

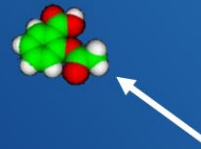
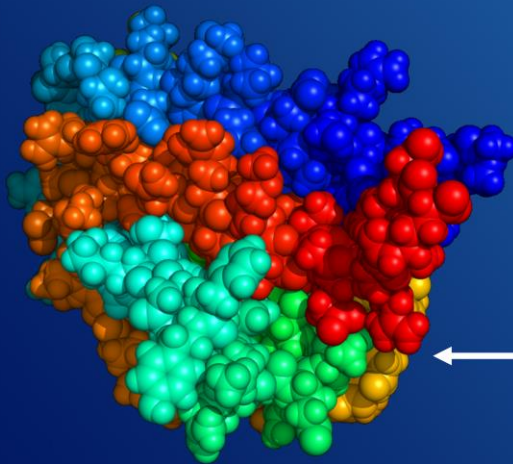


Recently, the topic of prescription drug prices has been the subject of intense scrutiny in the policymaking community, with many stakeholders calling for Medicare to take the lead in addressing rapidly rising drug prices.

In thinking about policy solutions to rising drug prices, it is important to recognize that Medicare exists within an American health care environment that involves a broad mix of not only public and private payers and local provider markets but also federal and state laws, agencies, and policies. These external environmental factors also have a significant influence on the prices Medicare pays for prescription drugs.

This brief provides background information on the drug development and approval process, as well as drug-related industries such as pharmacies and pharmacy benefit managers. It is intended to give an introduction to the complexities of these inter-related industries and to situate Medicare in this broader context. This is the second of two informational briefs that the Commission has created to provide background for thinking about Medicare drug policies; the first brief gives an overview of how Medicare pays for drugs.

Drugs versus biologics



Small molecule drug:
Synthesized via a chemical process (pictured: aspirin)

Biologic: Synthesized from a living organism or its products (pictured: EPO)

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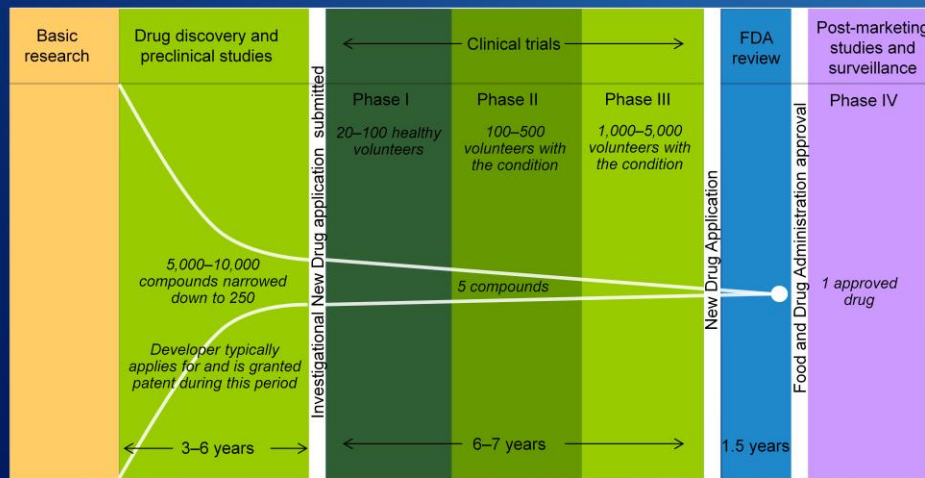
Note: EPO = erythropoietin

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There are two general categories of medicines: small-molecule drugs and large-molecule biologics. Most medicines currently on the market are small-molecule drugs—shown here on the upper right with the example of aspirin. Small-molecule drugs are synthesized through a chemical process and can usually be manufactured at a low cost. After an innovator has exclusively marketed a brand-name small-molecule drug for a period of time, other manufacturers may produce what are often nearly identical generic versions and market them at much lower prices. The Hatch-Waxman Act of 1984 laid out how and when generics may enter the market.

Biomedical science has moved toward developing large-molecule biologics, depicted on the left with the example of erythropoietin (EPO). Biologics are synthesized from living organisms or tissues, are more complex, and provide more targeted treatments for conditions like cancers and auto-immune diseases. Biologics are typically injectable or infusible, and they often require special handling such as refrigeration. A biosimilar product is a biological product that is approved based on showing that it is highly similar to a biological product already approved by the Food and Drug Administration (FDA), known as the reference product or “innovator,” and has no clinically meaningful differences from the reference product in terms of safety and effectiveness. Because of their complexity, biologics cost more to develop and produce, and unlike generic drugs, manufacturers of biosimilars cannot make exact duplicates of the reference product. Even innovators may see changes in their own reference product as they manufacture it over time. The first biologics have been around since the early 1980s, but it was not until 2010 that the Biologics Price Competition and Innovation Act laid out a pathway to approve biosimilars. The FDA approved the first biosimilar in March 2015.

The drug discovery, development, and review process



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Source: Adapted from Pharmaceutical Research and Manufacturers of America.

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This figure depicts the development process for innovator drugs. As research moves into discovery and preclinical trials, developers may evaluate thousands of compounds, narrow those down, and screen them for efficacy and toxicity. Before a compound can be tested in humans, its developers must file an Investigational New Drug application with the FDA. If approved, clinical trials on humans proceed in three phases to evaluate the drug's therapeutic effectiveness and side effects. Once the developer has filed a New Drug Application, the FDA reviews the evidence to make an approval decision. Typically there are issues to resolve, such as which indications can be listed on a drug's label. After the drug is on the market, the developer and the FDA monitor use for data on safety, effectiveness, and risks.

Relatively few compounds achieve FDA approval, so this process can be very costly. When analysts estimate the average cost of developing a new drug, they typically include the research and development (R&D) costs of both successes and failures. Estimates of the average cost also typically include the cost of capital—what investors give up when they tie up their resources in development projects. Development cost estimates vary widely, but one recent study by researchers at Tufts estimated that developing a new drug costs an average of \$2.6 billion: \$1.4 billion in R&D and \$1.2 billion for the cost of capital. The cost of capital has been a controversial point.¹ Despite the risk and cost associated with developing medicines, over the past 30 years, many companies do not appear to have had difficulty obtaining access to capital.

The processes for developing and getting approval for generics and biosimilars differ from the process for innovator drugs. To get a generic approved, companies usually refer to the innovator drug's clinical trial data and then try to demonstrate that their product is equivalent. For biosimilar approval, the manufacturer has to demonstrate that it is highly similar to the reference product through analytic studies, animal studies, and clinical studies unless the FDA determines that some of that process isn't necessary in a specific circumstance. One estimate puts the cost of getting a generic approved at \$1 million to \$5 million over 3 to 5 years.² Good data are generally lacking for biosimilars, but one manufacturer estimates that those products take 8 to 10 years to develop at an average cost of \$100 million to \$200 million.

Federal government's role

- Support biomedical research (e.g., National Institutes of Health)
- Aim to ensure safety and effectiveness of medicines
- Balance incentives for encouraging private innovation with incentives for price competition:
 - Provide financing
 - Basic research
 - Tax credits
 - Major payer for biopharma products
 - Grant temporary monopolies to innovators
 - Patent and Trademark Office awards 20-year patents
 - Food and Drug Administration (FDA) typically grants marketing approval typically well into patent life
 - Prohibit importation and control resale of drugs among purchasers

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The federal government plays many important roles in drug development. It supports biomedical research—most notably through the National Institutes of Health (NIH)—by directly conducting studies, as well as through extramural research. The government also ensures that new drug products are safe and effective through the FDA's approval process.

The government establishes policies that aim to balance encouraging innovation with promoting affordability. It also provides protection to innovators so that other firms cannot immediately produce copies of new drugs and compete away economic returns. Otherwise, innovators may not have sufficient financial incentive to invest in developing new drugs. Ultimately, though, it is also important for other manufacturers to enter the market so that there will be price competition.

Key tools that the government uses include financing and the award of temporary monopolies. The government finances basic research that provides the underlying knowledge base for developing drug therapies. The government also uses tax credits and grants to encourage private entities to conduct applied research and development. The government is a major payer for biopharmaceutical products through federal programs like Medicare and Medicaid.

The most important government tool is its power to award temporary monopolies. A developer first applies for patents when it has found a new compound, but well before it has gathered all the data it will need to get approval to sell the compound as a drug. Later in the development process, the FDA grants marketing approval to sell the drug after reviewing clinical studies about its safety and effectiveness and how long the FDA takes to review that evidence. Typically, FDA approval happens well into a drug's patent life, and the remaining length of patent protection depends on how quickly the developer can gather evidence about safety and effectiveness. Additionally, the law around FDA approval provides for a period of exclusivity that holds off competition from generics or biosimilars.

FDA approval triggers data- and market-exclusivity periods

- Data exclusivity
 - Innovator gets period of protection from competition
 - Generic/follow-on manufacturer may not apply to FDA using innovator's clinical test data for
 - 5 years for new chemical entities
 - 3 years for new indications of an existing drug
 - 12 years for biologics
- Market exclusivity—period of protection before FDA may approve a similar product
 - 180 days for first generic entrant
 - 7 years for orphan drugs
 - Pediatric drugs may get 6 months added to exclusivity

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FDA's approval process triggers periods of exclusivity, giving an innovator manufacturer temporary monopoly power in setting prices. There are two types of exclusivity for which a drug may be eligible, depending on its characteristics. The first type of exclusivity is called *data exclusivity*, during which firms that would like to introduce a generic or biosimilar may not use the innovator's clinical test data as part of their application to the FDA. The length of this period depends on the type of product: 5 years for new small molecule drugs, 3 years for new indications of a drug that has already been approved, and 12 years for biologics. If a follow-on manufacturer were willing to conduct its own trials and pursue FDA approval, in some cases it might be able to challenge an innovator's patents and introduce a competing drug.

The second category is called *market exclusivity*—which refers to an explicit period of protection before the FDA can approve a similar product. For example, the Hatch-Waxman Act of 1984 provides incentives for manufacturers to introduce generics by granting the first generic producer to achieve FDA approval a 180-day market exclusivity period. That first generic producer might not be able to charge as high a price as the brand-name drug, but the market exclusivity still provides some price protection by keeping out other generic competitors for a six-month period.

Other types of drugs that may receive market exclusivity include orphan drugs (targeting an indication with 200,000 or fewer patients) and drugs for pediatric use.

Emerging medicines

- **Numbers of new launches**
 - Varies from year to year, but generally growing
 - Increasing number of orphan drugs
 - Debates about numbers of first-in-class vs. “me too” products, speed of regulatory process, evidentiary standards
- **Recent approvals affecting Medicare**
 - Hepatitis C therapies
 - PCSK9 inhibitors for familial high cholesterol
 - Heart failure therapy
 - Long-acting insulin
- **Others in pipeline**

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The number of new launches of innovator drugs and biologics varies from year to year, but generally it has been increasing. At the same time, the number of orphan drugs has been growing. The government provides incentives to invest in developing orphan drugs through tax credits and market exclusivity.

New launches are not only affected by how much companies invest in R&D, but also by the pace of the regulatory review process. For example, the FDA has developed approaches that are intended to speed up its review of drugs for serious conditions that fill an unmet medical need or demonstrate improvement over existing therapies. Despite these newer approaches, some analysts continue to have concerns that the FDA process is too lengthy and expensive. Other analysts have concerns that too many new launches are “me too” drugs instead of first-in-class products, or that FDA’s expedited approaches and the use of surrogate endpoints to evaluate effectiveness have led to a review process that is too lenient.

Several new launches have implications for the Medicare program either because of the drug’s high launch prices or because a potentially large group of beneficiaries may be prescribed the drug. The most notable example includes hepatitis C therapies, which may reduce or end the progression of disease for infected patients but at prices that led to a double-digit spike in Part D spending in 2014. In 2015, the FDA approved the first of several PCSK9 inhibitors for familial high cholesterol as well as a new treatment for heart failure. In each of these cases, the new launches have been viewed as promising therapies for serious conditions but at high prices. The extent to which physicians prescribe these new treatments and whether plans and pharmacy benefit managers (PBMs) control dispensing will have significant implications for Medicare.

A number of other therapies in the development pipeline may also have important effects on the Medicare program, including next-generation immunotherapies for cancer and new compounds that aim to stall the progression of Alzheimer’s disease.

Factors affecting drug prices

- Demand side
 - Shift from out-of-pocket payment to third-party payment system
 - Shift from private to public insurance
 - Consolidation in the insurance industry
 - Discounts and rebates mandated by law
 - Increase in demand as a result of population aging
- Supply side
 - Increasing complexity of biopharmaceutical products
 - Emphasis on treatments for smaller disease populations (e.g., orphan drugs), often with few competing therapies
 - Cost of borrowing money
 - Patent and temporary monopoly granted by the government
 - Consolidation and/or specialization within the biopharmaceutical industry
 - Changes in the drug supply chain

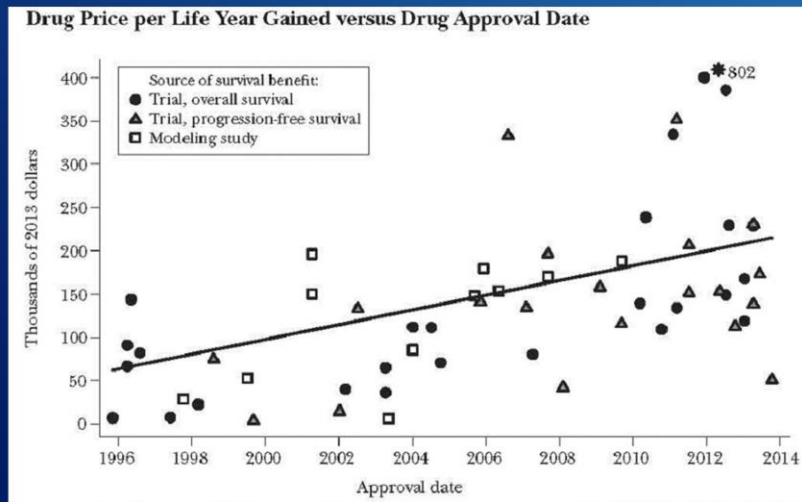
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There are many factors that may affect drug prices. For example, on the demand side, a shift from out-of-pocket payment to insurance can decrease price sensitivity and increase demand, and a shift from private to public insurance can affect prices. Consolidation in the insurance industry may provide insurers with more leverage when negotiating rebates and discounts with manufacturers. Discounts and rebates mandated by law for certain federal programs can affect both launch prices and how quickly manufacturers raise prices on existing products. The aging of the population can affect both demand and drug prices as more people receive their drug coverage from Medicare.

On the supply side, a shift toward more complex biopharmaceutical products such as specialty drugs and biologics tends to put upward pressure on prices. Policies that encourage development of treatments for smaller disease populations can shift the pipeline toward more expensive therapies. The cost of borrowing and patents and temporary monopolies granted by the government can also affect prices. Consolidations or specialization among biopharmaceutical manufacturers can reduce competition for specific therapies and increase the ability of manufacturers to raise prices or launch new drugs at a higher price. Finally, changes in the drug supply chain can affect individual actors' incentives and their relative power in specific markets.

Price of oncology drugs per life-year gained has increased over time



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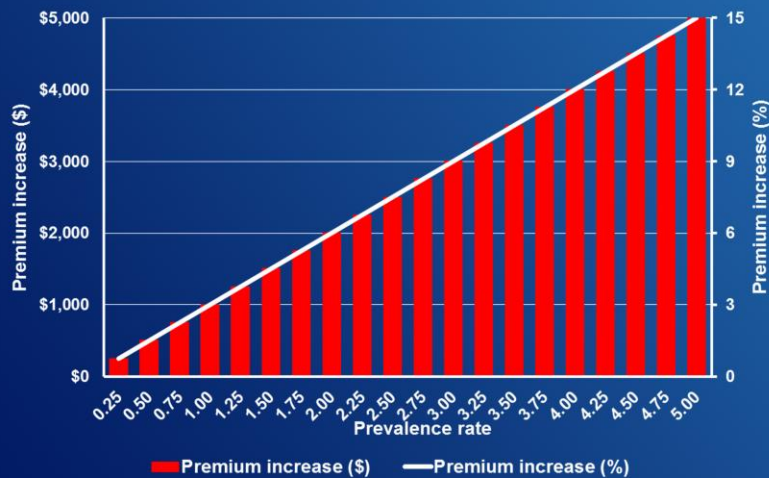
Source: Howard, David, Peter Bach, Ernst Berndt, and Rena Conti, "Pricing in the Market for Anticancer Drugs," *Journal of Economic Perspectives*, vol. 29, no. 1 (Winter 2015): 139–162.

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High launch prices for new drugs and biologics pose enormous challenges for Medicare and other payers. On the one hand, to the extent that a new therapy represents a real breakthrough in treatment, access to the treatment may extend a beneficiary's life or improve quality of life. On the other hand, because there are few published results of head-to-head trials of therapies, it can be hard to know the merits, risks, and relative value of a new therapy.

There has been an upward trend in launch prices of cancer drugs independent of additional treatment benefits. This chart shows trends in the pricing of 58 anticancer drugs approved by the FDA between 1995 and 2013. Each point shows a different drug, and the launch year is shown along the horizontal axis. Higher amounts on the vertical axis mean that the drug had a higher price relative to its survival benefits. This study found that newer drugs were not associated with greater survival benefits when compared with older drugs. The regression line shown above suggests that after adjusting for survival benefits and general inflation, launch prices for oncology drugs have increased by \$8,500 per year.

Wider use of specialty drugs could lead to higher premiums



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Source: Bradford R. Hirsch et al. "The impact of specialty pharmaceuticals as drivers of health care costs," *Health Affairs* 2014;33:1714-1720.

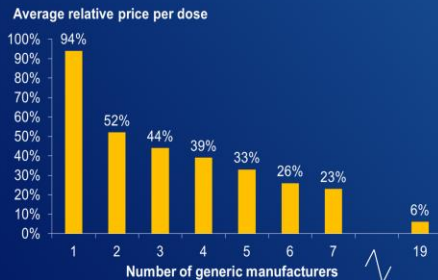
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Today, specialty drugs make up a large share of what is in the development pipeline. There is no one definition of a specialty drug, but generally they are expensive—in 2016, Medicare Part D uses a threshold of \$600 or more per month—and they often require special handling, such as refrigeration. Not all specialty drugs are biologics, but biologics are often specialty drugs.

This chart is from a study that asked the question: What happens to insurance premiums as beneficiaries begin to use the types of medicines that have prices similar to those emerging from the development pipeline? The authors assumed a simple insurance benefit design in which the enrollee pays out of pocket until they reach a \$3,500 cap. Next, they estimated what would happen if a new drug became available at a price of \$100,000 per treated patient. The chart shows that even if this drug is used to treat a relatively narrow population, it can have a substantial effect on premiums.

Currently, generic drug entry lowers prices for reference products more than biosimilars

Dramatic drop in prices as generic drug entry increases



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective™, 1999–2004, extracted Feb. 2005.

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Unlike generics, not all biosimilars are interchangeable with reference products

- More expensive than generics to develop and produce
- Estimates of price effect
 - CBO (2008) estimated 20% to 40% price reduction, varying by product and over time
 - European experience: prices of some biosimilars 20% to 30% lower than innovators
 - In third quarter of 2016, Medicare pays for first biosimilar at a price 13% lower than what it pays for the innovator

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Over the past 10 years, we have seen that generic competition can dramatically lower prices for small-molecule drugs. However, we should not expect biosimilars to have as dramatic an effect on the price of biologics.

When the FDA designates a generic as “A rated,” it is considered therapeutically equivalent, and in most cases pharmacists can substitute the generic for the brand without involving the prescriber. This ability to substitute generics for brand-name drugs has led to rapid downward pressure on prices. On the left is an estimate by the FDA of how the average relative price of a drug is affected as the number of generic manufacturers increases.

In addition, producers of biosimilars face substantially higher costs to bring a product to market than producers of generic small-molecule drugs. Whereas manufacturing makes up the bulk of costs for most generic products, biosimilars often have research and development costs as well as more substantial manufacturing costs. As a result, although there can be wide variation across products, biosimilars may be less able than generics to generate large price discounts off the reference product price. How much of an effect might biosimilars have on the prices of biologic products? The Congressional Budget Office (CBO) estimated that prices may be 20 percent to 40 percent lower than reference products, varying by product and over time.³ Several European countries have already been using biosimilars at prices 20 percent to 30 percent below those of innovators.⁴ For the third quarter of 2016, Medicare’s payment rate for the first FDA-approved biosimilar, Novartis Zaxio, is about 13 percent lower than the payment rate for Amgen’s cancer drug Neupogen.

Drug supply chain

- Manufacturers
- Wholesalers
- Pharmacies
- Pharmacy benefit managers (PBMs)

The next few slides will provide an overview of the drug supply chain, focusing on the retail sector. They will briefly summarize the roles of each actor, and then show, using a very simplified example, how drugs and payments flow through the retail supply chain.

Supply chain: Manufacturers

- Includes manufacturers of brand-name drugs, generic drugs, biologics, and biosimilars
- Develop and/or produce and market drug products
- Set list prices that are typically used as a reference point during price negotiations by supply chain actors
- Negotiate rebates and discounts with PBMs
- Pay a service fee to PBMs

Traditionally, biopharmaceutical manufacturers have fallen into one of three categories: those who specialize in brand-name (patented) products, in generic (off-patent) products, or in biologic products. Manufacturers of brand-name drugs market their products through direct-to-consumer advertising and “detailing,” or direct marketing by sales representatives to health care providers.

Manufacturers set list prices that are typically used as a starting point for price negotiations among the different actors in the supply chain. Where to set a list price depends on the availability of close substitutes, expectations about the size of rebates and discounts to purchasers, and prices of other products in the same therapeutic class. Manufacturers may negotiate rebates and discounts with pharmacy benefit managers, or PBMs, working on behalf of health plans or employers. Manufacturers may also make other types of payments to PBMs. What a manufacturer receives for the sale of its drug products reflects prices, discounts, and/or rebates that are negotiated by various actors in the supply chain.

Supply chain: Wholesalers

- Provide transactional and logistical efficiencies by linking a manufacturer with >60K outlets that administer or dispense drugs
- Help smaller pharmacies negotiate with generic manufacturers by creating formularies
- In 2013, about 85-90% of all revenues from drug distribution were generated by three companies (AmerisourceBergen, Cardinal Health, and McKesson)



Source: Fein, A. 2014. Retail generic drug inflation reaches new heights. *Drug Channels* blog, August 12. <http://www.drugchannels.net/2014/08/retail-generic-drug-inflation-reaches.html>.

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It is often more efficient for pharmacies to get their stock through wholesalers. Wholesalers provide a link between pharmaceutical manufacturers and over 60,000 pharmacies and outpatient dispensing outlets throughout the United States. A manufacturer can ship bulk quantities of a product to the relatively small number of wholesaler warehouses instead of shipping to thousands of individual outlets. Wholesalers store the drug products and then sell and deliver the products in much smaller quantities to their customers.

Wholesalers help smaller pharmacies by pooling their purchasing power to negotiate with generic manufacturers.

The wholesale sector is highly concentrated. In 2013, three companies generated about 85 percent to 90 percent of all revenues from drug distribution in the United States. Revenues for wholesalers typically come from the spread between what they pay to purchase drugs from manufacturers and what they receive in payments for the sales of those drugs to their retail and nonretail customers. They can also earn discounts—such as for prompt payment—and fees on services they provide to their customers.

Supply chain: Pharmacies

- Include chain and independent pharmacies, food stores with pharmacies, and mail-order pharmacies
- Account for about three-fourths of prescription drug market (remainder through nonretail providers such as hospitals)
- Stock a wide range of drugs and fill prescriptions on demand
- Negotiate rebates with manufacturers of multiple-source drugs (competition among manufacturers provides pharmacies with leverage)
- In 2013, five pharmacy chains accounted for about 65% of the prescription dispensing revenues (CVS Health, Walgreens, Express Scripts, Rite Aid, and Walmart)



Source: Fein, A. 2014. Retail generic drug inflation reaches new heights. *Drug Channels* blog, August 12. <http://www.drugchannels.net/2014/08/retail-generic-drug-inflation-reaches.html>.

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Retail pharmacies can be chain stores or independent pharmacies, food and big-box stores, and mail-order pharmacies. They serve about three-quarters of the consumer market for prescription drugs. The remainder is served by nonretail providers including hospitals, some HMOs, clinics, nursing homes, and federal facilities.

Pharmacies stock a wide range of drugs so that they are prepared to immediately fill most prescriptions on demand. Because of this need, they do not have much leverage to negotiate rebates or discounts with manufacturers of single-source brand-name drugs. For multiple-source drugs, they can choose which manufacturers' drugs to stock and dispense, which provides them with leverage to negotiate rebates and discounts.

The pharmacy sector is fairly concentrated among large chains. In 2013, the top five dispensing pharmacies accounted for about 65 percent of U.S. prescription dispensing revenues. Still, independent pharmacies have held on to their market share.

Pharmacies' profits come from the spread between what they pay to purchase drugs and what they receive for the sales. They typically earn higher profits from the sale of generic drugs.

Supply chain: Pharmacy benefit managers

- Administer a drug benefit on behalf of a health plan or an employer
 - Build pharmacy networks
 - Negotiate payment rates with pharmacies
 - Obtain rebates from manufacturers
 - Manage drug use and spending (e.g., tiered copay, prior authorization)
- Use formularies (list of covered drugs) as leverage in rebate negotiation
- About three-fourths of the prescription dispensing revenues are accounted for by four PBMs (Express Scripts, CVS Health, Prime Therapeutics, Optum Rx)

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Source: Fein, A. 2015. *2014–15 economic report on retail, mail, and specialty pharmacies*. Philadelphia, PA: Pembroke Consulting Inc. and Drug Channels Institute.

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Pharmacy benefit managers administer drug benefits on behalf of health plans and employers. They build pharmacy networks and play a key role negotiating payment rates with pharmacies and rebates and discounts with manufacturers.

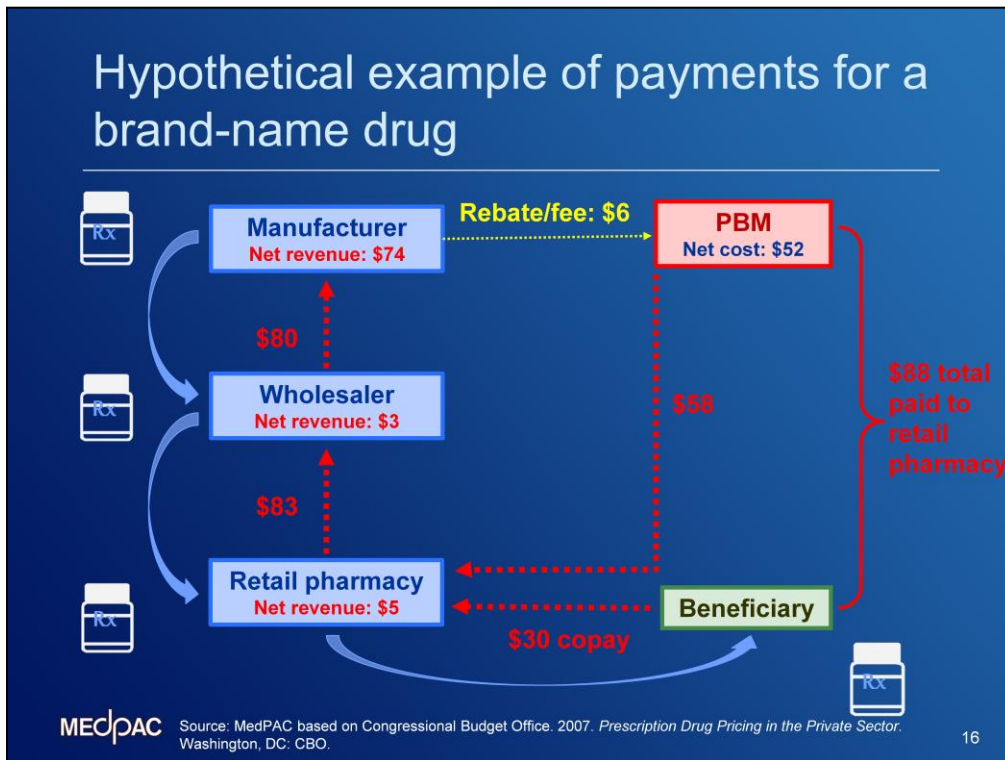
The formulary is one of the main cost-control mechanisms to manage plan members' drug use and spending. The amount of cost sharing, which drugs are covered, how much members must pay for each tier, and whether prior authorization is needed for a particular drug are all determined in discussions between the PBM and the health plan or the employer.

The formulary is also used to negotiate rebates and discounts with manufacturers. PBMs have the greatest leverage for brand-name drugs with close substitutes because manufacturers typically pay rebates in exchange for favorable placement on a formulary, or based on the market share that the manufacturer's drug receives. Manufacturers are unlikely to provide rebates or discounts on products with no competition unless the PBM can realistically exclude their products from coverage.

The market for PBMs is concentrated, with about three-quarters of the prescription dispensing revenues accounted for by four PBMs.

There is a real complexity in how PBMs operate and where they get their revenues. Because rebate amounts are proprietary, it is difficult to know with certainty, but their revenues likely come primarily from manufacturer rebates and fees they receive for managing the drug benefit. In some cases, they may take on an insurance risk and make money on the spread between what they pay to the pharmacy and what they receive from plans or employers.

Hypothetical example of payments for a brand-name drug



As prescription drugs move from manufacturers to wholesalers to retail pharmacies and to consumers, a complex set of market transactions takes place, depending on whether the product is a brand-name drug with patent protection, a brand-name drug that is off patent, or a generic drug. In this figure, we show an example of how payments flow for a brand-name drug with patent protection. Although the various transactions do not necessarily take place sequentially, the hypothetical example starts at the retail pharmacy. The red dotted lines represent payments from one actor to another, while blue arrows represent the transfer of the drug between actors.

In this simplified example, a PBM manages the drug benefit on behalf of an insurer. The beneficiary pays a monthly premium to be enrolled in the plan.

The PBM and pharmacy negotiated a price of \$88 for filling the prescription. The copay amount for this drug is \$30, so the beneficiary pays \$30 at the pharmacy counter. The remaining \$58 is paid by the PBM.

The pharmacy had paid \$83 to the wholesaler to stock this drug, so it makes \$5 on the sale of this drug, which is the spread between what it received from the PBM and the beneficiary, and what it paid to the wholesaler.

The wholesaler had purchased this drug from the manufacturer for \$80. So it makes \$3 on this drug, which is the spread between what it received from the pharmacy and what it paid to the manufacturer.

The manufacturer sold the drug to the wholesaler for \$80, but since it had negotiated a rebate of \$6 with the PBM, the manufacturer's net revenue for the sale of this drug is \$80 minus \$6, or \$74.

The net cost to the PBM for this transaction is \$58 offset by the \$6 rebate it negotiated with the manufacturer, or \$52.

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