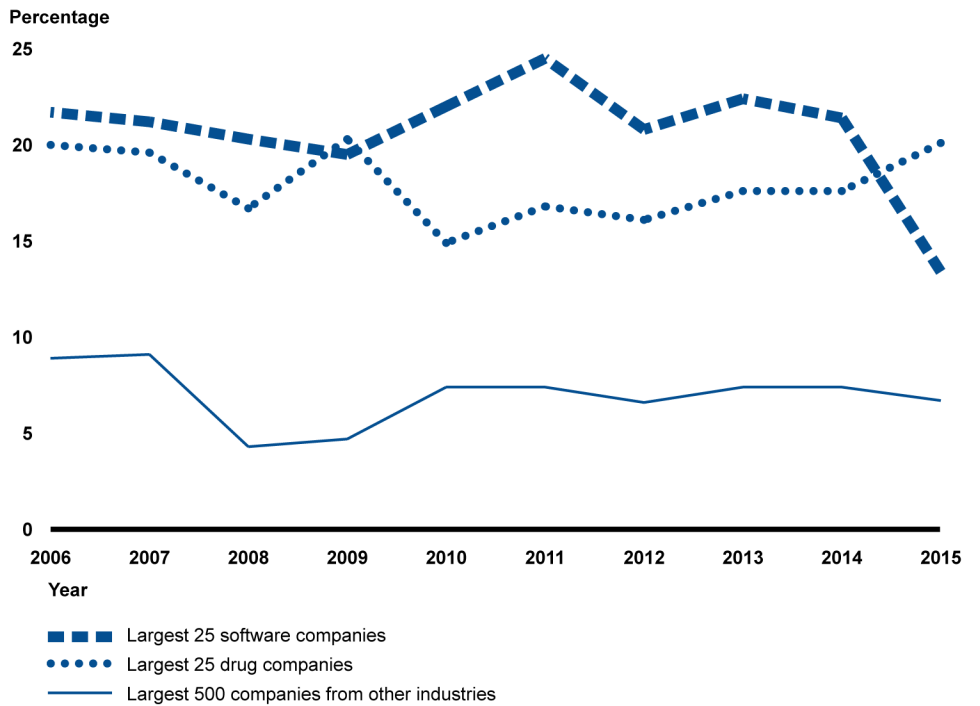
representing a wide range of industries.³⁴ We included the software industry separately because, like the drug industry, it has been cited as having high R&D investment and low production and distribution costs, though caution should be taken in making this comparison.³⁵ Among the largest 25 software companies (by 2015 software revenue), the average profit margin began at 21.7 percent in 2006 and remained relatively stable through 2014, before decreasing to 13.4 percent in 2015 (see fig. 5).³⁶ As a broader comparison, the average profit margin among the largest 500 companies was consistently lower than the average among the largest 25 drug companies and software companies. Among the largest 500 companies, the average profit margin decreased from 8.9 percent in 2006 to 6.7 percent in 2015.

³⁴Estimate is based on an analysis of the largest 25 software companies and 441 of the 500 largest companies in the market continuously from 2006 through 2015 and excludes pharmaceutical, biotechnology, and software companies. Profit margins were weighted by companies' total sales revenue for each year. Thirteen of the largest 25 pharmaceutical/biotechnology companies (by 2015 pharmaceutical and biotechnology revenue) would have otherwise been among the largest 500 companies (by 2015 total worldwide revenue), as would three of the largest 25 software companies.

³⁵Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, Pub. No. 2589 (Washington, D.C.: October 2006). Although there may be similarities between certain drug and software industry trends, the circumstances behind those trends could differ. A more in-depth comparison of these industries was outside the scope of our review.

³⁶Estimate is based on an analysis of the largest 25 software companies (by 2015 software revenue) of 345 software companies in the market continuously from 2006 through 2015. Profit margins were weighted by companies' software sales revenue for each year. Among smaller software companies, the average profit margin began at 5.5 percent in 2006 and increased to 5.9 percent in 2015. The average profit margin among all software companies began at 17.9 percent in 2006 and decreased to 12.1 percent in 2015.

Figure 5: Average Profit Margin for Drug Companies, Software Companies, and the Largest 500 Companies from Other Industries, 2006-2015



Source: GAO analysis of Bloomberg data. | GAO-18-40

Note: Profit margins for drug companies were weighted by their pharmaceutical and biotechnology sales revenue. Profit margins for software companies were weighted by their software sales revenue. Drug and software companies were excluded from the largest 500. Profit margins for the largest 500 companies were weighted by their total sales revenue, minus any pharmaceutical, biotechnology, or software sales revenue that may have been reported. Bloomberg calculates profit margin as (net income/revenue)*100. This ratio is computed on a post-tax basis.

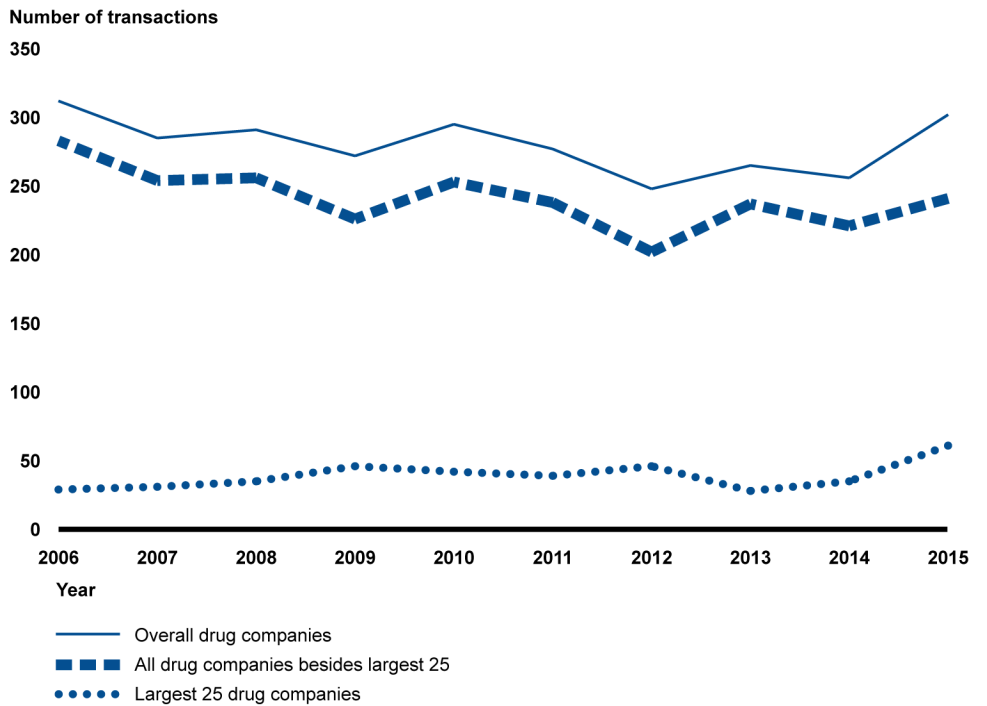
The Number of Mergers and Acquisitions Generally Held Steady from 2006 through 2015, but the Values Fluctuated

The annual number of mergers and acquisitions involving drug companies generally held steady between 2006 and 2015, with some fluctuations in intervening years, based on our review of Bloomberg data.³⁷ Overall, the number of transactions generally held steady, with 312 in 2006 and 302 transactions in 2015 (see fig. 6). The number of mergers and acquisitions involving one of the largest 25 companies (by 2015 pharmaceutical and biotechnology revenue) increased from 29 transactions in 2006 to 61 transactions in 2015.³⁸ In contrast, the number of transactions in our data for the smaller drug companies decreased from 283 transactions in 2006 to 241 transactions in 2015. See appendix II for additional information on merger and acquisition activity of 10 large companies in the drug industry as of 2014.

³⁷Number of mergers and acquisitions reflects the total number of known transactions between 2006 and 2015, including transactions among companies that were not in the market for the entire period. Transactions include drug companies (including both pharmaceutical and biotechnology) merging with or acquiring an asset from a pharmaceutical or biotechnology company, potentially including the company itself. Acquisitions may include the purchase of licenses.

³⁸Transactions were identified as being conducted by one of the largest 25 companies if the company Bloomberg designated as the “acquirer” in the transaction was one of the largest 25 companies by 2015 pharmaceutical and biotechnology revenue.

Figure 6: Total Number of Mergers and Acquisitions Conducted by Drug Companies, Overall, Largest 25, and All Others 2006-2015



Source: GAO analysis of Bloomberg data. | GAO-18-40

Note: Merger and acquisition transactions were attributed to the largest 25 if the company Bloomberg designated as the “acquirer” in the transaction was one of the largest 25 drug companies by 2015 pharmaceutical and biotechnology sales revenue. Transactions attributed to all other companies included those for which Bloomberg designated a company other than one of the largest 25 as the “acquirer.”

While the number of transactions generally held steady between 2006 and 2015, the total value of transactions completed over this period fluctuated considerably.³⁹ These fluctuations were driven by a small number of high value transactions, which tended to occur among the largest 25 companies (see fig. 7). For example, in 2009, there were three transactions each valued above \$20 billion in real dollars, all of which were conducted by companies in the largest 25:

- Pfizer Inc. acquired Wyeth LLC for about \$71 billion,

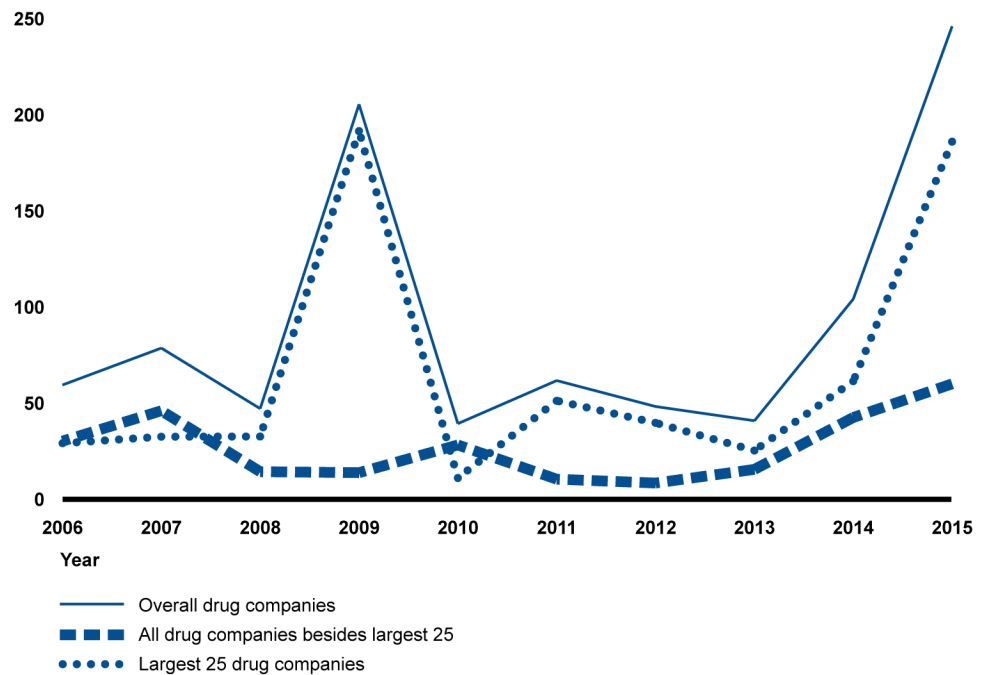
³⁹In any given year, approximately 40 to 50 percent of transactions did not have a value disclosed. Bloomberg officials told us that transactions involving private companies often have undisclosed values.

- Merck & Co Inc. acquired Schering-Plough Corp. for about \$56 billion, and
- Roche Holding AG acquired Genentech Inc. for about \$48 billion.

In 2015, about half of the total merger and acquisition transaction value came from five transactions each valued over \$10 billion in real dollars, including one very large transaction by Allergan for about \$72 billion. The other four transactions also involved companies among the largest 25. Much as the total value of mergers and acquisitions fluctuated considerably from year to year, median disclosed transaction values generally increased between 2006 and 2015, with considerable fluctuation among years.

Figure 7: Total Disclosed Value of Mergers and Acquisitions Conducted by Drug Companies, Overall, Largest 25, and All Others, 2006-2015

Dollars in billions (in 2015 dollars)



Source: GAO analysis of Bloomberg data. | GAO-18-40

Notes: Totals do not include transactions with undisclosed values. Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

Merger and acquisition transactions were attributed to the largest 25 if the company Bloomberg designated as the “acquirer” in the transaction was one of the largest 25 drug companies by 2015 pharmaceutical and biotechnology sales revenue. Transactions attributed to all other companies included those for which Bloomberg designated a company other than one of the largest 25 as the “acquirer.”

Concentration in the Drug Industry Varied by the Level of the Industry Considered

For the overall drug industry, the share of total sales accounted for by the 10 largest companies—a measure of concentration—declined between 2007 and 2014, the years for which public data were available from QuintilesIMS.⁴⁰ The largest 10 companies (by 2014 pharmaceutical revenue) had 48.9 percent of the drug industry’s sales revenue in 2007; by 2014, their share of the industry sales revenue declined to 38.2 percent.⁴¹ Concentration, which can be measured by share of sales, provides a basic indication of the competitiveness of companies in an industry or specified market level within an industry. Competition in the drug industry generally is examined at the level where products are viewed as substitutes, according to FTC officials. Substitutes can be products that are the same molecular entity or, in some cases, different molecular entities that treat the same condition.

At levels narrower than the entire industry, such as drugs within the same therapeutic class or of the same molecular entity (levels that are more relevant to competition), concentration in shares of sales can be higher than in the overall industry.⁴² For example, EvaluatePharma reported that the three largest companies in the anti-diabetics market accounted for

⁴⁰QuintilesIMS is a company that collects health care data and offers analytic services. For data charts, see: QuintilesIMS, "Top 20 Global Corporations 2014," *2014 and 2013 Top-Line Market Data*, accessed April 14, 2017, https://www.imshealth.com/FILES/WEB/CORPORATE/NEWS/TOP-LINE%20MARKET%20DATA/2014/TOP_20_GLOBAL_CORPORATIONS_2014.PDF; QuintilesIMS, "Top 20 Global Corporations 2012," *2012 and 2011 Top-Line Market Data*, accessed April 14, 2017, https://www.imshealth.com/FILES/WEB/CORPORATE/NEWS/TOP-LINE%20MARKET%20DATA/2012/TOP_20_GLOBAL_CORPORATIONS_2012.PDF.

⁴¹Analysis is based on the 10 largest companies for which data were available for each of 2007 through 2014. Much of the change in aggregate market share for the largest 10 companies (by 2014 pharmaceutical revenue) resulted from Pfizer’s decline in market share from about 9.3 percent in 2007 to 4.8 percent in 2014. Seven of the 10 companies experienced small decreases in market share, while 2 companies—Novartis and Teva—experienced small increases (0.03 percent and 0.13 percent, respectively).

⁴²A generic or biosimilar may compete with the brand-name drug at the molecular level since it is bioequivalent (in the case of chemically synthesized drugs) or highly similar to the reference product with no clinically meaningful differences (in the case of biologics).

67.5 percent of the sales in that market in 2014.⁴³ Similarly, the three largest companies in the anti-rheumatics market accounted for 56.8 percent of the sales in that market in 2014, and the three largest companies in the anti-virals market accounted for 72.4 percent of the sales in that market, with the leading anti-viral manufacturer accounting for over half (52.8 percent) of worldwide anti-viral sales.⁴⁴

Concentration can also vary for drugs of the same molecular entity, as some generic drugs may have different numbers of manufacturers than others. For example, as of 2017, 14 companies have approved ANDAs for lisinopril, a drug for hypertension—that is, 14 companies have generic versions of the drug approved for manufacture.⁴⁵ By comparison, only one company has an approved ANDA for efavirenz, a drug used to treat HIV infection. Greater numbers of generic manufacturers generally reduce concentration, as generic manufacturers compete with one another in addition to brand-name manufacturers. More broadly, one recent study found that of the novel drugs approved in tablet or capsule formulation since the 1984 Hatch-Waxman Act and eligible for generic competition, more than one-third had three or fewer generic approvals.⁴⁶

⁴³EvaluatePharma, *World Preview 2015, Outlook to 2020* (Boston, MA: Evaluate, 2015). EvaluatePharma collects and analyzes health care data. EvaluatePharma estimated that in 2014, the 10 largest companies by prescription drug sales controlled about 44 percent of the overall pharmaceutical industry market, which still reflects lower concentration than in the therapeutic areas noted above.

⁴⁴EvaluatePharma reported that in 2016, the three largest companies in the anti-diabetics market held 62.2 percent of the market; the three largest companies in the anti-rheumatics market held 56.6 percent of the market; and the three largest companies in the anti-virals market held 75.8 percent of the market, with the leading anti-viral manufacturer accounting for 57.1 percent of worldwide anti-viral sales. See EvaluatePharma, *World Preview 2017, Outlook to 2022* (Boston, MA: Evaluate, 2017).

⁴⁵Although 14 companies are approved to manufacture generic lisinopril, the number of manufacturers actively manufacturing the drug may be lower.

⁴⁶R. Gupta, A. S. Kesselheim, N. Downing, J. Greene, and J. S. Ross, "Generic Drug Approvals Since the 1984 Hatch-Waxman Act," *JAMA Internal Medicine*, vol. 176, no. 9 (2016). See also E. R. Berndt, R. M. Conti, and S. J. Murphy, *The Landscape of US Generic Prescriptions Drug Markets, 2004-2016*, National Bureau of Economic Research Working Paper 23640 (2017). The latter study reported that the share of generic drugs (by dosage form, such as a tablet or injectable) with two or fewer manufacturers was relatively stable at about 50 percent between 2004 and 2016, which represents a relatively high concentration.

Industry Experts Noted Market Pressures Have Driven Structural Changes in the Industry, Such as in the Types of Acquisitions and Increased Specialization in Therapeutic Areas

Experts we interviewed noted that market pressures such as rising R&D costs, fewer drugs in the R&D pipeline, and the growth in sales of generic drugs have driven various structural changes in the drug industry, such as in the types of acquisitions being sought. Not all companies respond to those pressures in identical ways. For example, some experts said that some companies that traditionally manufactured brand-name drugs are expanding into the manufacturing of generic drugs. These brand-name companies may acquire a generics manufacturer to adjust the portfolio of drugs they manufacture or gain access to a generics business. Similarly, some traditionally generic manufacturers are expanding into brand-name manufacturing to acquire product lines with more generous profit margins. For both brand-name and generic manufacturers, expanding the size of their drug portfolio may improve their bargaining position with PBMs, according to two economists we interviewed.⁴⁷ Experts also said that traditionally large companies are increasingly relying on mergers and acquisitions to obtain access to new research and are conducting less of their own research in-house. In addition, experts told us that investment in the development of traditional chemically synthesized drugs has produced increasingly lower financial returns, resulting in some traditional pharmaceutical companies turning to invest more in the development of more complicated and costly biologics. Many experts highlighted the proliferation of biotechnology companies as large pharmaceutical companies seek to acquire promising new research developments.

Many experts told us that market pressures have also driven some drug companies to move towards specialization in certain therapeutic areas, including through mergers and acquisitions. As one example, GlaxoSmithKline acquired most of Novartis's vaccine business in 2015, bolstering its own line of vaccines and helping to raise its share of sales of the worldwide vaccine market.⁴⁸ Simultaneously, Novartis acquired GlaxoSmithKline's oncology business, enabling both companies to shed one line of business and focus on the newly acquired therapeutic areas.

⁴⁷PBMs negotiate drug prices with manufacturers on behalf of insurance companies. Manufacturers may hold additional bargaining power in negotiations with PBMs if they have large drug portfolios.

⁴⁸GlaxoSmithKline's vaccine market share was 20 percent in 2014 and 23 percent in 2016, according to data reported by EvaluatePharma. See EvaluatePharma, *World Preview 2015, Outlook to 2020* (Boston, MA: Evaluate, 2015) and EvaluatePharma, *World Preview 2017, Outlook to 2022* (Boston, MA: Evaluate, 2017).

Experts again noted that one reason companies may be specializing through mergers and acquisitions is because of the increasing cost of R&D—acquiring promising new or developed research or product lines helps companies mitigate R&D investment risk. Acquiring existing lines of business from competitors within a therapeutic area may also help a company increase its presence in a particular therapeutic area.

Another widely cited factor influencing structural changes in U.S. industries—including the drug industry—involves tax-influenced mergers, called corporate inversions. An inversion is a type of merger where a U.S. corporation merges with or acquires a company located in a foreign jurisdiction—often a lower-tax country—and reorganizes so the resulting parent corporation is located in the foreign country.⁴⁹ This can reduce a corporation’s overall tax liability—often by reducing its U.S. tax liability.⁵⁰ While taxes are one of many factors that may influence trends in mergers and acquisitions as discussed above, the incentive for drug companies to reduce tax burdens through inversions can be significant.⁵¹ In 2016, the Treasury Department issued new regulations to curb inversions.⁵²

⁴⁹For additional context on inversions, including those in the drug industry, see Congressional Budget Office, *An Analysis of Corporate Inversions*, Pub. No. 53093 (Washington D.C.: September 2017).

⁵⁰One report indicates there have been at least eight drug company mergers or acquisitions that resulted in a change to incorporate in another country, usually a low-tax country, from 2010 to 2016. See Bloomberg, “Tracking Tax Runaways,” accessed August 28, 2017, <http://www.bloomberg.com/graphics/tax-inversion-tracker>. These potentially tax-influenced mergers or acquisitions include some large drug companies, such as Actavis, which has since acquired Allergan to become one of the world’s largest drug companies by drug sales revenue.

⁵¹As an example, Pfizer has attempted multiple mergers with foreign companies. Most recently, its merger attempt with Allergan was cancelled when, in 2016, the Treasury Department issued regulations designed to make it harder to invert.

⁵²See Treasury notice of regulations, accessed August 28, 2017, <http://www.treasury.gov/press-center/press-releases/Pages/jl0405.aspx>.

**Pharmaceutical
Company-Reported
Research and
Development
Spending Grew
Slightly, while
Biologics and Orphan
Drugs Were a Greater
Share of New Drug
Approvals**

Pharmaceutical company-reported R&D spending grew slightly from 2008 through 2014, while federally funded spending decreased slightly over the period. Industry spending focused on drug development rather than earlier-stage research, whereas direct federal spending, such as through NIH grants, funded a greater amount of basic research. Claims for the orphan drug credit, one of several federal tax incentives encouraging drug development, increased sharply from 2005 through 2014. Biologics and orphan drugs accounted for an increasing share of new drug approvals from 2005 through 2016. Studies we reviewed and experts we interviewed suggested that potential revenues, costs, and policy incentives influenced brand-name drug company R&D investment decisions.

Pharmaceutical Company-
Reported Research and
Development Spending
Increased Slightly, While
Federally Funded
Spending Decreased
Slightly, from 2008 through
2014

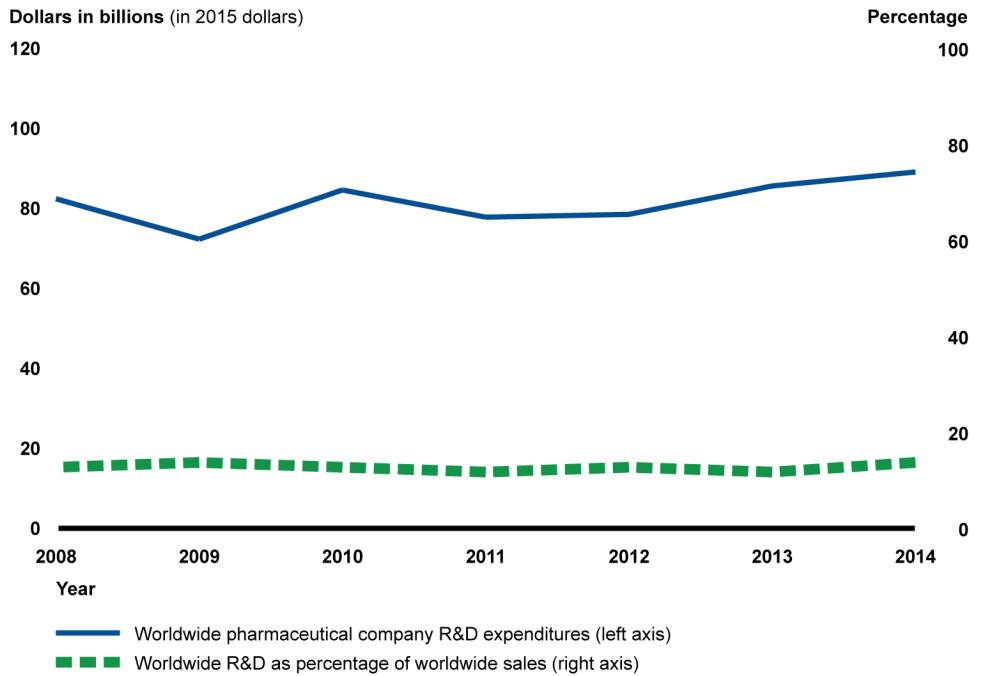
Our analysis of industry survey data from NSF indicate that worldwide R&D spending by U.S.-owned pharmaceutical companies and U.S.-based R&D by foreign companies increased slightly (8 percent) in real dollars from \$82 billion in 2008 to \$89 billion in 2014, the years for which comparable data were available (see fig. 8).⁵³ According to NSF survey data, the share of this spending that pharmaceutical companies paid others to perform also increased over the period. Estimates of worldwide R&D expenditures as a percentage share of total worldwide sales averaged 13 percent and ranged from 11.5 to 14.2 percent over the period 2008 to 2014.⁵⁴ This amount, according to estimates from QuintilesIMS, is larger than the 7.6 percent of total pharmaceutical sales revenue that the industry spent on marketing and promotion in 2014; however, due to differences in the different sources' methodology and data, publicly reported figures are not necessarily comparable.⁵⁵

⁵³Industry R&D expenditures and sales estimates presented here are from the Business Research, Development, and Innovation Survey maintained by NSF. Data represent pharmaceutical company-reported spending for R&D conducted in the United States regardless of the location of the parent company and spending for R&D conducted abroad by U.S.-owned pharmaceutical companies. It does not include spending by biotechnology companies, which we reported separately because these estimates were less available and reliable. R&D expense includes the amount a company pays from its own funds for R&D that is done for the company's benefit and includes company-performed R&D in both its domestic and foreign locations plus R&D the company pays others to perform.

⁵⁴We also examined R&D spending estimates reported by PhRMA for its member companies, which are generally large pharmaceutical companies. PhRMA member companies' reported worldwide R&D spending grew 2.5 percent in real dollars from \$53 billion in 2008 to \$54 billion in 2014. Companies reported that this represented an average of 17 percent of worldwide sales each year, more than the 14 percent represented by NSF's estimates. PhRMA represents fewer companies than in the spending and sales represented by NSF. In addition, PhRMA's R&D spending estimates include spending for Phase IV clinical trials conducted after the drug has come to market, whereas such postmarket spending is excluded from NSF's estimates. PhRMA reported that postmarket research accounted for about \$9 billion or 17 percent of total reported R&D spending in 2014.

⁵⁵According to estimates reported by QuintilesIMS—formerly IMS Health—the pharmaceutical industry spent about \$71 billion worldwide on marketing in 2014. This included \$44 billion on promoting drugs directly to providers—known as detailing—\$8 billion for free samples, \$8 billion for meetings, and \$5 billion for direct-to-consumer advertising. See QuintilesIMS, *Global Pharmaceuticals Marketing Channel Reference 2015* (France: 2015). Analysis of marketing and promotion spending was outside the scope of our review.

Figure 8: Estimated Worldwide Pharmaceutical Company-Reported Research and Development (R&D) Expenditures and Expenditures as Percentage of Worldwide Sales, 2008 – 2014



Source: GAO analysis of National Science Foundation (NSF) Business Research, Development, and Innovation Survey data. | GAO-18-40

Notes: Data represent self-reported R&D spending paid for by pharmaceutical companies and performed in the United States regardless the location of the parent company and R&D spending conducted abroad by U.S.-owned companies. Pharmaceutical companies include respondents with spending relevant to North American Industry Classification System code 3254 for pharmaceuticals and medicines; it does not include biotechnology companies. All survey estimates have a relative standard error of 2 percentages or less. Data do not include industry spending for clinical trials conducted after the drug has come to market.

Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

The NSF Business Research, Development, and Innovation Survey data indicated worldwide R&D spending for respondent biotechnology companies was \$9.2 billion in 2009, dropped to \$2.7 billion in 2010, rose to \$6.7 billion in 2011, then decreased to \$1.7 billion in 2013, the years

for which worldwide data were available.⁵⁶ The percentage of biotechnology company-reported R&D to worldwide biotechnology sales ranged widely from 43 percent in 2011 to 7 percent in 2013.⁵⁷

Pharmaceutical companies reported spending a greater share of sales on R&D than comparably large, R&D-intensive industries and all aggregated manufacturing and non-manufacturing industries, according to comparable Business Research, Development, and Innovation Survey data (see table 2). For example, in 2014, self-reported R&D expenditures as a percentage of total sales were higher for pharmaceutical companies than for other comparably large, R&D-intensive sectors such as semiconductor and other electronic components, software publishers, and computer system design services.⁵⁸

⁵⁶Data represent companies classified as North American Industry Classification System (NAICS) code 541711 for biotechnology research and development. NSF survey data for these biotechnology companies were less consistently and reliably available. Specifically, R&D expenditure estimates were not available for 2008 or 2014 and estimates for years between varied greatly and with large standard errors.

⁵⁷Other sources suggest biotechnology companies spent upwards of \$20 billion on R&D in 2012. See H. Moses, D. H. M. Matheson, S. Cairns-Smith, B. P. George, C. Palisch, and E. R. Dorsey, "The Anatomy of Medical Research: US and International Comparisons," *JAMA*, vol. 313, no. 2 (2015).

⁵⁸Caution should be taken in directly comparing spending by these industries, despite certain similarities. A more in-depth comparison of these industries was outside the scope of our review.

Table 2: Worldwide Estimated Research and Development Expenditures and Sales Reported by Companies in Selected Industries, 2013 and 2014

Industry	Worldwide sales (US\$ billions)		Worldwide R&D expenditures (US\$ billions)		R&D as % of Sales	
	2013	2014	2013	2014	2013	2014
All manufacturing industries	8,586.6	8,320.5	277.8	289.8	3.2	3.5
Pharmaceuticals and medicines	741.5	625.7	85.6	89.1	11.5	14.2
Semiconductor and other electronic components	351.9	388.1	40.1	41.7	11.4	10.8
Medical equipment and supplies	330.4	308.7	14.2	12.5	4.3	4.0
Aerospace products and parts	451.1	464.3	14.3	13.7	3.2	3.0
All nonmanufacturing industries	5,116.3	5,189.5	109.2	113.8	2.1	2.2
Software publishers	671.3	585.8	48.2	46.7	7.2	8.0
Computer systems design and related services	142.8	147.8	9.9	10.4	6.9	7.0
Biotechnology research and development	25.9	18.4	1.7	^a	6.7	^a

Source: GAO analysis of National Science Foundation (NSF) Business Research, Development, and Innovation Survey data | GAO-18-40

Notes: Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

^aBiotechnology company-reported R&D estimates were not available for 2014.

Direct federal spending for biomedical research, primarily funded through NIH, decreased 3.8 percent in real dollars from \$27 billion in fiscal year 2008 to \$26 billion in fiscal year 2014, after a peak of \$32 billion in 2010, according to our analysis of federal survey data from NSF.⁵⁹ NIH was the primary federal source for biomedical research and accounted for \$26 billion of spending in 2008 and \$25 billion in 2014. According to federal officials we interviewed, other agencies that fund biomedical research that could be relevant to drug R&D were the Department of Defense and the NSF.

In addition, state and local governments, foundations, charities, and venture capital also funded biomedical R&D, according to studies and experts we interviewed. Estimates of this spending are much smaller than

⁵⁹Data represent federal agency obligations for basic and applied research in the fields of biological sciences, medical sciences, and other life sciences as measured by the Survey of Federal Funds for Research and Development maintained by NSF. Obligations represent amounts for orders placed, contracts awarded, services received, and similar transactions committed to by agencies during a given period, regardless of when funds were appropriated and when future payment of money is required.

those for industry and federal agencies. In 2015, National Health Expenditure estimates show that state and local governments spent \$6.7 billion on research and non-industry private funders spent \$5.3 billion.

Pharmaceutical Company-
Reported Spending
Focused on Drug
Development and Federal
Spending Focused on
Basic Research

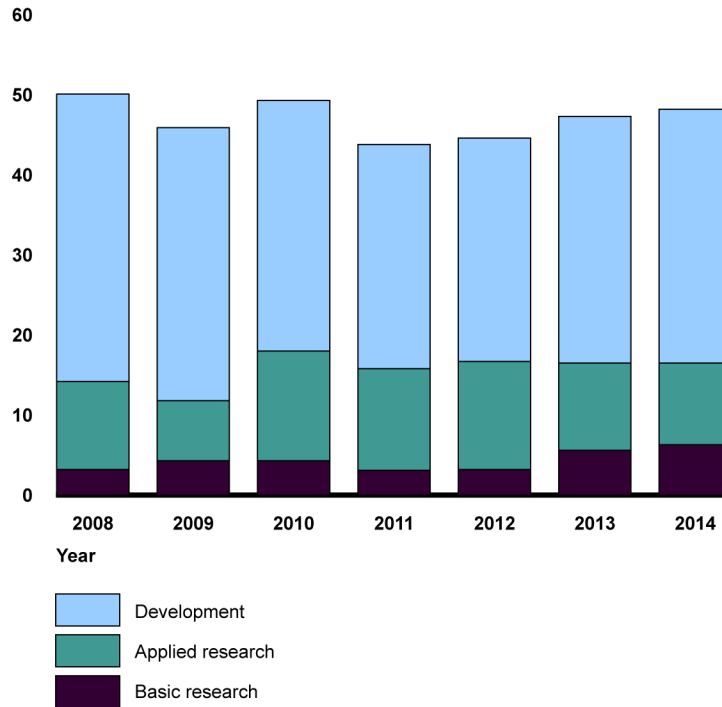
Pharmaceutical company spending from 2008 through 2014 focused on drug development, while federal spending focused on earlier-stage basic research. For example, in 2014 pharmaceutical companies reported allocating 13 percent of total reported domestic R&D spending on basic research, 21 percent on applied research, and 66 percent on development (see fig. 9).⁶⁰

⁶⁰For the purpose of the Business Research Development and Innovation Survey, NSF defines basic research to include activities aimed at acquiring new knowledge or understanding without specific immediate commercial applications or uses. Applied research includes activities aimed at solving a specific problem or meeting a specific commercial objective. Development includes systematic use of research and practical experience to produce new or significantly improved goods, services, or processes.

For the purposes of NSF's Survey of Federal Funds for Research and Development, research is classified as either basic or applied according to the objectives of the sponsoring agency. In basic research the objective is to gain more complete knowledge or understanding of the fundamental aspects of phenomena and of observable facts, without specific applications toward processes or products in mind. In applied research the objective is to gain knowledge or understanding necessary for determining the means by which a recognized need may be met. Development is systematic use of the knowledge or understanding gained from research, directed toward the production of useful materials, devices, systems, or methods, including design and development of prototypes and processes.

Figure 9: Estimated Domestic Pharmaceutical Company-Reported Research and Development (R&D) Expenditures by Type, 2008 - 2014

Dollars in billions (in 2015 dollars)



Source: GAO analysis of National Science Foundation (NSF) Business Research, Development, and Innovation Survey data. | GAO-18-40

Notes: Data represent self-reported R&D spending paid for by pharmaceutical companies and performed in the United States regardless of the location of the parent company, and R&D spending conducted abroad by U.S.-owned companies. Pharmaceutical companies include respondents with spending relevant to North American Industry Classification System code 3254 for pharmaceuticals and medicines. All survey estimates have a relative standard error of 2 percentages or less. Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

Basic research includes activities aimed at acquiring new knowledge or understanding without specific immediate commercial applications or uses. Applied research includes activities aimed at solving a specific problem or meeting a specific commercial objective. Development includes systematic use of research and practical experience to produce new or significantly improved goods, services, or processes. Data do not include industry spending for clinical trials conducted after the drug has come to market.

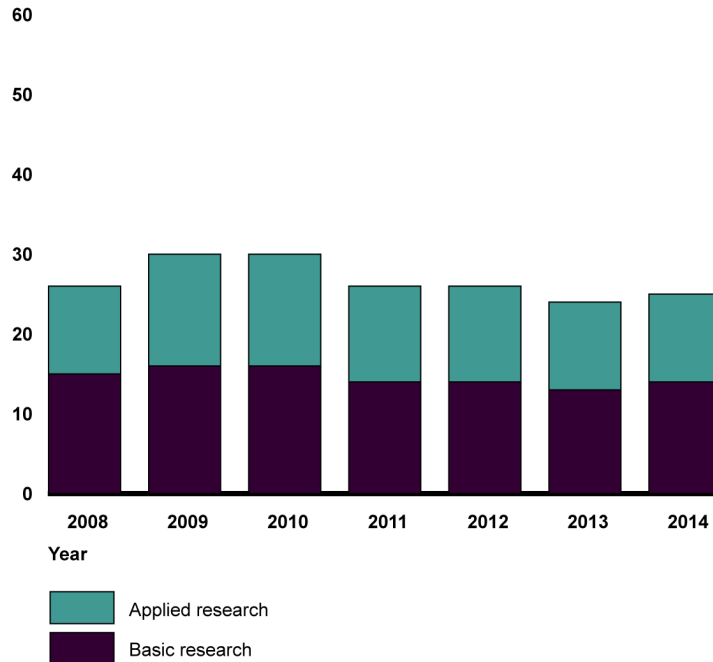
By comparison, federal spending consistently funded a greater amount of basic research, according to our analysis of data from NSF's Survey of Federal Funds for Research and Development. Studies show that basic research often supplies the innovation upon which the industry develops

drugs.⁶¹ For example, as shown in figure 10 below, NIH obligated 54 percent, or \$13.6 billion of its total \$25 billion of drug related spending, for basic research in fiscal year 2014. This is more than twice as much as the \$6.3 billion that NSF data show pharmaceutical companies reported spending domestically for basic research that year. NIH also funded applied research that includes more targeted research and activities aimed at translating basic research into new treatments for patients. For example, NIH supports clinical research through the National Center for Advancing Translational Sciences and several other NIH Institutes and Centers. This includes supporting pre-clinical and early-stage clinical trials; promoting and initiating collaborations and partnerships among industry, academia, and other stakeholder communities, such as patient advocacy groups, to address research barriers; and facilitating data sharing, according to agency officials. In accordance with the definition of “development” provided by NSF for the Survey of Federal Funds for Research and Development, NIH classifies R&D activities as “research.” Therefore, NIH does not report any of its activities as strictly drug development, according to agency officials.

⁶¹For example, a 2011 study found that publicly funded research played a role in nearly half of drugs approved between 1988 and 2005. See B. N. Sampat and F. R. Lichtenberg, “What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?” *Health Affairs*, vol. 30, no. 2 (2011). See also A. A. Toole, “The Impact of Public Basic Research on Industrial Innovation: Evidence From the Pharmaceutical Industry,” *Research Policy*, vol. 41 (2012) and A. S. Kesselheim, Y. T. Tan, and J. Avorn, “The Roles of Academia, Rare Diseases, and Repurposing in the Development of the Most Transformative Drugs,” *Health Affairs*, vol. 34, no. 2 (2015).

Figure 10: National Institutes of Health Obligations for Drug-Related Basic and Applied Research, Fiscal Year 2008 – 2014

Dollars in billions (in 2015 dollars)



Source: GAO analysis of National Science Foundation (NSF) Federal Funds for Research and Development Survey data. | GAO-18-40

Notes: Data represent agency-reported obligations for basic and applied research in academic areas including biological sciences, medical sciences, and other life sciences. Data may overestimate federal spending directly applicable to drug research as it may include funds for biomedical research not directly relevant to drugs. Data are adjusted to fiscal year 2015 U.S. dollars using the gross domestic product price index. Obligations represent amounts for orders placed, contracts awarded, services received, and similar transactions committed to by agencies during a given period, regardless of when funds were appropriated and when future payment of money is required.

Basic research includes activities aimed at acquiring new knowledge or understanding without specific applications toward processes or products in mind. Applied research includes systematic study to gain knowledge or understanding necessary to determine the means by which a recognized and specific need may be met. Obligations do not include any spending specifically for development.

Studies and experts we interviewed suggested that the relative roles of R&D funders and performers are evolving. For example, some experts noted that there is less distinction between public and private investment in R&D than in the past because publicly funded research institutions, such as universities, are frequently involved in financial relationships with industry for commercial development. Some industry experts also noted NIH’s role in fostering these collaborations. As previously noted, there has been a proliferation of smaller, biotechnology-focused companies and greater use of acquisition and licensing agreements by larger, traditional

pharmaceutical and biotechnology companies to build their earlier-stage product pipelines rather than conducting early research in-house. Experts suggested that this trend is a response to the increasing complexity and cost of R&D concurrent with the advent of biotechnology and waves of patent and exclusivity expirations for large companies.

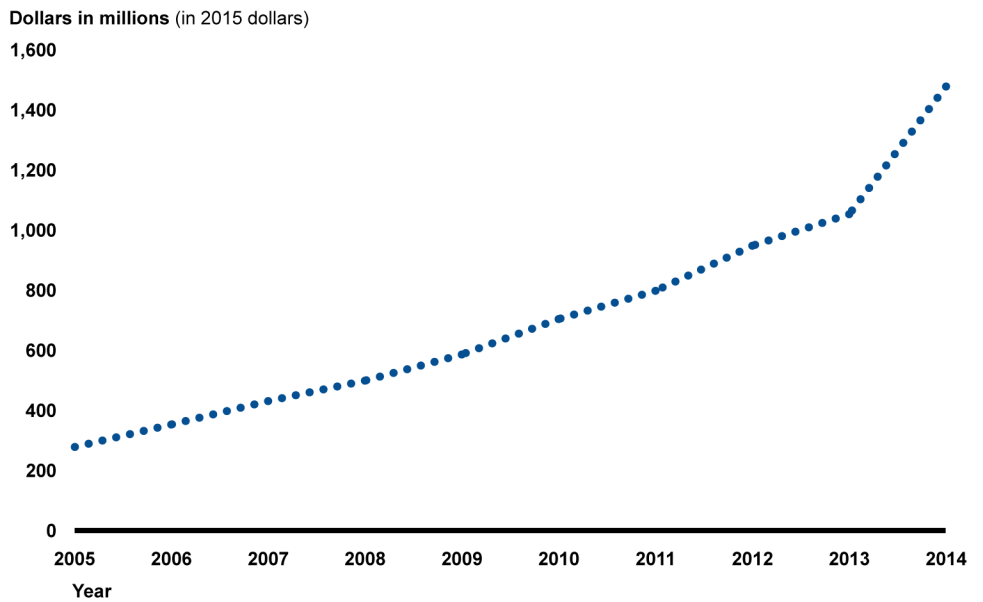
In addition, traditional pharmaceutical companies also performed less R&D internally than in the past, according to NSF data. Worldwide R&D spending paid for and performed by pharmaceutical companies decreased in real dollars from \$61.7 billion in 2008 to \$58.2 billion in 2014 and as a share of total worldwide R&D spending. Conversely, the share of the worldwide pharmaceutical R&D spending that was paid for by the company and performed by others, such as through purchased R&D services, increased from 25 percent in 2008 to 35 percent in 2014.

Federal Tax Provisions Encourage Drug R&D, with Claims for the Orphan Drug Credit Increasing Sharply

Similar to the R&D spending trend identified above from the NSF data, various IRS tax data consistently indicate that drug R&D activities did not change significantly—with the exception of the orphan drug credit, which over time increased sharply. Inflation-adjusted claims by all industries for the orphan drug credit increased five-fold between 2005 and 2014, from about \$280 million to about \$1.5 billion (see fig 11).⁶²

⁶²All or nearly all claims for the orphan drug credit each year were from drug-related corporations. Specifically, nearly all claims were from pharmaceutical manufacturers, drug wholesalers, and scientific research and development corporations, including corporations that conduct biotechnology research and development.

Figure 11: Orphan Drug Credit Claims, 2005-2014



Source: GAO analysis of Internal Revenue Service data. | GAO-18-40

Notes: All or nearly all claims for the orphan drug credit each year were from drug-related corporations.

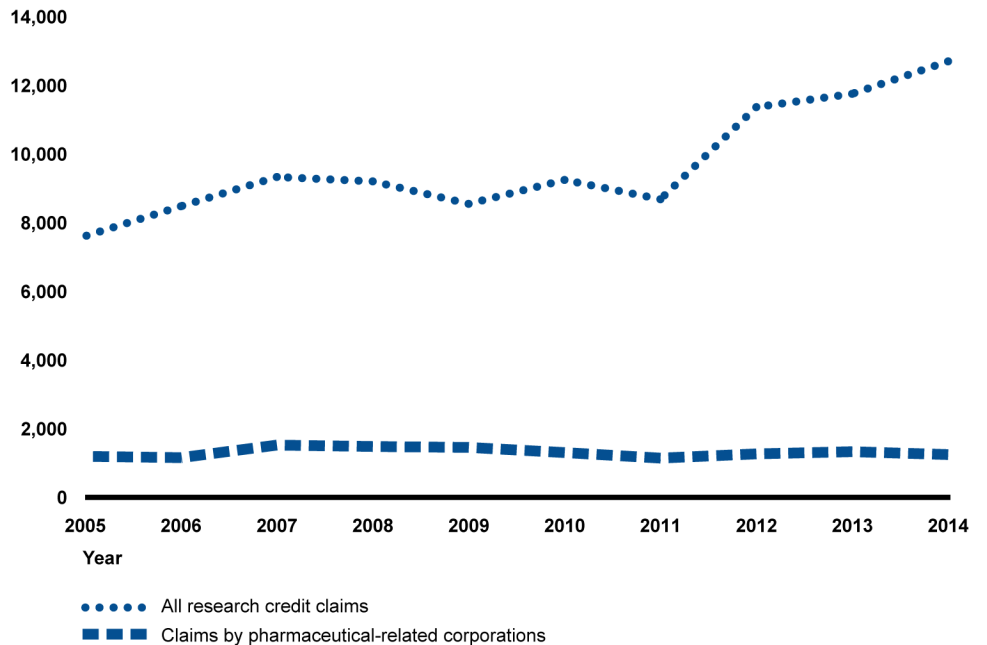
Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

Claims for the other tax credit that incentivizes drug development—the research credit—were more stable than the orphan drug credit between 2005 and 2014. As shown below in figure 12, IRS estimates of research credit claims for pharmaceutical-related corporations reached a high of \$1.5 billion in 2007, but then fell to about \$1.2 billion in 2014, a level close to the beginning of the period. This may be due in part to the fact that we were not able to obtain a specific estimate for the research credits claimed by biotechnology companies.⁶³ By comparison, research credit claims grew for all industries over the period, particularly from 2012 to 2014.

⁶³IRS data on scientific research and development corporations includes corporations that conduct biotechnology research and development but also includes companies doing research in areas unrelated to drug development. Therefore we did not report data for claims by companies in this category.

Figure 12: Research Credit Claims for All Industries and Pharmaceutical-Related Corporations, 2005-2014

Dollars in millions (in 2015 dollars)



Source: GAO analysis of Internal Revenue Service data. | GAO-18-40

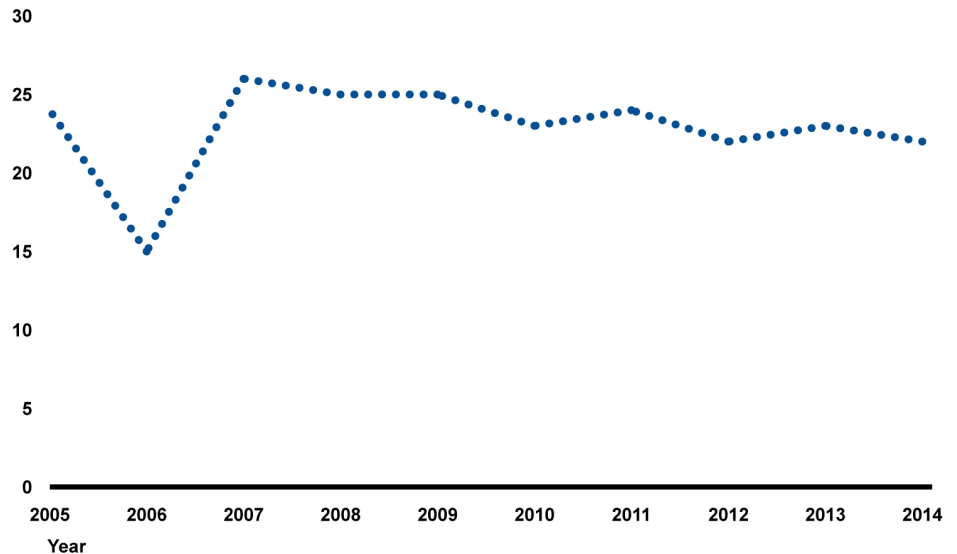
Notes: Pharmaceutical-related corporations include pharmaceutical manufacturers and drug wholesalers. They do not include corporations that primarily conduct biotechnology research and development.

Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

According to IRS data, between 2005 and 2014 the pharmaceutical manufacturing industry spent, on average, about \$22.5 billion per year (in real dollars) in qualified research spending that factored into the calculation of the research credit (see fig. 13). Spending peaked in 2007 at \$25.5 billion and then generally declined from 2007 to 2014. This amount of spending—reported on tax returns as meeting the requirements of qualified research spending as noted above—is less than half of the research spending reported by NSF’s Business Research, Development, and Innovation Survey data. These research spending differences can reflect both differences in the definitions of research spending in each data source and in the specific industry definitions used in the different data sources.

Figure 13: Qualified Research Expenses for Pharmaceutical Corporations, 2005 – 2014

Dollars in billions (in 2015 dollars)



Source: GAO analysis of Internal Revenue Service data. | GAO-18-40

Note: Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

The ability of companies to deduct research expenditures in the year they are incurred simplifies tax accounting for research spending and reduces the after-tax cost of research investments. The amount of research spending deducted by large pharmaceutical corporations that submitted an IRS form M-3 has been largely consistent between 2010 and 2013, the years for which data were available (see table 3). Specifically, research expenditure deductions in real dollars increased to \$30.7 billion in 2013 after a low over the period of \$24.9 billion in 2012. The table also shows that the amounts shown as research expense on the financial statements of the same corporations were slightly higher than the amount deducted on tax returns in each year.⁶⁴

⁶⁴IRS form M-3 is designed to reconcile financial statement reporting with amounts reported on tax returns. Financial reporting can differ from tax reporting because (1) the underlying consolidated group of companies may differ, and (2) the rules defining items may differ between financial and tax accounting.

Table 3: Research Expense Deductions by Large Pharmaceutical Corporations, 2010-2013 (amounts in billions of 2015 dollars)

Year	Amounts of research spending reported per financial statement	Amounts deducted for research expense on tax return
2010	30.7	29.6
2011	30.6	29.9
2012	27.8	24.9
2013	31.8	30.7

Source: GAO analysis of Internal Revenue Service schedule M-3 data for large pharmaceutical corporations | GAO-18-40

Note: Data are adjusted to 2015 U.S. dollars using the gross domestic product price index.

Novel Drugs Consistently Accounted for About Thirteen Percent of New Drugs Approved in the United States from 2005 through 2016, and Biologics and Orphan Drugs Each Grew as a Share of Approvals

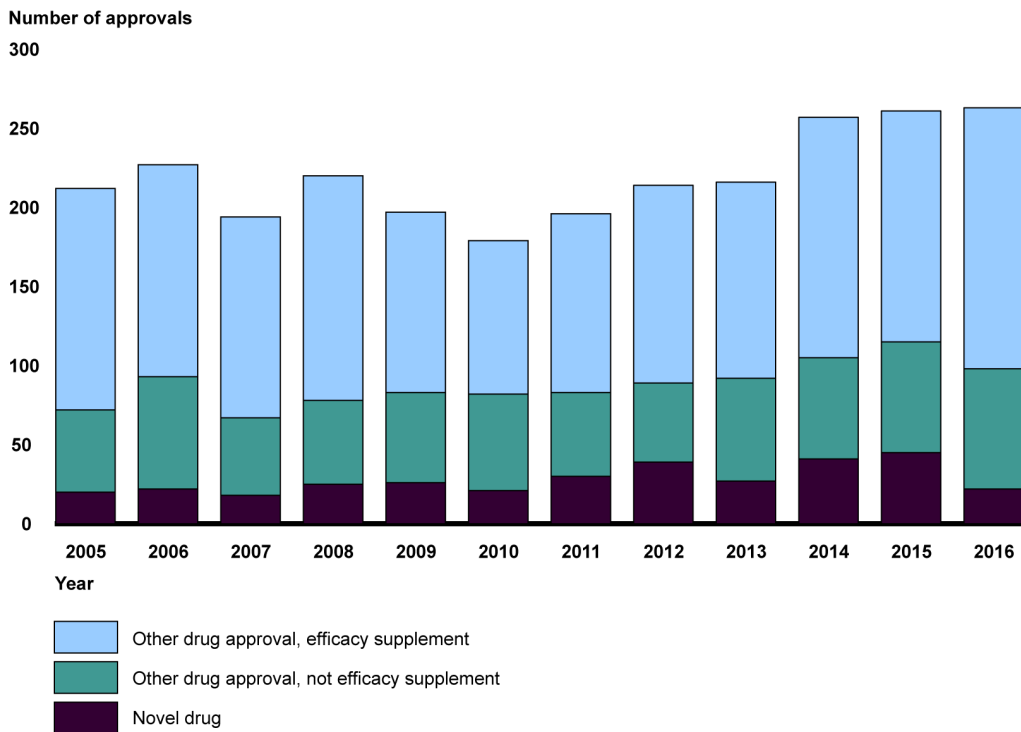
The number of approvals for drugs FDA considered novel drugs increased from 20 in 2005 to 45 in 2015 but declined to 22 approvals in 2016, according to FDA data and reports (see fig. 14).⁶⁵ Novel drugs accounted for between 8 and 18 percent of all drug approvals each year and averaged 13 percent over the period.⁶⁶ The remaining majority of drug approvals each year included those not considered novel because they had chemical substances that were previously approved by FDA or were modifications to existing drugs.⁶⁷

⁶⁵Novel drugs are those that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. They generally include drugs reviewed by FDA either as new molecular entities under NDAs or new therapeutic biologics under BLAs. From January to August 2017, FDA had already approved 28 drugs it considered novel drugs. Complete data for 2017 were outside the scope of our review.

⁶⁶Note that this analysis does not include approvals for ANDAs (i.e., generic versions of drugs). In addition, the analysis focuses on brand-name drug approvals and does not reflect NDA and BLA applications received by FDA.

⁶⁷Specifically, these include NDA- and BLA-related efficacy supplements, NDAs that were not new molecular entities, and certain other BLAs. Although drugs FDA considers novel drugs are often used as a measure for industry innovation, some experts highlight the incremental nature of innovation and the value of certain drug modifications to patients. For example, a new dosage or route of administration for an existing drug may improve patients' compliance with treatment.

Figure 14: Drugs Approved by the Food and Drug Administration, 2005 - 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-40

Notes: Data include new drug applications (NDA) and biologic license applications (BLA) approved by FDA's Center for Drug Evaluation and Research. FDA's Center for Biologics Evaluation and Research also reviews certain BLAs such as blood products, vaccines, and allergenic products; we did not include these in our review.

FDA considers most new therapeutic biologics approved under BLA and NDAs approved as new molecular entities to be novel drugs. Other drug approvals includes those approvals not considered novel drugs, including NDA- and BLA-related efficacy supplements, NDAs that were not new molecular entities, and certain other BLAs. An efficacy supplement to an already approved NDA or BLA is submitted to propose changes to the way an approved drug is marketed or used, such as adding or modifying an indication or claim, revising the dose or dose regimen, providing a new route of administration, or changing the marketing status from prescription to over-the-counter use.

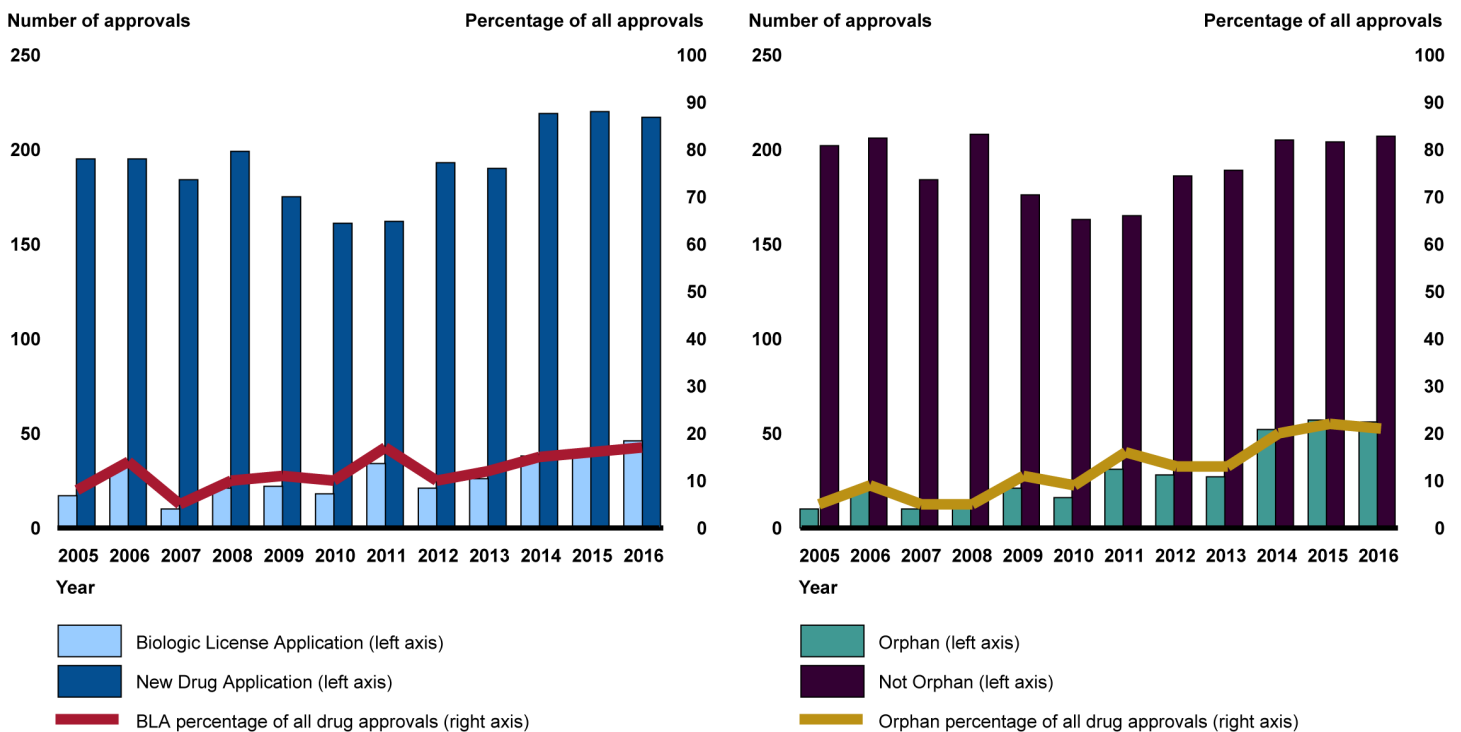
Biologics and orphan drugs each represented an increasing share of all drug approvals from 2005 through 2016. As shown in figure 15, biologics grew from 8 percent of all drug approvals in 2005 to 17 percent in 2016.⁶⁸

⁶⁸This includes BLAs approved by FDA's Center for Drug Evaluation and Research, which reviews therapeutic biologics. FDA's Center for Biologics Evaluation and Research also reviews certain BLAs such as blood products, vaccines, and allergenic products, which we did not include in our review. Including BLAs approved by the Center for Biologics Evaluation and Research could increase the ratio of BLAs to all approvals.

Biologics also represented an increasing share of the subset of all approvals that were considered novel drugs—from 10 percent of novel drugs approved in 2005 to 32 percent in 2016.

Orphan-designated drugs as a share of all drug approvals grew even more dramatically from 5 percent of all drug approvals in 2005 to 21 percent in 2016 (see fig.15). Orphan drugs as a share of novel drug approvals ranged from 22 percent in 2007 to 42 percent in 2015.

Figure 15: Drug Approvals by Application Type and Orphan Drug Designation Status, 2005 – 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-40

Notes: Data include new drug applications (NDA) and biologic license applications (BLA) approved by FDA's Center for Drug Evaluation and Research. FDA's Center for Biologics Evaluation and Research also reviews certain BLAs such as blood products, vaccines, and allergenic products; we did not include these in our review.

Orphan drugs are those designated and approved with orphan status by FDA. The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons, but for which the manufacturers are not expected to recover the development and marketing costs.

We also examined drug approval trends by product category. The product categories that led the largest number of drug approvals fluctuated over time, but oncology drugs were among the most frequently approved in all but 2 years from 2005 through 2016.⁶⁹ Of the 263 drugs approved by FDA in 2016, the most common product categories were oncology (55 approvals) and metabolism and endocrinology (38 approvals). For the 22 novel drug approvals in 2016, the most common product categories were oncology (5 approvals) and neurology (4 approvals).

Studies and Experts Suggest Potential Revenues, Costs, and Policy Incentives Influenced Drug Industry Research and Development Investment Decisions

Studies and industry experts we interviewed, including economists and industry association officials, suggested several drivers for drug company R&D investment decisions. These investment choices were influenced by revenue, cost, and regulatory and other policy incentives:

- **Potential revenues:** High revenue potential, typically associated with a large potential number of patients or the potential for high drug prices, is an important incentive for R&D investment, according to experts and some research. Studies show that potential market size, measured by revenue, is a determinant of R&D investment and market entry for both brand-name and generic drug companies.⁷⁰ Companies also seek to maximize potential revenues by investing in the development of drugs that can command high prices, and drugs that address unmet medical needs or differentiate them from competitors. This includes investment in drugs for niche markets that may have limited competition, such as orphan drugs. Experts also noted that some companies invest to extend patent protection or exclusivity periods for existing drugs as a means to extend revenue generation by delaying or limiting the effect of generic competition—sometimes referred to as “evergreening” or “patent hopping.”
- **Cost reduction:** Drug development costs, particularly for novel drugs, are increasing and companies have sought various ways to reduce their costs or limit risk. Experts we interviewed suggested that drug companies have attempted to reduce costs by focusing on drugs for

⁶⁹FDA product category generally corresponds to the FDA review division (e.g., oncology or psychiatry drugs).

⁷⁰For example, see P. Dubois, O. de Mouzon, F. Scott-Morton, and P. Seabright, “Market Size and Pharmaceutical Innovation,” *The RAND Journal of Economics*, vol. 46, no. 4 (2015), and M. Pauley and K. Myers, *A Ricardian-Demand Explanation for Changing Pharmaceutical R&D Productivity*, National Bureau of Economic Research working paper 22720 (2016).

which clinical trials are perceived to be less costly, drugs perceived as more likely to receive FDA approval, modifications to existing drugs rather than the development of novel drugs, outsourcing of clinical trials, and acquisition of R&D projects already underway.

- **Policy incentives:** Often regulatory and other policy incentives influence potential revenues and risks and, in turn, R&D investment, according to experts. For example, exclusivity periods and patent protection, expedited review programs, and tax incentives were cited as influencing R&D investment. The supply of new science from federally funded research may also influence company investment decisions. Expectations about payer reimbursement could also influence potential pricing and investment decisions, according to some experts. For example, one expert noted that payers typically do not resist high prices for oncology drugs.

These drivers may also explain the observed brand-name drug approval trends for biologics, orphan drugs, and drugs for certain disease areas. For example:

- **Biologics:** Some experts noted that recent technological advances have spurred opportunity and investment in new biologics. The longer period of FDA market exclusivity for biologics relative to traditional chemically synthesized drugs may also be attractive to drug developers. In addition, there are currently few biosimilar drugs available to compete for market share once BLA exclusivity expires. Though FDA had approved seven biosimilars for marketing between 2010—the year the approval pathway for biosimilar biological products was established—and September 2017, and was reviewing additional applications, some experts suggest that the added cost and difficulty in developing biosimilars may hinder entry of biologics' competitors relative to the entry seen for traditional generics.⁷¹
- **Orphan drugs:** In addition to the exclusivity and orphan drug credit incentives to develop orphan drugs, an industry expert we interviewed also suggested that it is easier to get FDA approval for orphan drugs, and another suggested that it is less costly to develop them. In

⁷¹Three of the seven FDA-approved biosimilars were currently being marketed, as of September 2017. Sales of the remaining biosimilars are delayed, largely due to patent disputes, according to news reports. See Bloomberg, "FDA Clears Biotech Drug Copycats, But Buying Them Isn't So Easy," accessed October 17, 2017, <https://www.bloomberg.com/news/articles/2017-09-18/fda-clears-biotech-drug-copycats-but-buying-them-isn-t-so-easy>.

addition, orphan drugs can often garner high prices compared to non-orphan drugs, according to an industry report.

- **Disease areas:** Certain drug classes or disease areas, such as drugs for oncology or multiple sclerosis drugs, can garner higher prices and, in turn, more R&D investment because they often have fewer competitors, are often administered by providers who are insensitive to price, or are perceived as particularly life-saving, according to some experts we interviewed. In addition, some experts suggested that NIH investment in oncology research and gains in personalized medicine have resulted in many more research opportunities in which companies can invest.⁷² For example, many new oncology drugs are approved for treatment of tumors with specific genetic markers, and research suggests these drugs are more likely to succeed in clinical trials and face a less-elastic demand curve that, in turn, can facilitate higher pricing.

According to several experts we interviewed, a company's R&D focus on fewer therapeutic areas of more profitable drugs or niche markets may come at the expense of drug development in less lucrative disease areas—those that affect many patients but in which drugs are more costly to bring to market or have existing generic competition—for example, cardiovascular disease. According to a study of drug development pipeline data, the number of new drugs in all phases of clinical development to treat cardiovascular disease, a leading cause of death in the United States, declined from 1990 to 2012, whereas the number of new cancer drugs increased over the period.⁷³

⁷²While most medical treatments are designed for the average patient, precision medicine, sometimes known as “personalized medicine,” is an innovative approach to disease prevention and treatment that takes into account differences in people's genes, environments and lifestyles. Advances in precision medicine have led to new discoveries and several new FDA-approved treatments that are tailored to specific characteristics of individuals, such as their genetic makeup or the genetic profile of an individual's tumor.

⁷³See T. J. Hwang, J. C. Lauffenburger, J. M. Franklin, and A. S. Kesselheim, “Temporal Trends and Factors Associated with Cardiovascular Drug Development, 1990-2012,” *JACC: Basic to Translational Science*, vol. 1, no. 5 (2016).

Research Suggests Market Concentration Affects Drug Prices, and Mergers May Affect Drug Company Innovation

Research we examined in our literature review suggests that the level of competition in a relevant market influences drug prices. Competition also matters for innovation. Certain empirical economic studies suggest that mergers among brand-name drug companies can negatively impact companies' innovation post-merger.

Research Finds High Market Concentration Is Associated with Higher Drug Prices

The relationship between competition and drug price is well documented in the drug industry, and industry experts and available research point out that competition dynamics differ for brand-name and generic drugs. Brand name companies producing drugs under patent or exclusivity protection have monopoly pricing power unless alternative drugs that treat the same condition are available. For brand-name products that face competition from such therapeutic alternatives, companies compete on price, differentiation from competitors, or both.⁷⁴ We and others have reported that brand-name drug companies consider the availability and price of therapeutic alternatives along with potential market size, the perceived value of the drug relative to competitors, and other factors when determining the price for a new drug.⁷⁵ Conversely, generic drugs compete on price with the brand-name or other generic manufacturers of the same drug. As we have reported, and as experts we have interviewed agreed, generic drug companies compete primarily on price.⁷⁶

Based on our literature review, we did not identify any empirical studies that examined the impact of drug industry concentration changes from mergers and acquisitions on drug prices post-merger. However, empirical studies we reviewed suggest that less competition—that is, a more highly

⁷⁴Brand-name companies may differentiate their drugs based on the drug's novelty or its perceived value, such as its ease of use.

⁷⁵See GAO, *Brand Name Prescription Drug Pricing: Lack of Therapeutically Equivalent Drugs and Limited Competition May Contribute to Extraordinary Price Increases*, [GAO-10-201](#) (Washington, D.C.: Dec. 22, 2009).

⁷⁶We have also reported on generic drug prices with respect to Medicare Part D. See GAO, *Generic Drugs under Medicare: Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, [GAO-16-706](#) (Washington, D.C.: Aug. 12, 2016).

concentrated market—is associated with higher drug prices, particularly for generic drugs. The following summarizes studies we reviewed on the effect of generic and brand-name competition:

- **Generic competition:** Most notably, once brand-name drugs lose patent and marketing exclusivity and generic versions of drugs enter the market, drug prices fall and continue to decline as additional generic manufacturers enter. The price moderating effect of generic competition is well documented by FDA, FTC, the IMS Institute for Healthcare Information, and other research. FDA found that for drugs sold from 1999 through 2004, the first generic competitor reduced the drug price only slightly lower than the brand-name on average, but the second generic competitor reduced the drug price by nearly half.⁷⁷ For drugs that attracted nine or more generic manufacturers, the average generic price fell 80 percent or more. The IMS Institute for Healthcare Information reported similar findings in 2016 based on its review of generics that entered the market between 2002 and 2014.⁷⁸ The introduction of generics reduced the price of those drugs by 51 percent in the first year and 57 percent in the second year with price reductions driven, in part, by the increasing number of competitors. In addition, a 2017 study of 1,120 drugs available as generics between 2008 and 2013 determined that drugs with less market competition, measured by higher concentration, had higher price increases over the period compared to drugs in the cohort with the lowest concentration.⁷⁹
- **Brand-name competition:** For brand-name drugs, studies show that the presence of therapeutic alternatives in the market reduces the launch price—the price the company sets for a new drug. For example, an often-cited 1998 study of launch prices for 130 new

⁷⁷Department of Health and Human Services, U.S. Food and Drug Administration, “Generic Competition and Drug Prices,” accessed May 1, 2017, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm>.

⁷⁸IMS Institute for Healthcare Informatics, *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*, (Parsippany, N.J.: IMS Institute for Healthcare Informatics, 2016).

⁷⁹C. V. Dave, A. S. Kesselheim, E. R. Fox, P. Qiu, and A. Hartzema, “High Generic Drug Prices and Market Competition Levels: A Retrospective Cohort Study,” *Annals of Internal Medicine*, vol. 167, no. 3 (2017). See also E. R. Berndt, R. M. Conti, and S. J. Murphy, *The Landscape of US Generic Prescription Drug Markets, 2004-2016*, National Bureau of Economic Research Working Paper 23640 (2017).

molecular entities showed that a greater number of brand-name therapeutic alternatives was associated with substantially lower launch prices for new brand-name drugs compared to their predecessors.⁸⁰ More recently, there are examples of therapeutic alternatives creating market pressure on, and thus reducing prices of, brand-name drugs, such as multiple brand-name hepatitis C therapies that became available between 2013 and 2014.⁸¹

Research has also found that some brand-name drug companies are able to maintain or even raise prices for their drugs—despite competition from therapeutic or generic alternatives—for various reasons, such as product differentiation or brand loyalty stemming from marketing or prescribing patterns. For example, brand-name companies may actually increase prices for some of their drugs to capture the price-insensitive segment of the market.⁸² Research also suggests that the extent of price reductions resulting from the entry of generic drugs into a market can differ by the characteristics of the drug and may be less dramatic for biosimilar drugs than traditional generic drugs. For example, the 2016 IMS report noted that price reductions under these circumstances occurred faster for oral drugs than for injectable drugs, which often attract fewer generic competitors. Another 2017 study examining the state of generic competition found that injectables and drugs with other formulations, such as topical or inhaled drugs, were more likely than oral drugs to have only one or two manufacturers.⁸³ Certain literature we reviewed and experts

⁸⁰Z. J. Lu and W. S. Comanor, “Strategic Pricing of New Pharmaceuticals,” *The Review of Economics and Statistics*, vol. 80, no. 1 (1998).

⁸¹A. S. Kesselheim, J. Avorn, and A. Sarpatwari, “The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform,” *JAMA*, vol. 316, no. 8 (2016). These biologic hepatitis C therapies, including Sovaldi and Harvoni (both from Gilead) and AbbVie’s Viekira Pak, reduced treatment times considerably and had very high launch prices. The introduction of the additional therapies allowed certain insurers to negotiate lower prices, but did not necessarily lower the initial launch prices.

⁸²See for example, T. L. Regan, “Generic Entry, Price Competition, and Market Segmentation in the Prescription Drug Market,” *International Journal of Industrial Organization*, vol. 26, no. 4 (2008); and O. Richard and L. Van Horn, “Persistence in Prescriptions of Branded Drugs,” *International Journal of Industrial Organization*, vol. 22, no. 4 (2004).

⁸³E. R. Berndt, R. M. Conti, and S. J. Murphy, *The Landscape of U.S. Generic Prescription Drug Markets, 2004-2016*, National Bureau of Economic Research Working Paper 23640 (2017). See also R. Gupta, A. S. Kesselheim, N. Downing, J. Greene, and J. S. Ross, “Generic Drug Approvals Since the 1984 Hatch-Waxman Act,” *JAMA Internal Medicine*, vol. 176, no. 9 (2016), for information on competition levels.

we interviewed suggested that biosimilars will moderate prices for biologic drugs, but not to the same extent as traditional generics do because they are more costly to manufacture and may be less consistently substituted for the brand-name drug; however, more time and research will be needed to understand the effects given the small number of biosimilars on the market.⁸⁴

Studies Find Competition Matters for Innovation, and Some Suggest a Negative Impact of Mergers on Drug Company Innovation

Competition is also relevant to innovation, according to economic studies we examined. As noted, brand-name drug companies compete to develop new products and differentiate their products from therapeutic alternatives. The analysis of how competition affects innovation is a fact-specific process. There is empirical evidence suggesting that, in certain circumstances the incentive to invest in R&D could be enhanced with more competitors. For example, a 2014 study examining multiple manufacturing and non-manufacturing industries demonstrated a positive relationship between competition and innovation (measured by patents), productivity, and R&D expenditures.⁸⁵ While drug innovation comes from multiple sources and increasingly from smaller innovative biotechnology companies, the industry relies on large drug companies to invest in the expensive clinical trials needed to develop and bring new innovations to market.

We also identified several merger retrospective studies. These studies suggest that there are varied impacts of drug company merger and acquisition on innovation, including both inputs (e.g., R&D spending) and outputs (e.g., patents and new drug approvals).

⁸⁴A recent study found that introduction of the first biosimilar moderated prices of the drug somewhat. See F. Scott Morton and L. T. Boller, "Enabling Competition in Pharmaceutical Markets," Hutchins Center Working Paper 30 (2017). Other studies estimated biosimilar competition will more closely resemble competition among brand-name drugs. See H. G. Grabowski, D. B. Ridley, and K. A. Schulman, "Entry and Competition in Generic Biologics," *Managerial and Decision Economics*, vol. 28, no. 4/5 (2007).

⁸⁵J. A. Correa & C. Ornaghi, "Competition & Innovation: Evidence from U.S. Patent and Productivity Data," *The Journal of Industrial Economics*, vol. 62, no. 2 (2014). Ongoing research suggests a similar relationship for companies in the drug industry. A 2015 working paper examining financing decisions of drug companies between 1950 and 2012 indicates that as competition increased total R&D expenditures increased in turn. See R. T. Thakor and A. W. Lo, *Competition and R&D Financing Decisions: Theory and Evidence from the Biopharmaceutical Industry*, National Bureau of Economic Research working paper 20903 (2015).

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- A 2009 study of 27 large, brand-name drug company mergers found that the mergers had a statistically significant negative impact on company R&D spending and patent issuance in the third year post-merger compared to non-merging companies.⁸⁶ The authors concluded that the findings contradict the idea that mergers deliver advances in innovation that could outweigh possible anticompetitive risks.
 - A 2007 study of 165 large mergers between 1988 and 2000 suggested that large companies sought to merge in response to patent expiration or product pipeline gaps, and small companies sought to merge as a response to financial trouble. When controlling for companies' propensity to merge, small merging companies—defined as companies valued less than \$1 billion—grew more slowly in R&D spending, sales, and R&D employees post-merger compared to similar non-merging companies. However, the study did not find these effects to last beyond one year and did not find differences in these growth rates between large merging companies and non-merging companies. Overall, the authors concluded that while merger in the drug industry is a response to being in trouble for both large and small companies, there is no evidence that it is a solution.⁸⁷
 - Another 2009 study examined the number of approvals for new molecular entities—innovative drugs—as a means to examine outputs rather than only R&D spending. The study suggests that while mergers and acquisitions may help small companies, they are not an effective way for larger companies to increase output of new molecular entities. For example, for a sample of 30 mergers and acquisitions with 10 years of data before and after the merger, the study found that for large companies the number of new molecular entities did not increase and may actually have declined slightly following merger or acquisition. Smaller companies, however,

⁸⁶C. Ornaghi, "Mergers and Innovation in Big Pharma," *International Journal of Industrial Organization*, vol. 27, no. 1 (2009).

⁸⁷P. M. Danzon, A. Epstein, and S. Nicholson, "Mergers and Acquisitions in the Pharmaceutical and Biotech Industries," *Managerial and Decision Economics*, vol. 28, no. 4/5 (2007).

experienced an increase in new molecular entities after merger or acquisition.⁸⁸

- Other studies suggest mergers and acquisitions may have a positive impact on innovation using certain measures. For example, a 2006 study of 160 acquisitions involving drug companies between 1994 and 2001 estimated that companies with declining R&D pipeline and sales were more likely to engage in acquisition and that outsourcing R&D through acquisitions was a successful strategy to stabilize declines in drug R&D pipelines. This study estimated that 71 percent of acquiring companies either maintained or improved the health of their research pipelines after merger.⁸⁹

Agency Comments

We provided a draft of this report to the Department of Health and Human Services, FTC, IRS, and NSF for review. These agencies provided technical comments, which we incorporated as appropriate.

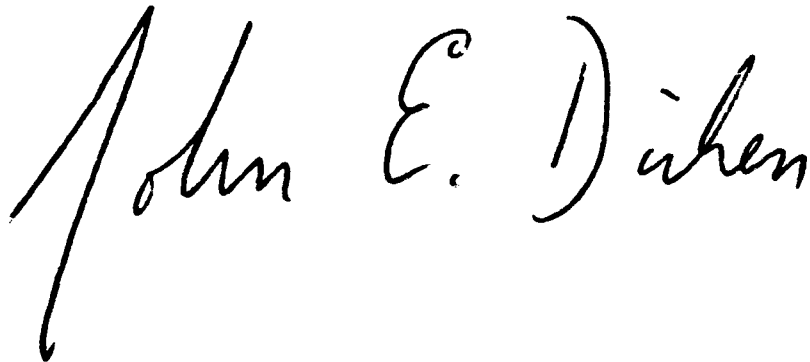
⁸⁸B. Munos, "Lessons from 60 Years of Pharmaceutical Innovation," *Nature Reviews Drug Discovery*, vol. 8, no. 12 (2009). Similarly, a 2009 study of 24 large mergers found that merged companies' product portfolios declined post-merger, whereas comparable unmerged companies' portfolios increased. The study also found that merged companies limited R&D spending growth immediately after a merger, but quickly increased R&D spending thereafter. K. A. Getz, R. Zuckerman, J. A. DiMasi, and K. I. Kaitin, "Drug Development Portfolio and Spending Practices After Mergers and Acquisitions," *Drug Information Journal*, vol. 43, no. 4 (2009).

⁸⁹M. J. Higgins and D. Rodriguez, "The Outsourcing of R&D Through Acquisitions in the Pharmaceutical Industry," *Journal of Financial Economics*, vol. 80 (2006).

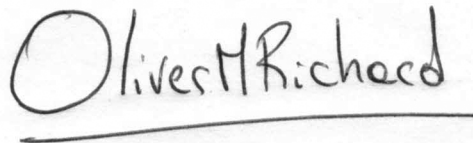
As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, relevant agencies, and other interested parties.

In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact John E. Dicken at (202) 512-7114 or DickenJ@gao.gov or Oliver Richard at (202) 512-8424 or RichardO@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix III.

A handwritten signature in black ink that reads "John E. Dicken". The signature is written in a cursive style with a large, sweeping initial "J".

John E. Dicken
Director, Health Care

A handwritten signature in black ink that reads "Oliver Richard". The signature is written in a cursive style and is underlined with a single horizontal line.

Oliver Richard
Director, Applied Research and Methods

Appendix I: Scope and Methodology

This appendix provides further details on our scope and methodology in addressing each of our three reporting objectives, which are to describe: (1) how the financial performance and structure of the drug industry have changed over time; and (2) how reported research and development spending and new drug approvals have changed; and (3) what is known about the potential effects of consolidation on drug prices and new drug development. In addition, the appendix describes how we selected officials to interview and the steps we took to assure the reliability of the data we analyzed.

How the Financial Performance and Structure of the Drug Industry Have Changed Over Time

Analysis of Sales Revenue and Profit Margins

To describe reported pharmaceutical and biotechnology sales revenue and profit margins, we used the Bloomberg Terminal to identify pharmaceutical and biotechnology companies that were still active as of the time of our review.¹ Bloomberg uses a proprietary hierarchical classification system (the Bloomberg Industry Classification System) to categorize companies into different primary industries. We used the Bloomberg Terminal's company classification browser to obtain an initial set of companies that currently have reported pharmaceutical or biotechnology revenue. We restricted the drug companies in our review to those that were categorized under the "Pharmaceutical & Biotechnology" Bloomberg Industry Classification System (BICS) level 2 category, which indicated that Bloomberg characterizes the company as being primarily a pharmaceutical or biotechnology company. Using this list, we downloaded each company's reported pharmaceutical and biotechnology sales revenue, total sales revenue, profit margin, return on assets, and return on equity for each company's fiscal years 2006 through 2015, which were the most current data available. To provide a comparison, we followed the same procedure to obtain data for software companies over the same period. We selected software companies as a comparison because they

¹The Bloomberg Terminal is a software system that Bloomberg sells as a service. The system provides financial analytics, transaction information, securities data, and news, among other features.

have high research and development (R&D) and low manufacturing costs similar to drug companies.² Sales revenues were adjusted to reflect real 2015 U.S. dollars using the gross domestic product price index.

When examining sales revenues, profit margins, return on assets, and return on equity, analyses were limited to the subset of companies with complete data over the 10-year period for the variables included in the analysis. We did not have a count of how many companies might have existed throughout the review period, but which had no data available on any of the variables we examined. Profit margin, return on assets, and return on equity were each weighted by the company's industry-specific sales revenue (pharmaceutical and biotechnology or software) prior to averages being computed. To identify the "largest 25" companies for analyses, we first restricted data to companies that had data for the variables being examined for 2006 through 2015, then identified the 25 drug companies with the largest pharmaceutical and biotechnology revenue in 2015. This provided a consistent cohort of large companies to examine longitudinally for each analysis.

We also examined profit margins for the largest 500 companies by total worldwide 2015 sales revenue. We obtained a list of the largest 500 companies in 2015 from the Bloomberg Terminal that were still active during our review. Using this list, we downloaded each company's BICS level 2 category; total sales revenue; pharmaceutical, biotechnology, and software revenues; and profit margins for each company for fiscal years 2006 through 2015. We removed any companies primarily classified by Bloomberg under one of those industries since we had analyzed these separately. For the remaining companies in our largest 500, we subtracted any reported pharmaceutical, biotechnology, and software revenues from their total sales revenues since some companies may have reported such revenues despite not being classified primarily as one of these types of companies. We then weighted each of the remaining companies' profit margins by their remaining total sales revenue prior to calculating an average. This weighting differed slightly from the industry-specific sales weighting used in the earlier analyses of drug and software companies' profit margins. For the software industry, the Congressional Budget Office only indicated that it had high R&D and low manufacturing costs similar to drug industry; it did not suggest the same for other lines of

²For example, see Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, Pub. No. 2589 (Washington, D.C.: October 2006).

business that software companies might additionally be involved in. Because we had no reason to isolate industry-specific revenues for our remaining largest 500 companies, we weighted their profit margins by their total sales revenues. As with the prior profit margin analyses, analysis of the largest 500 sales weighted profit margins were limited to companies with data available for each of company fiscal years 2006 through 2015.

Analysis of Mergers and Acquisitions

For analyses of mergers and acquisitions, we again relied on data from the Bloomberg Terminal. We restricted our search to mergers and acquisitions that were completed from January 1, 2006, to December 31, 2015, and which featured a drug company on both sides of the transaction (e.g., as the acquirer and as the acquired company in the case of acquisition of a full company). The “largest 25” companies were determined by their 2015 pharmaceutical and biotechnology sales revenue only—because not every company could be expected to have a merger or acquisition transaction in every year, we did not make this a requirement to be included in the merger and acquisition analyses. We used what Bloomberg reported to be the completed transaction values in our analyses, and we adjusted the values to consistently reflect real 2015 dollars.

Many companies were not included in analyses due to incomplete data, therefore the results of our analyses of these data do not reflect the entire industry. Bloomberg obtains much of its information from public filings, which provide companies considerable leeway in deciding what to report and how. For mergers and acquisitions, approximately 40 to 50 percent of the completed transactions in Bloomberg’s data between 2006 and 2015 did not have disclosed transaction values. Bloomberg officials told us that transaction values are often missing for private companies.

Analysis of Concentration

To examine overall industry concentration we used pharmaceutical industry and company-specific sales data from QuintilesIMS from 2007 through 2014, the years for which data were publicly available.³ We also

³QuintilesIMS is a company that collects health care data and offers analytic services. For data charts, see: QuintilesIMS, “Top 20 Global Corporations 2014,” *2014 and 2013 Top-Line Market Data*, accessed April 14, 2017, https://www.imshealth.com/FILES/WEB/CORPORATE/NEWS/TOP-LINE%20MARKET%20DATA/2014/TOP_20_GLOBAL_CORPORATIONS_2014.PDF; and QuintilesIMS, “Top 20 Global Corporations 2012,” *2012 and 2011 Top-Line Market Data*, accessed April 14, 2017, https://www.imshealth.com/FILES/WEB/CORPORATE/NEWS/TOP-LINE%20MARKET%20DATA/2012/TOP_20_GLOBAL_CORPORATIONS_2012.PDF.

examined publicly available industry reports and generic drug approvals data for discussion of concentration across different therapeutic areas. Our findings on industry concentration and the variation of concentration across therapeutic classes is limited to these examples.

How Reported Research and Development Spending and New Drug Approvals Have Changed

Analysis of Research and Development Spending

To examine how reported R&D spending changed over time, we analyzed data from the Business Research, Development and Innovation Survey maintained by the National Science Foundation's (NSF) National Center for Science and Engineering Statistics for years 2008 through 2014, the most recent years for which data were consistently available. The Business Research, Development and Innovation Survey data are collected annually from a probability sample of for-profit companies with a U.S. presence, which are classified in select manufacturing and nonmanufacturing industries based on their North American Industry Classification System (NAICS) code.⁴ We analyzed aggregate company-reported worldwide R&D expenditures and worldwide sales for respondent companies designated with NAICS code 3254 for pharmaceuticals and medicines.⁵ We also examined pharmaceutical

⁴Company responses are classified into the NAICS code that accounted for the largest amount of total domestic R&D performance. NAICS codes are the classification system used by the Census Bureau and Internal Revenue Service (IRS).

⁵Data represent company-reported spending for R&D conducted in the United States regardless of the location of the parent company and spending for R&D conducted abroad by U.S.-owned companies. It does not include spending or sales for foreign operations of foreign companies. R&D is defined by NSF as planned, creative work aimed at discovering new knowledge or developing new or significantly improved goods and services. R&D expense includes the amount a company pays from its own funds for R&D that is done for the company's benefit and includes company-performed R&D in both its domestic and foreign locations plus R&D the company pays others to perform. R&D expense is similar to information companies report in financial statements to the Securities and Exchange Commission with certain NSF-designated exceptions. NSF specifies that reported R&D expense does not include expenses for Phase IV clinical trials conducted after a drug has come to market. The NSF data also do not include expenses resulting from acquisition of another company with unfinished R&D projects.

company-reported domestic R&D expenditures by character of work—basic research, applied research, or development—as defined by NSF as well worldwide and domestic R&D expenditure by performer (whether R&D was paid for and performed by the company, or paid for by the company to be performed by others). We also examined worldwide expenditures and sales for companies designated as biotechnology research and development companies (NAICS 541711); however estimates were not available for 2008 or 2014 and were less reliable in the years between. We therefore reported biotechnology expenditures and sales separately from pharmaceutical companies and limited the majority of our analysis to pharmaceutical companies. For comparison, we also examined worldwide R&D expenditure and sales for comparably large industries with high R&D intensity as well as all manufacturing and all non-manufacturing industries. All spending and sales data were adjusted to real 2015 U.S. dollars using the gross domestic product price index. We also examined the Business Research, Development and Innovation Survey sample selection and sampling error information for each year of the survey.⁶ Finally, we compared worldwide and domestic R&D expenditure and sales trends to spending and sales reported by Pharmaceutical Research and Manufacturers of America (PhRMA)—a national trade association.⁷

To examine federal spending trends, we analyzed publicly available data from NSF's National Center for Science and Engineering Statistics' Survey of Federal Funds for Research and Development on obligations for research in biomedical related fields made by federal agencies identified as funding drug-related research between fiscal years 2008 and 2014, years consistent with available industry data from NSF's Business Research, Development, and Innovation Survey. Data represent federal agency obligations for basic and applied research in the fields of biological sciences, medical sciences, and other life sciences as reported by federal agencies.⁸ Obligations were adjusted to real fiscal year 2015

⁶All survey estimates have a relative standard error of 2 percentages or less, unless otherwise noted.

⁷See Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Membership Survey, 2016*, accessed November 21, 2016 at <http://www.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf>.

⁸Obligations represent amounts for orders placed, contracts awarded, services received, and similar transactions committed to by agencies during a given period, regardless of when funds were appropriated and when future payment of money is required.

U.S. dollars using the gross domestic product price index. We identified agencies that fund drug-related research based on interviews with officials from the National Institutes of Health (NIH), NSF, and other industry experts.⁹ The Survey of Federal Funds for Research and Development is a census of federal agencies that conduct R&D, and provides data on obligations by agency and field of science rather than by specific industry or use. Our estimates of federal spending may be imprecise because the data preclude us from pinpointing spending specific to drug R&D projects, and because the type of research that federal agencies typically fund often has an impact on many different research areas that may not be specific to drugs. We also reviewed budget documents from NIH and reviewed select studies for spending estimates by non-federal or industry sources.¹⁰

In addition, we obtained estimates of R&D spending by state and local governments and non-industry private funders for 2015 from National Health Expenditure account estimates. These estimates include spending for all biomedical research by these categories and thus also likely overestimate spending specific to drug development.

Analysis of Tax Incentives

To identify tax provisions that provide incentives for drug research and development, we reviewed reports by the Joint Committee on Taxation and the Congressional Research Service. We obtained and analyzed aggregate tax return data from the Internal Revenue Service (IRS) Statistics of Income division for the orphan drug credit and research credit claimed by relevant industries and all returns (all industries) for years 2005 to 2014, the latest ten years for which data were available.¹¹ Specifically, we analyzed claims from companies with IRS Principle Business Activity codes for pharmaceutical manufacturing, drug wholesalers, and scientific research. IRS's industry codes are based on NAICS definitions, and corporations are instructed to report the industry code for which it derives the highest percentage of its total receipts. These data are reviewed by Statistics of Income division staff for accuracy. The scientific research industry category includes corporations

⁹In addition to NIH, other agencies include the Department of Defense and NSF.

¹⁰H. Moses, D. H. M. Matheson, S. Cairns-Smith, B. P. George, C. Palisch, and E. R. Dorsey, "The Anatomy of Medical Research: US and International Comparisons," *JAMA*, vol. 313, no. 2 (2015).

¹¹We did not have access to the underlying tax return data for individual corporations in this engagement.

conducting biotechnology research and development, but also includes firms conducting research in nanotechnology and physical, engineering, and life sciences. As a result, we chose not to report research credits claimed by corporations in the broader scientific research industry category as being related to drug development, but we do report orphan drug credits claimed by corporations in this industry category. We also obtained and examined reported qualified research expenses for pharmaceutical manufacturing companies for years 2005 to 2014. IRS' Statistics of Income division produces estimates based on a representative stratified sample of corporate returns.¹² IRS provided additional information on the corporations that reported claiming the orphan drug and research credits; in both cases a high percentage of the claims came from large corporations that are included in the stratified sample with certainty. As a result, we concluded that the estimated credit totals are reliable given that the estimates are largely based on returns that were certain to be included in the sample. The amount of research and orphan drug credits claimed represents claims rather than amounts utilized due to limitations of the general business credit.¹³ Reported estimates therefore may reflect the upper bounds of what was utilized from claimed amounts. IRS also provided additional data on total deductions claimed for qualified research expenditures and amounts reported on financial statements from Form M-3, for 2010 to 2013. These data were limited to large corporations that filed form M-3, which is required for corporations with \$10 million or more of assets. All claims were adjusted to 2015 U.S. dollars using the gross domestic product price index.

Analysis of Drug Approvals

To examine trends in new drug approvals, we obtained and analyzed data from the Food and Drug Administration (FDA) for new drug applications (NDA) and biologic license applications (BLA) and NDA- and BLA-efficacy supplements approved by the FDA's Center for Drug

¹²Tax credit data reflect claims for corporations only, excluding S-corporations, regulated investment companies, and real estate investment trusts.

¹³The general business credit is a limited non-refundable credit consisting of the sum of 36 separate credits available to corporations, including the orphan drug credit and research credit. If the amount of general business credits claimed exceeds the limitation, the excess or unspent funds can be carried forward or back. For this reason, the amount of orphan drug or research credits claimed can exceed the amount utilized in a given year. For example, in 2006 the pharmaceutical industry claimed \$902 million of research credits, but was only able to utilize a total of \$885 million of general business credit claims, leaving at least some of the claimed research credits unused.

Evaluation and Research between 2005 and 2016, the most recent ten years of available data at the time of our review.¹⁴ We determined which drugs FDA considered novel drugs by reviewing publicly available reports and resolving any discrepancies with agency officials.¹⁵ We analyzed these data to determine the type of drugs FDA approved, such as the product category and whether the drug was designated an orphan drug.

Finally, we interviewed agency and industry experts and reviewed relevant academic, government, and industry literature on R&D investment trends and reasons for such trends.

What Is Known about the Potential Effects of Consolidation on Drug Prices and New Drug Development

Literature Search on Consolidation Impacts

To determine what is known about the impact of drug industry consolidation on drug price and drug development, we reviewed studies obtained from a literature search. To identify relevant publications, we used a number of bibliographic databases, including ProQuest, Scopus, PubMed, National Technical Information Service, Lexis, Social Science Research Network, and the National Bureau of Economic Research. We reviewed the following document types: scholarly peer reviewed material, government reports, working papers, and policy research organization publications published by a U.S. publication from 2005 forward. We concluded our searches in August 2017. To the resulting list of publications, we added articles identified in our own background research and articles suggested by industry experts, including certain heavily cited papers published prior to 2005. From the revised list, we selected publications that empirically evaluated the effect of drug industry consolidation (mergers and acquisitions) on drug price or innovation (new

¹⁴FDA's Center for Biologics Evaluation and Research also reviewed certain BLAs such as blood products, vaccines, and allergenic products; we did not include these in our review.

¹⁵These sources include annual Novel Drugs Summary reports and annual New Molecular Entity Drug and New Biologic Approvals reports published by FDA's Center for Drug Evaluation and Research.

drug development or R&D spending). We also selected publications that included empirical analyses of drug industry or subindustry concentration or competition and drug price or drug development. Finally, we reviewed the data sources and methodology used to support the assertions of each publication and included those that met our methodological criteria. See the bibliography at the end of this report for the 22 publications included in our review.

Interviews

To inform our understanding of the drug industry for all three objectives including structural changes that have taken place, reasons for consolidation trends, drivers of drug company R&D investment trends, and any impacts of consolidation on drug price or innovation, we interviewed drug industry experts including three drug trade associations, four advocacy organizations, two financial ratings agencies, and officials from the FDA, IRS, NSF, Federal Trade Commission (FTC), and NIH.¹⁶ We selected these experts to obtain a variety of industry perspectives. We also interviewed seven academic economic experts about economic factors influencing consolidation and other structural changes, R&D investments, and potential consolidation impacts. We selected these economic experts based on citations in our literature review and suggestions from FDA and FTC officials.

Data Reliability

To ensure that the data used to produce this report were sufficiently reliable, we took several steps. We performed data reliability checks on the data we obtained from the Bloomberg Terminal, such as comparing select companies' financial data to company annual reports, checking for outliers, and discussing reliability issues with Bloomberg representatives. We did not independently verify the accuracy or completeness of the information reported by the companies. We verified the reliability of NSF's Business Research, Development and Innovation Survey data used in this report by reviewing relevant documentation, including relative standard errors for specific measures, and by interviewing agency officials who were knowledgeable with the data. We also interviewed knowledgeable NSF officials regarding the reliability of reported Federal Funds for Research and Development survey data and compared reported obligations to NIH budget documents. To verify the reliability of

¹⁶FDA and NIH are agencies within the Department of Health and Human Services.

aggregate tax return information, we reviewed relative standard errors for reported measures and interviewed knowledgeable agency officials. We verified the reliability of FDA-provided information by cross-referencing it against other published FDA sources and by interviewing knowledgeable agency officials. After taking these steps, we determined the data were sufficiently reliable for the purposes of our reporting objectives.

We conducted this performance audit from April 2016 to November 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings based on our audit objectives.

Appendix II: Mergers and Acquisitions of Ten Large Drug Companies from 2006 through 2015

The following table reflects mergers and acquisition transactions from 2006 through 2015 for 10 large drug companies, as measured by their 2014 pharmaceutical and biotechnology revenue. Transactions reflect those reported in Bloomberg that were completed from January 1, 2006, through December 31, 2015, and had values of at least \$500 million in real 2015 dollars.

Table 4: Merger and Acquisition Transactions of Ten Large Drug Companies, 2006-2015

Transaction year	Transaction description	Transaction value (\$billions)
Amgen Inc.		
2013	Amgen Inc. purchased Onyx Pharmaceuticals Inc.	8.8
2012	Amgen Inc. purchased Amgen Rockville Inc.	0.9
2012	Amgen Inc. purchased Mustafa Nevzat Pharmaceuticals	0.7
2006	Amgen Inc. purchased Abgenix Inc.	2.6
AstraZeneca PLC		
2015	AstraZeneca PLC purchased ZS Pharma Inc.	2
2015	AstraZeneca PLC purchased Actavis's branded respiratory business in the United States and Canada	0.6
2014	AstraZeneca PLC purchased Almirall's respiratory franchise	0.9
2014	AstraZeneca PLC purchased Bristol-Myers Squibb's interests in a diabetes alliance	2.7
2012	AstraZeneca PLC purchased Ardea Biosciences Inc.	1.2
2007	AstraZeneca PLC purchased Medimmune LLC	16.6
2006	AstraZeneca PLC purchased Cambridge Antibody Technology Group Ltd.	0.9
GlaxoSmithKline PLC		
2015	GlaxoSmithKline PLC purchased Novartis's vaccines portfolio (excluding influenza)	5.3
2012	GlaxoSmithKline PLC purchased Human Genome Sciences Inc.	3.1
2009	GlaxoSmithKline PLC purchased certain UCB SA product portfolios	0.7
2009	GlaxoSmithKline PLC purchased Stiefel Laboratories Inc.	3.6
2008	GlaxoSmithKline PLC purchased Sirtris Pharmaceuticals Inc.	0.6
2007	GlaxoSmithKline PLC purchased Domantis Ltd.	0.5
2007	GlaxoSmithKline PLC purchased Reliant Pharmaceuticals Inc.	1.9
2006	Stiefel Laboratories Inc. purchased Connetics Corp.	0.8
Johnson & Johnson		
2014	Johnson & Johnson purchased Alios BioPharma Inc.	1.8
Merck & Co. Inc.		
2015	Merck & Co. Inc. purchased Cubist Pharmaceuticals LLC	8.3
2014	Merck & Co. Inc. purchased Idenix Pharmaceuticals LLC	3.6

**Appendix II: Mergers and Acquisitions of Ten
Large Drug Companies from 2006 through
2015**

Transaction year	Transaction description	Transaction value (\$billions)
Merck & Co. Inc.		
2013	Cubist Pharmaceuticals LLC purchased Trius Therapeutics LLC	0.6
2009	Merck & Co. Inc. purchased Schering-Plough Corp	56.1
2007	Merck & Co. Inc. purchased Sirna Therapeutics Inc.	1
2007	Schering-Plough Corp purchased Organon BioSciences BV	16.4
Novartis AG		
2015	Novartis AG purchased GlaxoSmithKline PLC's oncology portfolio	14.5
2012	Novartis AG purchased Fougera Pharmaceuticals Inc.	1.6
2006	Novartis AG purchased NeuTec Pharma Ltd.	0.6
2006	Novartis AG purchased Novartis Vaccines & Diagnostics Inc.	6.6
Pfizer Inc.		
2015	Pfizer Inc. purchased Hospira Inc.	16.8
2011	Pfizer Inc. purchased KP Pharmaceuticals LLC	3.5
2009	Pfizer Inc. purchased Wyeth LLC	70.9
2008	KP Pharmaceuticals LLC purchased Zoetis Products LLC	1.4
2006	Pfizer Inc. purchased Exubera product rights	1.5
Roche Holding AG		
2014	Roche Holding AG purchased InterMune Inc.	7.9
2014	Roche Holding AG purchased Seragon Pharmaceuticals Inc.	0.7
2009	Roche Holding AG purchased Genentech Inc.	48.5
2007	Genentech Inc. purchased Tanox Inc.	0.8
Sanofi		
2011	Sanofi purchased Genzyme Corp.	20.9
2009	Sanofi purchased Fovea Pharmaceuticals SASU	0.6
2009	Sanofi purchased Zentiva NV	2.5
2008	Sanofi purchased Sanofi Pasteur Holding Ltd.	0.5
2008	Sanofi purchased Symbion Consumer	0.6
2007	Zentiva NV purchased Eczacibasi's generic drugs unit	0.7
2006	Genzyme Corp. purchased AnorMed Inc	0.6
Teva Pharmaceutical Industries Ltd.		
2015	Teva Pharmaceutical Industries Ltd. purchased Auspex Pharmaceuticals Inc.	3.1
2011	Teva Pharmaceutical Industries Ltd. purchased Cephalon Inc.	6.6
2011	Teva Pharmaceutical Industries Ltd. purchased Taiyo Pharmaceutical Industry Co. Ltd.	1
2010	Cephalon Inc. purchased Mepha AG	0.7
2008	Teva Pharmaceutical Industries Ltd. purchased Barr Pharmaceuticals Inc.	9.7
2006	Teva Pharmaceutical Industries Ltd. purchased IVAX Corp.	11.7

Appendix II: Mergers and Acquisitions of Ten Large Drug Companies from 2006 through 2015

Transaction year	Transaction description	Transaction value (\$billions)
Teva Pharmaceutical Industries Ltd.		
2006	Barr Pharmaceuticals Inc. purchased PLIVA Farmaceutika DD	2.7

Source: GAO analysis of Bloomberg data. | GAO-18-40

Notes: Transactions reflect a company Bloomberg designated as the “acquirer” in the transaction merging with or acquiring an asset from another company, potentially including the company itself. Transactions are limited to those with values of at least \$500 million in real 2015 dollars.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contacts

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Staff Acknowledgments

In addition to the contact named above, Robert Copeland, Assistant Director; Yesook Merrill, Assistant Director; Rebecca Abela, Analyst-in-Charge; Reed Meyer; Brandon Nakawaki; Edward Nannenhorn; Laurie Pachter; and Matthew Rabe made key contributions to this report. Also contributing were George Bogart, Muriel Brown, Sandra George, Sarah Gilliland, and Giselle Hicks.

Bibliography of Research Articles Used in GAO Literature Review

We reviewed literature to identify what is known about the impact of drug industry consolidation on drug price and drug development. We included publications that empirically evaluated the effect of drug industry consolidation (mergers and acquisitions) on drug price, of which we did not identify any publications. We also reviewed publications that included empirical analyses of the impact of concentration or competition on drug price.

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