Stemming the Escalating Cost of Prescription Drugs: A Position Paper of the American College of Physicians

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This American College of Physicians position paper, initiated and written by its Health and Public Policy Committee and approved by the Board of Regents on 16 February 2016, reports policy recommendations from the American College of Physicians to address the escalating costs of prescription drugs in the United States. Prescription drugs play an important part in treating and preventing disease. However, the United States often pays more for some prescription drugs than other developed countries, and the high price and increasing costs associated with prescription medication is a major concern for patients, physicians, and payers. Pharmaceutical companies have considerable flexibility in how they price drugs, and the costs that payers and patients see are dependent on how payers are able to negotiate discounts or rebates. Beyond setting list prices are issues of regulatory approval, patents and intellectual property, assessment of value and cost-effectiveness, and health plan drug benefits. These issues are linked, and comprehensive efforts will be needed to affect how drugs are priced in the United States.

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High-profile cases of high-priced drugs entering the market and price increases for traditional, generic, specialty, and biologic medications have thrust the issues of prescription drug price, value, and spending to the forefront of health care discussions. In a Kaiser Family Foundation poll, over 70% of those surveyed felt that drug prices were too high and that companies were too concerned about making profits (1). Patients, physicians, payers, and politicians have taken notice of the potential effect of drug price on access to needed medications and are asking questions not only about how pharmaceutical companies determine a drug’s price, but also how we can better assess the pricing, cost, and value of a drug. Pricing (the base price of a drug before negotiations, rebates, and discounts), cost (the actual dollar amount paid by patients, health plans, or the government for a drug), and value (the benefit of a drug relative to its cost) are intertwined, and as policymakers look for solutions, they must consider all 3 issues in order to understand the broader implications of policies or regulatory action.

The benefits associated with prescription drugs cannot be ignored. The drive to create new drugs and seek improved treatments has resulted in a broad and constantly evolving market for prescription drugs in the United States. As new developments in the diagnosis and treatment of disease are discovered, Americans are using these drugs as part of their daily lives. Today, 7 out of 10 Americans are taking at least 1 prescription drug (2). However, not all patients can absorb the out-of-pocket costs for these drugs. Approximately 18% of retail prescription drugs were paid for out of pocket in 2012, and patients used various techniques to reduce costs, including not taking a medication as prescribed (7.8%), asking the doctor for a lower-cost medication (15.1%), purchasing drugs from another country (1.6%), or using alternative therapies (4.2%) (3). Whereas drug prices are variable, demand for prescription medication is fairly inelastic.

Although the current U.S. market includes important advances in disease treatment, the United States is the only country in the 34-member Organisation for Economic Co-operation and Development (OECD) that lacks some degree of government oversight or regulation of prescription drug pricing. The OECD includes 13 countries that are considered high-income: Australia, Canada, Denmark, France, Germany, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, and the United States. Comparatively, the United States spends more on pharmaceuticals than these other high-income countries (4). An analysis of OECD data showed that the United States had the highest level of per capita spending on prescription drugs in 2010 compared with Australia, Canada, France, Germany, Switzerland, and the United Kingdom (5). In addition, the United States tends to introduce new drugs to the market faster than other countries and use these new products more, influencing increases in prescription drug spending (5). The government and private insurance companies are the primary purchasers of drugs in the United States. Medicare, Medicaid, benefits administered under the Veterans Health Administration, and private payers have different methods for obtaining prescription drugs, re-

See also:

Web-Only Appendix: Full Position Paper

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Stemming the Escalating Cost of Prescription Drugs

bates, discounts, negotiation, and administration of drug benefits, which creates a disparate system.

After some years of slowing growth in prescription drug spending, high-cost entrants to the market and increases in the price of prescription drugs already on the market have resulted in increased growth rates, and analysts expect that the United States will see the largest increase in per capita spending among the developed markets between 2013 and 2018 (6). Various components have been mentioned as contributing to the rise in prescription drug costs, including lack of pricing transparency, regulatory barriers, a shortage of comparative clinical data between the cost-effectiveness and value of a drug, health plan benefit structures, and a patent system with loopholes that allows companies to extend monopolies on brand-name drugs while lower-cost alternatives are shut out of the market. All of these issues must be dealt with to achieve meaningful change.

Addressing the many issues surrounding prescription drug pricing may not be as straightforward as unilateral action by a single actor. The research, development, regulatory, and payment systems for prescription medication are deeply intertwined, and the pressing issue of drug pricing and payment will require comprehensive efforts to increase transparency, accountability, and stewardship. Every day, physicians see how prescription drugs affect the lives of their patients. The American College of Physicians (ACP) supports policies and proposals that give patients the best available information and access to prescription medications at the lowest cost possible, while acknowledging the need for a strong pharmaceutical market that fosters investment in and development of new treatments.

This executive summary provides a synopsis of the full position paper, which appears in Appendix 1 (available at www.annals.org).

METHODS

The ACP’s Health and Public Policy Committee developed these positions and recommendations. This committee is charged with addressing issues that affect the health care of the U.S. public and the practice of internal medicine and its subspecialties. The committee identified studies, reports, surveys, relevant news articles, policy documents, and other sources of public information on the pricing of prescription drugs; cost of prescription drugs; cost of drugs to patients and payers; and other aspects of the research, development, regulation, and marketing of prescription drugs. Draft recommendations were reviewed by ACP’s Board of Regents, Board of Governors, Council of Early Career Physicians, Council of Resident/Fellow Members, Council of Student Members, Council of Subspecialty Societies, and outside expert reviews. The position paper and recommendations were reviewed by the ACP Board of Regents and approved on 16 February 2016.

RECOMMENDATIONS

1. ACP supports transparency in the pricing, cost, and comparative value of all pharmaceutical products:
   a. Pharmaceutical companies should disclose:
      i. Actual material and production costs to regulators;
      ii. Research and development costs contributing to a drug’s pricing, including those drugs which were previously licensed by another company.
   b. Rigorous price transparency standards should be instituted for drugs developed from taxpayer-funded basic research.
2. ACP supports elimination of restrictions of using quality-adjusted life-years (QALYs) in research funded by the Patient-Centered Outcomes Research Institute (PCORI).
3. ACP supports the following approaches to address the rapidly increasing cost of medications:
   a. Allow greater flexibility by Medicare and other publicly funded health programs to negotiate volume discounts on prescription drug prices and pursue prescription drug bulk purchasing agreements (7, 8);
   b. Consider legislative or regulatory measures to develop a process to reimport certain drugs manufactured in the United States, provided that the safety of the source of the reimported drug can be reasonably assured by regulators;
   c. Establish policies or programs that may increase competition for brand-name and generic sole-source drugs.
4. ACP opposes extending market or data exclusivity periods beyond the current exclusivities granted to small-molecule, generic, orphan, and biologic drugs. ACP supports robust oversight and enforcement of restrictions on product-hopping, evergreening, and pay-for-delay practices as a way to increase marketability and availability of competitor products.
5. ACP supports research into novel approaches to encourage value-based decision making, including consideration of the following options:
   a. Value frameworks;
   b. Bundled payments;
   c. Indication-specific pricing;
   d. Evidence-based benefit designs that include explicit consideration of the pricing, cost, value, and comparative effectiveness of prescription medications included in a health plan’s benefit package.
6. ACP believes payers that use tiered or restrictive formularies must ensure that patient cost-sharing for specialty drugs is not set at a level that imposes a substantial economic barrier to enrollees obtaining needed medications, especially for enrollees with lower incomes. Health plans should operate in a way consistent with ACP policy on formularies and pharmacy benefit management.
7. ACP believes that biosimilar drug policy should aim to limit patient confusion between originator and biosimilar products and ensure safe use of the biosimilar product in order to promote the integration of biosimilar use into clinical practice.
CONCLUSION

Recent trends show that increases in the price of prescription drugs have drawn the interest and concern of patients, payers, government officials, and physicians, particularly in the cases of very substantial price increases for some generic drugs, and in the price of existing brand-name drugs and specialty drugs (9). The United States often pays more than other high-income countries for the same drugs, and despite discounts, rebates, coupons, and assistance programs, high and increasing drug prices still threaten to keep patients from getting the drugs they need. Through collaboration and innovation, stakeholders have the ability to effect change by supporting transparency in how drugs are priced, developing and piloting novel approaches to evaluate and pay for drugs through evidence-based practices that reward advancements in the medical field, assuring access to needed prescription medication by not placing disproportionate economic burden on patients, encouraging informed patient participation in their health care decision making, and ensuring a truly competitive marketplace.

From the American College of Physicians, Washington, DC.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

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References
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APPENDIX 1: STEMMING THE ESCALATING COST OF PRESCRIPTION DRUGS: A POSITION PAPER OF THE AMERICAN COLLEGE OF PHYSICIANS

Background

Drug Pricing in the United States

The complex factors that go into how a drug is priced can be difficult to understand and highly variable. Often, the terms “price,” “cost,” and “value” are used without explicit understanding of what is being referred to; small nuances in language can lead to confusion. For the purpose of this paper, “price” refers to the wholesale acquisition price or “list price” of a drug without applicable rebates, coupons, or discounts, and “cost” is the amount paid by a patient or health plan after all rebates, coupons, or discounts are applied. The concept of “value” in the biopharmaceutical field is highly variable and depends on the perceptions of clinicians and patients. Generally, the value of a drug is the benefit it provides relative to cost.

Unlike many other countries, the United States lacks regulatory authority to control the price of drugs or devices or take into account value as a coverage consideration. As a result, pharmaceutical companies may price drugs at will, and there is very little transparency or understanding of how companies arrive at the price of a drug. Representatives of the pharmaceutical manufacturing industry maintain that the price of the drug is necessary to promote continued investment in private research and development and the comparative benefit the drug provides to patients, and to encourage future innovation. However, these claims tend to conflict with available information.

The Tufts Center for the Study of Drug Development estimated that the current cost of drug development and approval in the United States is approximately $2.6 billion (10). In 2001, Tufts estimated this cost to be about $802 million (in 2000 dollars) (11). This estimate has been challenged by other researchers as being inaccurate or overstated; a 2014 article in the New England Journal of Medicine article criticized the Tufts figure for placing too much importance on the cost of capital ($1.2 billion, nearly one half the cost estimate), lacking transparency in the compounds and companies analyzed, and not taking into account public subsidies received by pharmaceutical companies (12).

Owing to the multifaceted nature of drug development and a high failure rate for drugs in the early stages of the development pipeline, it can be difficult to pinpoint how much money put into research and development of drugs that are abandoned or ultimately fail to gain regulatory approval is carried over into the pricing of other drugs. Most drugs that fail to make it to market do so in the preclinical phase of development; however, some companies spend considerable amounts of money for drugs that fail in late-stage trials. Pfizer invested $800 million to develop a potential blockbuster cholesterol drug, only to find that it increased the risk for death in a large-scale, 15,000-person clinical trial (13). However, as mentioned in the New England Journal of Medicine article, the $1.2 billion figure “[was] assessed at 10.6% per year compounded—despite the fact that bonds issues by drug companies often pay only 1% to 5%” (12). Industry advocates report that approximately 20% of marketed drugs earn back research and development costs (14).

Some analysts have challenged the claims that price is reflective of research, development, and capital costs. Funding from private companies is required to bring new drugs over the drug development “valley of death” and to market; large investments are made annually by private companies on research and development (15). However, a good deal of basic research originates through government-funded grants or agreements. In addition, publicly available financial data have given greater insight into how pharmaceutical companies use the money they spend on drugs. A study published in PLoS Medicine found that companies seem to spend twice as much on drug promotion as on research and development (16).

Pharmaceutical company mergers bring up several concerns regarding real investment in research and development. One example is the acquisition of Wyeth by Pfizer in 2008. Before the merger, the 2 companies spent a combined total of $12 billion on research and development. In 2013, the new company spent $6.55 billion (17). A portion of this reduction can be attributed to eliminating redundancies; however, the merger of 2 companies would decrease collective investments by nearly one half. Pharmaceutical company acquisition and subsequent increase in price of existing drugs is also notable. In the case of Daraprim (pyrimethamine), Turing Pharmaceuticals purchased the rights to the drug and subsequently increased the price. The company did not spend any money on research or development of that specific drug, but maintained that the price would go to funding research and development...
of a future drug that would make Daraprim obsolete (18).

Finally, although market forces clearly play a role in keeping pricing competitive and sustainable, competition alone may not be effective in encouraging innovation or controlling costs, especially without the price transparency required for true price competition to take place. Rewarding innovation is critical to the development of new therapies. However, several drugs on the market are considered “me-too” drugs—that is, drugs that are similar to products already on the market and provide little, if any, added benefit. For example, AstraZeneca originally manufactured the blockbuster acid reflux treatment Prilosec (omeprazole magnesium). When Prilosec’s patent expired in 2001, the company immediately launched Nexium (esomeprazole sodium), an almost identical drug with a minor formulation change that earned the company billions more in sales.

The value of me-too drugs continues to be debated; similar drugs manufactured by competing companies may put pressure on the competitor drug to lower price or deter price increases (19). Determining new delivery systems or dosing for drugs may also result in a net gain if those methods can be used to improve future drugs. However, me-too drugs may also reduce investment in research and development or innovation.

Free-market forces are also not always effective in leveling costs in certain drug classes. Oncology drugs are an example of this: Generic versions are priced very low, whereas brand-name, patented drugs are priced high and continue to increase (20).

Increase in Spending on Prescription Drugs

In 2013, prescription drug costs accounted for 9.3% of the United States’ total health expenditure, with a growth rate of 2.4% over the previous year, or approximately $263.5 billion (21). In 2014, prescription drug spending grew 12.2% to $297.7 billion and accounted for 9.9% of total health expenditures (22). Of note, the national health expenditure assessment of the percentage share of prescription drug spending does not include pharmaceutical spending in physician or hospital settings, and some have estimated that the percentage is higher (23). According to the National Health Expenditure Projection, prescription drug spending is expected to grow 5.4% for 2016-2019 and 6% for 2020-2023, owing to “... improving economic conditions, an expected rising trend of expensive specialty drugs being purchased through retail channels, and anticipated clinical guidelines designed to encourage drug therapies at earlier stages of treatment” (23). In 2014, total spending for health care in the United State increased 5.3%, faster than the 2.9% growth rate seen in 2013 and partially attributed to “rapid growth in spending on retail prescription drugs” (24).

The recent growth in the prescription drug spending rate is in contrast to the decline in the growth rate in drug spending experienced since 2003. By 2007, prescription drug spending growth slowed to 1.6%, despite a 9.9% average growth between 1997 and 2007 (25). Part of this slowing is the effect of the Drug Price Competition and Patent Term Restoration Act (also known as the “Hatch-Waxman Act”), passed in 1984. The Hatch-Waxman Act aimed to increase the availability of generic drugs after patent expiration by eliminating the requirement that generic drug manufacturers do the same type of clinical testing as for new brand-name drugs and by making certain adjustments to patent protections. The act was successful in speeding generic medications to market. Generic medications are relatively cheap and simple to produce, and they account for 8 in 10 prescriptions filled in the United States (26).

Generic drugs have traditionally encouraged competition and driven costs down. The patent protection for many branded drugs, including several blockbuster drugs, expired in 2012, allowing a flood of generic drugs to enter the marketplace. Several other global, high-selling drugs—including Celebrex (cecloxib), Symbicort (budesonide and formoterol), Gleevec (imatinib), and Cialis (tadalafil)—will go off patent by 2018, at which point the market will reach a lull (6). Once generic versions of widely used drugs became available, there can be considerable savings. A notable example is the case of Lipitor (atorvastatin), a cholesterol-lowering drug made by Pfizer. In the third quarter of 2011, Lipitor saw $1.97 billion in sales. After the patent on Lipitor expired in late 2011, sales of the drug dropped by almost 50%, to $841 million (27). The savings from the use of generic drugs increased 14% between 2012 and 2013, for about $30 billion in additional savings (28). To account for this loss in revenue, companies refocus on newer, brand-name drugs.

A major factor in the increase in overall spending for prescription drugs is the prevalence and rising use of high-priced specialty medications. Specialty drugs are sometimes described as “large-molecule” products, produced by using advanced techniques that require special handling and administration compared with “small-molecule” traditional drugs (29). Across the spectrum, specialty drugs are also defined as drugs that treat life-threatening or complex chronic illness; are priced at $600 per month or more; and require patient education, monitoring, and management over the course of the drug cycle (30).

Many specialty drugs are biologics, which are drugs derived from living tissues, sugars, or proteins. One of the first biologics approved in the United States was human insulin; biologics now include ground-
breaking therapies for cystic fibrosis, rheumatoid arthritis, cancer, and various chronic diseases. Although specialty drugs only accounted for 1% of prescriptions written, they made up 25% of the $263.3 billion spent on prescription drugs (31). The average daily cost of a biologic is $45, compared with $2 for traditional small-molecule drugs (32). All biologic drugs are considered specialty drugs, but not all specialty drugs are biologics.

Although many high-priced drugs are associated with use in rare diseases, small populations, or life-threatening diseases for which no alternatives exist, the market is expanding to include advancements over existing therapies in larger disease populations. Two primary examples are the hepatitis C drugs Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir) and the recently approved class of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that lower low-density lipoprotein cholesterol levels (33). Sovaldi and Harvoni are significant advancements over older, more toxic treatments and can reduce viral levels so effectively that some refer to the drug as a cure. Sovaldi costs $84 000 for an 8-week course of treatment, or about $1000 per pill (34). If every person infected with hepatitis C in the United States, estimated to be around 3 million, were treated with Sovaldi, it would cost hundreds of billions of dollars. Harvoni combines Sovaldi with another drug and is priced slightly higher, at around $95 000 for a 12-week course of treatment.

The PCSK9 inhibitors, which are a groundbreaking advancement in the treatment of cholesterol, must be injected once or twice a month. One of these drugs, Repatha (evolocumab), has been priced at $14 100 annually. This number does not seem high compared with the sticker shock of Sovaldi or Harvoni; however, unlike the hepatitis C drugs, which have a specific treatment cycle, PCSK9 inhibitors must be taken as maintenance therapy for an undetermined period. One of the largest pharmacy benefit managers, Express Scripts Holding Company, announced in October 2015 that they had reached an agreement with the makers of the PCSK9 inhibitors that included rebates, restrictions on who can receive the therapy, protections against price increases, and a spending cap. Express Scripts does not expect to spend more than $750 million on the drugs in 2016 (35).

Potential Contributors to Unsustainable Prescription Drug Pricing

Lack of Price, Cost, or Value Transparency

For decades, pharmaceutical manufacturers have claimed that pricing is based on research and development costs and innovation, and is well regulated by market forces. The spike in prices and increase in prices for drugs already on the market have made many stakeholders wary, especially because many of these new therapies treat small populations and there are few data to support that overall health care costs are reduced. People are particularly worried about high-priced drugs for hepatitis C, because health plans have seen increases in expenditures as a result of this particular set of drugs (36). An actuarial study by consulting firm Milliman assessed the cost to the U.S. health care system in the absence of a cure for hepatitis C. The report found that, without a cure, 350 000 more patients would be living with advanced stages of hepatitis C between 2015 and 2025, at a cost of $115 billion (37). Although some high-priced drugs may prove to decrease costs in the long run, high prices give certain drugs the perception of value without adding benefit. An analysis of oncology drugs approved between 1996 and 2014 found that the price of oncology drugs per life-year gained has increased over time (38).

Regulatory Process

Companies seeking to market a prescription drug in the United States must have the drug approved by the U.S. Food and Drug Administration (FDA), the agency charged with protecting and advancing public health and ensuring the safety and efficacy of drugs, devices, veterinary drugs, biological products, the nation’s food supply, cosmetics, and products that emit radiation. It is the FDA’s charge to ensure that drugs are safe and effective for their indication, but the agency is not required to take into account the value of a new drug compared with existing therapies.

Obtaining FDA approval has long been criticized by the pharmaceutical industry for being arduous, timely, and costly, delaying a drug’s ability to be marketed and begin making a profit. In the early 1990s, an underfunded FDA resulted in a backlog of new drugs reaching the U.S. market. This ultimately led to passage of the Prescription Drug User Fee Act (PDUFA), which allows the FDA to charge companies fees in exchange for being held to performance goals and approval timelines. As a result of PDUFA, the median approval times for standard and priority review drugs in fiscal year 2013 dropped to 12 months and 7.9 months, respectively, and patients have greater access to medications (39). This reduction in approval time means drugs hit the market faster and companies are quicker to recoup their investment costs. Some analysts argue that the process is still too long and costly, and there are specific concerns about generic drug applications. There is currently a backlog in generic drug applications, and generic drugs are not entering the market as quickly as had been anticipated with the passage of the Generic Drug User Fee Act, which is based in the same fee-for-timeline concept as PDUFA (40).
Drugs can move through the regulatory approval process more rapidly if they qualify for fast-track designation, accelerated approval, priority review, or breakthrough therapy designation. These approaches help expedite the process of getting lifesaving drugs for serious diseases to market. For drugs moving through the accelerated approval pathway, a drug for a serious condition filling an unmet medical need may be approved by using a surrogate end point or intermediate clinical end point (41). The number of drugs for which FDA approval is applied and granted has increased in the past decade. A report released by the FDA on novel drug approvals showed that the agency approved 45 new molecular entities in 2015—nearly double the average number of new molecular entities approved from 2006 through 2014—and 87% of these drugs were also approved on the first cycle of review, without requests from the agency for more information (42).

In addition, some classes of drugs are now approved faster in the United States than internationally. An analysis of oncology drugs approved by the FDA and its European counterpart, the European Medicines Agency, between 2003 and 2010 found that the FDA approved more brand-name oncology drugs during that time than did the European Medicines Agency (43).

The most recent PDUFA reauthorization, the FDA Safety and Innovation Act, included the newest expedited approval designation: the breakthrough therapy designation. Breakthrough therapies are those that are intended to treat serious or life-threatening disease, and for which preliminary clinical evidence shows that they provide significant improvement over existing therapies. If a drug is granted breakthrough designation, the FDA will speed the development and review of the drug, including additional communication between the FDA and the manufacturer. To date, 28 drug approvals have been designated as breakthrough therapies.

Breakthrough therapies are also more likely to be specialty drugs and carry high price tags. Drugs approved with a breakthrough therapy designation include numerous oncology drugs, Sovaldi and Harvoni, and the cystic fibrosis drug Kalydeco (ivacaftor) (44). Because these drugs are typically approved through the accelerated approval process, additional safety and efficacy reporting is required during postmarket surveillance. The FDA can require that risk evaluation and management strategies be developed for certain new drugs to address potential issues early.

Collection of postmarket data is important for the continued evaluation of safety in drugs that are approved rapidly on the basis of limited clinical trial data or surrogate end points. To date, no drugs that have been awarded breakthrough therapy designation and approved by the FDA have been removed or had approval revoked; however, the breakthrough therapy designation is relatively new, and long-term postmarket safety data are limited.

Although the number is small compared with the overall number of drugs approved by the FDA, a handful of drugs approved through the accelerated approval process have been recalled or had approval revoked for an indication—demonstrating the importance of postmarket data collection. For example, Avastin (bevacizumab) was approved in 2008 for use in combination with paclitaxel for the treatment of certain types of breast cancer. Preliminary studies found that the combination improved progression-free survival. However, follow-up studies found no difference in overall survival among patients using Avastin; on average, patients had less than 3 months of progression-free survival, and there was a high rate of severe side effects (45). The FDA revoked approval for the use of Avastin in breast cancer, although the drug is still available for the indication off-label.

Lack of Competition in the Marketplace

Drugs that gain FDA approval are granted varying marketing exclusivity periods—5 years for chemical products, 7 years for orphan drugs, and 12 years for biologics—that are a statutory provision granted to a drug if all statutory requirements are met (46). This period may run concurrently with a drug’s patent protection, extend beyond the life of a patent, or expire before the patent does. Other drugs are prevented from obtaining FDA approval and entering the market before that period ends. The Affordable Care Act included the Biologics Price Competition and Innovation Act (BPCIA), which directed the FDA to establish an expedited approval pathway for biosimilar products, similar to what the Hatch-Waxman Act did for generic drugs. The BPCIA included a 12-year period of data exclusivity for biologics starting from the approval date of the product. During this period, the FDA cannot consider a biosimilar application that relies on the clinical trial data for the “originator” or “reference” biologic. The law also included provisions designed to prevent evergreening (47) (in which a pharmaceutical company producing a brand-name drug makes minor or modest changes that provide no therapeutic advantage to a drug’s formulation to extend the life of the patent) and a process for resolving patent disputes (48).

The FDA does not control the length of patents or have authority to change patent terms; the U.S. Patent and Trademark Office may issue a patent to a drug at any point during development that covers various claims. The patent expires 20 years from the date of filing, although the life of a patent can be extended through new formulations of the drug, new routes of
administration, new indications, or use of the drug in combination with another drug (49).

Because patent laws can allow more flexibility than marketing and data exclusivities, pharmaceutical companies may use loopholes within the system to extend the patent protection of a drug. Product-hopping or evergreening extends the monopoly on the brand-name drug and can keep a competitor drug out of the market. In some cases of evergreening, a company will introduce a nearly identical version of a brand-name drug before patent expiration and allow the original brand-name drug’s patent to expire, promoting the new drug as an improvement over the previous brand-name drug. Product-hopping; evergreening; and some pay-for-delay agreements, in which a brand-name drug company settles potential patent litigation with a manufacturer of generic drugs, effectively keeping the generic drug off the market, have been flagged as anti-competitive by the U.S. Federal Trade Commission and other government officials, although these practices remain legal.

Limited competition can also drive up the price of a medication. A recent example is price increases for naloxone. The drug, used as a treatment for opioid overdose, has been used in hospitals as an injectable drug since 1971. In the late 1990s, successful pilot programs were launched for use of naloxone outside the hospital setting by local law enforcement and community health professionals to reverse overdose. In the wake of the current heroin epidemic, police forces around the country have been authorizing the use of naloxone and training officers in how to administer the drug via an intranasal spray. Although the cost of the injectable drug is minimal, only one company manufactures an intranasal form of naloxone and has raised the price from $20 to $40 per dose (50). The price increase calls into question the impact on state budgets and access to this life-saving drug.

Increasingly, the pharmaceutical marketplace is narrowing its focus to highly innovative, biologic, or specialty drugs for which there are few, if any, competitors, creating monopolies and limiting the cost-controlling power of competition. Sovaldi and Harvoni, both made by Gilead, have had a significant impact on the hepatitis C treatment market. Although hepatitis C treatments already existed, the vast improvement over those therapies resulted in some existing drugs being withdrawn from the market (51). In its first full year on the market, Sovaldi became the second best-selling drug in the United States, at $10.3 billion in sales in 2014 (52). Harvoni generated $3.58 billion in sales in the first quarter of 2015, with $3.02 billion in the United States alone. During that period, Sovaldi sales dipped to $972 million from $2.27 billion in the first quarter of the previous year (53).

AbbVie introduced similarly priced competitor products, Viekira Pak (a multi-pill combination of dasabuvir, ombitasvir, paritaprevir, and ritonavir) and Technivie (a combination of ombitasvir, paritaprevir, and ritonavir). Although many felt that this would create a challenge to the Sovaldi-dominated market, an October 2015 warning letter from the FDA to the makers of Viekira Pak requiring an update to the label to reflect the potential for “serious liver injury mostly in patients with underlying advanced liver disease” calls into question whether the drug will have the effect that analysts thought (54).

The generic manufacturing market is becoming consolidated, and progressively some generics are being manufactured by a single company or are disappearing from the market. Single-source generics are more expensive than other generics; some health plans place these drugs in the preferred drug tier in absence of a competitor, resulting in higher costs to the patient (55, 56). Consolidation of pharmaceutical manufacturing companies may be contributing to the single-source generic problem, as well as aging factories and production issues. When a drug goes into shortage for quality issues, a company may decide that it is more expensive to correct manufacturing issues and go through the FDA process for getting the generic drug back on the market. Companies that do not already manufacture a similar drug are unlikely to produce a drug with a lower return on investment than a higher-priced brand-name drug or biologic.

Increases in the Price of Brand-Name and Generic Marketed Drugs

Increases in drug spending are related to the overall increase in drug prices at all stages of a drug’s lifecycle. The prices of numerous drugs have increased after coming to market, without justification or transparency. A report by Elsevier found that of a sample of 4421 drug groups, 222 groups increased in price by 100% or more over the course of 1 year, and 17 groups had price increases of more than 1000%. One of the drugs whose price increased by over 1000% is tetracycline, a common antibiotic prescribed for bacterial infections (57). The AARP Public Policy Institute found that more than one third of brand-name drugs used for chronic conditions that had been on the market since 2005 increased more than $1600 per year for 8 years (58). In addition, the retail price for commonly prescribed dermatologic drugs between 2009 and 2015 showed a considerable increase, with many of the increases occurring after 2011 (59).

One of the most recent high-profile cases of a drug price increase has been that of Daraprim. Although no companies make a generic form of the drug, Daraprim, which went off patent in 1953, recently experienced a
price increase from $13.50 per pill to $750 per pill—a 5000% increase—after it was purchased by Turing Pharmaceuticals. Despite considerable backlash from the public and media noting the practical and ethical issues behind the company’s rationale for the price increase, the price of Daraprim remains unchanged.

Cancer therapies tend to be some of the highest-priced specialty drugs; 11 of the 12 cancer drugs approved by the FDA in 2012 cost $100,000 or more (60). Gleevec (imatinib), originally priced at $24,000 when it launched in 2001 (approximately $32,000 in 2015 dollars when adjusted for inflation), now costs $90,000 (60). The safety and effectiveness of the drug have not changed—only the price. Analyses of FDA-approved cancer drugs found little difference in the average wholesale price of novel cancer drugs and next-in-class drugs, suggesting that they are priced independent of novelty and simply at what the market can bear (61). Similar pricing differences are seen with multiple sclerosis drugs: The price of the first-generation disease-altering drugs has increased at an annual rate of 5 to 7 times that of inflation, despite the introduction of competitor drugs (62).

These increased prices can negatively affect the supply chain; pharmacies receive lower reimbursements than the price they must pay for the drugs, patients may not fill their prescriptions, and physicians may have to prescribe alternative therapies (63). This trend is also not confined to specialty or generic drugs: Many of the top-selling prescription drugs have also increased in price. The price of Viagra (sildenafil) increased 159% between 2007 and 2014; Xyrem (sodium oxybate) for narcolepsy increased 841%; and Humulin (insulin isophane), a diabetes medication, increased 354% (64).

The rising cost of diabetes treatment is particularly troubling to physicians and patients. According to the Centers for Disease Control and Prevention, 29 million people in the United States have diabetes, and it is estimated 387 million have diabetes worldwide (65). The American Diabetes Association estimates that the total cost of diagnosed diabetes has risen to $245 billion in 2012, from $174 billion in 2007 (66). Thirty percent of direct costs went to prescription medications to treat complications of diabetes and to antidiabetic agents and diabetes supplies. Diabetes drugs accounted for 5 of 27 branded drugs with a price increase of at least 20% between 2014 and 2015 (67). Primarily because of rising drug costs, spending on insulin and diabetes medications is expected to rise 18.3% over the next 3 years.

**Lack of Available Biosimilars**

Biosimilars, also referred to as “follow-on biologics,” are off-brand but highly similar to reference or “originator” biologic products and are expected to help curb the prevalence of high-priced biologics. Over 700 follow-on biologics are in development worldwide, and it has been suggested that biosimilars will account for about $25 billion in sales from off-patent biologics by 2020 (68). Although sometimes referred to as the “generic” version of biologics, they are not considered by federal regulators to be generic, because the nature of the biologic drug and sensitivities to manufacturing and handling do not result in exact duplication. Some biosimilars may be deemed interchangeable with their originator product, but obtaining status as a biosimilar does not automatically indicate interchangeability—unlike generics, which are chemically identical to their brand-name counterparts.

In March 2015, the FDA approved Zarxio (filgrastim-sndz), the first biosimilar for the U.S. market, under the BPCIA biosimilar approval pathway. It was made available for sale on 2 September 2015 after legal attempts by the originator product’s manufacturer to keep the drug from market failed. The drug is priced 15% lower than the originator product (69), and estimates suggest that Zarxio could save the health system $6 billion over the next decade (70). The originator product, Neupogen (filgrastim), was originally licensed in the United States in 1991.

Biosimilars have been available in Europe since 2006, and 22 biosimilars are available in the European Union. A 2013 report found that the biosimilar market in Europe has helped to improve competition and increase access to biologic medicines, although overall uptake and financial impact remains modest (69). The United States and international markets differ in their ability to regulate the cost of drugs and available research and effectiveness data; however, this example, as well as the reduction in prices and costs associated with the introduction of generic drugs in the United States, suggests future cost-savings associated with biosimilars. In addition, despite the modest gains seen in the European Union, analysts think that the United States may be faster to adopt the use of biosimilars because the European Union does not allow interchangeability (68). A RAND Corporation analysis predicts that biosimilars could lead to a $44.2 billion reduction in direct spending on biologic drugs between 2014 and 2024 (71).

Several biosimilars are in the pipeline, but it remains to be seen when these drugs will be approved and for what indications, and whether the originating manufacturers will exhaust all legal challenges in keeping the biosimilars from entering the market, as in the situation with Zarxio. Once biosimilars are available, the potential cost-savings will depend on the extent to which they are utilized; if physicians and patients are willing to use a biosimilar product instead of a biologic, cost-savings are more likely to be realized.
Paying for Prescription Drugs in Public and Private Health Plans

How health plans pay for prescription drugs varies by the insuring body: Medicaid, Medicare, and private insurers all have different policies that govern what type of agreements they can broker with pharmaceutical companies, what drugs they must provide, or what kind of discounts they can get in acquiring drugs. Pharmaceutical companies have argued that you cannot judge the price of a drug on the basis of its wholesale acquisition cost (“sticker price”) because it does not reflect the actual price paid by health plans or individuals. Manufacturers often negotiate discounts with pharmacy benefit managers, state Medicaid programs, private insurers, wholesalers, and other organizations.

Medicare programs pay for drugs in distinct ways, depending on which program the enrollee uses; some programs are prohibited by statute from negotiating drug prices directly with pharmaceutical companies (72). Under traditional Medicare, Part B and certain other drugs that follow from Part B services are paid for by using a formula of the drug’s average sales price plus 6% of that price. The average sales price represents an average of all rebates or discounts the pharmaceutical company charges on the commercial market (73). Medicare beneficiaries can also enroll in the Medicare Part D prescription drug benefit program, or obtain coverage through a Medicare Advantage plan.

Prices and costs in Medicare also differ depending on how and where the drug is administered. Typically, drugs are administered either at home by the patient, in which case the drug falls under the pharmacy benefit (Part D), or by physicians or health care professionals in a clinical setting, in which case the drug falls under the medical benefit (Part B). Drugs that are administered through the pharmacy benefit have generally been the lower cost of the 2 options, although recently there has been a shift and some drugs, such as some oral chemotherapy agents, cost more than those administered through the medical benefit. Oral cancer drugs were noted by one study to be the primary contributor to overall increases in Medicare specialty-drug spending in recent years (74).

State Medicaid programs reimburse pharmacies for the ingredient costs of a prescription drug and a fee to the pharmacy for those drugs provided under the pharmacy benefit. Consumer cost-sharing caps apply in Medicaid programs, and nearly all Medicaid programs and Medicaid managed care plans charge nominal copayments, which vary on the basis of the type of drug (brand-name or generic) or whether it is considered a preferred drug in the state’s Medicaid program (75). Medicaid programs receive the lowest price offered to any payer outside government agencies as part of the Medicaid Drug Rebate Program and are required to cover all FDA-approved drugs. This creates unique challenges for state Medicaid plans, particularly with the introduction of sofosbuvir drugs (Sovaldi and Harvoni).

An analysis of Medicaid programs found a wide variety of protocols and preauthorization requirements before a patient is given sofosbuvir drugs as a treatment. Thirty-one states consider Sovaldi a “nonpreferred” drug, whereas 17 states designate the drug as “preferred” and do not require evidence of medical necessity. All but 2 states require prior authorization, and many states require abstinence from alcohol and illicit drugs, or both, for durations of 1 to 12 months before treatment. The analysis also found that many state Medicaid policies conflict with the recommendations of the Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD) on the use of sofosbuvir drugs (76). The IDSA/AASLD guidelines recommend that patients abstain from alcohol or drug use but do not recommend withholding the drug until the conditions are met. Several states also require subspecialist consultation before receiving treatment. In addition, CMS issued a letter in 2015 urging state Medicaid programs to improve accessibility to hepatitis C medications (77).

Recommendations

1. ACP supports transparency in the pricing, cost, and comparative value of all pharmaceutical products:
   a. Pharmaceutical companies should disclose:
      i. Actual material and production costs to regulators;
      ii. Research and development costs contributing to a drug’s cost, including those drugs which were previously licensed by another company.
   b. Rigorous price transparency standards for drugs developed from taxpayer-funded basic research.

   The call for increased price transparency, especially for high-priced specialty or orphan drugs, is not new and is an important component in driving value-based incentives. The term “price transparency” has become prominent after the Daraprim pricing controversy, and it has been included as part of proposals by political candidates and echoed in the public outcry over the price of drugs.

   Pricing methodologies for biomedical products are notoriously covert, and it is difficult to pinpoint to what extent a price reflects research, development, marketing, or administration costs. Pharmaceutical companies are required to disclose sale price information for a limited number of drugs. Companies report information on average sales prices for Medicare Part B drugs to CMS quarterly; however, the average sales price includes discounts, rebates, and other payments and differs from the list price. Pharmaceutical companies are often publicly held and disclose information on their research and development and marketing portfolios,
which has allowed outside analysts to review how, and how effectively, companies use their research and development budgets. The average amount that a company spends on research and development per drug may vary, depending on the number of drugs each company is developing and how many gain regulatory approval.

Pharmaceutical companies consider some information that may affect their business, including information on pricing methodology or clinical data gathered that competitors can use to develop their own strategies, as proprietary information or trade secrets. Manufacturing costs for biologic and specialty drugs are higher than those to produce traditional, small-molecule drugs. Biologics are highly sensitive to manufacturing and environmental conditions, and even innovator products can show differences in drug composition over time as a result. Biologic drugs must be produced in special facilities and use materials that can be 20 to 100 times more expensive than those used to produce small-molecule drugs (78). If certain materials required to make the drug are in shortage, this may also contribute to the price of a drug, especially in the generic market. Although these costs amount to a smaller portion of the overall price of a drug, the material and production costs of a drug are generally not considered proprietary and would be a rational first step in establishing greater transparency standards.

The ACP understands and acknowledges that marketing costs are inherent to the ability of a company to recoup the cost of investment into drugs and remain in business. However, many of the largest pharmaceutical companies are spending more on marketing and administration than they are on research and development. The practice of direct-to-consumer (DTC) advertising for prescription drugs is concerning. In accordance with existing policy, ACP believes that DTC is in appropriate because it may undermine the patient-physician relationship and foster confusion. In absence of a ban on DTC advertising, ACP supports broad efforts by federal regulators to ensure that information about a drug’s effectiveness and safety, and about alternative treatments, is clearly disclosed to patients.

Although it does not represent a majority of marketing costs, DTC advertising has been shown to have a direct effect on patients asking questions about the drug with their physician. The FDA issued 3 surveys targeted at physicians and consumers that found an increase in awareness of DTC advertisements. Although these advertisements may motivate consumers to have conversations with their physicians about prescription drugs, 75% of physicians surveyed felt the DTC advertisements caused patients to think that a drug works better than it does, compared with 58% of consumers (79).

Companies that use basic research funded through the government as part of the development of a drug should be held to a high standard of pricing scrutiny. The National Institutes of Health (NIH) have historically made the largest government investments in basic research and play a key role in spurring new innovations and breakthroughs. In fiscal year 2015, the NIH invested nearly $30.3 billion in medical research (80). An analysis of publicly available data found that the NIH represented 28% of research sponsors (81). Between 1988 and 2005, federal research funding contributed to 45% of all drugs approved by the FDA and 65% of drugs that received priority review (82). Economic analyses show that NIH investments have a high return on investment in the public sector, with every dollar of NIH funding leading to an average of $2.13 in lifetime pharmaceutical sales (83). Without this assistance, the cost of discovery, research, and development on the part of pharmaceutical companies may be prohibitive. At a minimum, pharmaceutical manufacturing companies should disclose any grants, licensing agreements, or other investments by the federal government in the discovery, research, and development of the drug, in addition to material, production, and other research and development costs.

2. ACP supports eliminating the restriction of using quality-adjusted life-years (QALYs) in research funded by the Patient-Centered Outcomes Research Institute (PCORI).

More and more, physicians, patients, and other stakeholders are questioning the value of drugs relative to their price. Many of the new specialty drugs coming to the market represent real breakthroughs and benefits for patients, and the market should encourage future innovation. Those innovations do not mean that all other drugs should also be priced at the same level. Independent organizations, such as the Institute for Clinical and Economic Review and PCORI, already develop and evaluate clinical effectiveness data compared with other treatments.

Establishing an evidence base of clinical effectiveness data is the crux of transitioning to a health care system that pays for and rewards value. The PCORI is charged with funding comparative clinical effectiveness research (CER) and works to improve study methodology for CER (84). The PCORI has funded millions of dollars in head-to-head CER that can inform physicians and help patients understand all therapeutic options available as they relate to existing therapies and encourage informed decision-making and patient involvement. However, by statute, PCORI is prohibited from using QALYs as “a threshold to establish what type of health care is cost effective or recommended” (85).

A QALY is a metric of cost-effectiveness research that takes into account the quantity and quality of life associated with a treatment and assigns an index num-
ber to that treatment. Quality-adjusted life-years are commonly used in cost-utility studies to determine the cost of a treatment per QALY and compare medical interventions; however, they have been criticized for lacking sensitivity to patient preferences or goals (86). Being able to incorporate QALYs into cost-effectiveness studies will help patients and physicians compare the cost and health benefits of treatments and facilitate a better understanding of the value of different treatments. Part of a patient’s overall determination of value may include the cost-effectiveness of the treatment along with the benefits or risks of a drug.

Existing ACP policy supports CER to measure the effectiveness of health care services and clinical management strategies and that all health care payers, including Medicare and other government programs, should use both comparative effectiveness and cost-effectiveness in the evaluation of a clinical intervention. The ACP policy also notes that cost should never be the sole criterion for evaluating a clinical intervention (87). Not only do comparative effectiveness data inform value judgments they can also help physicians and patients understand all available options as they relate to existing therapies, encouraging informed decision-making and involvement by patients in their health care choices.

3. ACP supports the following approaches to address the rapidly increasing cost of medications:

a. Allow greater flexibility by Medicare and other publicly funded health programs to negotiate volume discounts on prescription drug prices and pursue prescription drug bulk purchasing agreements (7, 8);

b. Consider legislative or regulatory measures to develop a process to reimport certain drugs manufactured in the United States, provided that the safety of the source of the reimported drugs can be reasonably assured by regulators;

c. Establish policies or programs that may increase competition for brand-name and generic sole-source drugs.

Whereas employer and self-insured plans are able to negotiate and use their bargaining power to lower the price of drugs, Medicare and Medicaid programs are directed by statutes that can impede their ability to obtain the best prices. When the Medicare Part D program was created in 2003, the legislation prohibited Medicare from negotiating directly with pharmaceutical companies; however, the law attempted to encourage competition and create ongoing incentives for plan sponsors to keep premiums low.

Plan sponsors negotiate rebates from drug manufacturers through pharmacy benefit managers (PBMs), third-party entities that negotiate with manufacturers on the plan’s behalf. Pharmacy benefit managers have been highly effective in doing so: In 2008, the Office of the Inspector General found that Part D sponsors reported $6.5 billion in drug manufacturer rebates, or about $275 per beneficiary (88). A 2014 report by the Congressional Budget Office also found PBMs to be effective in driving down the cost of prescription drugs for beneficiaries, but suggested that the program could be strengthened by statutory changes enacted by Congress, such as requiring that Medicaid’s statutory rebates be expanded to low-income Part D beneficiaries (89).

Medicare Part D pays on average more than other federal health care programs: 73% more than Medicaid and 80% more than the Veterans Health Administration. The Veterans Health Administration operates as a closed system and provides care directly to veterans. It purchases drugs and other pharmaceuticals directly from manufacturers and has a national formulary that does not exist in Medicare or Medicaid (90).

An article published in Annals of Internal Medicine analyzing how effective the Part D drug plan has been since its inception found a 14% increase in prescription drug use (91). In 2013, Medicare Part D spent $103.7 billion on drugs (92). The cost of Medicare Part D is likely to increase as baby boomers enter the system, and both the costs per beneficiary and overall spending on Part D are expected to increase between 2014 and 2024 (93).

The ACP has a long-standing policy of advocating for the ability of Medicare Part D to negotiate drug prices and rebates directly with pharmaceutical manufacturers as a way to keep costs to the system down. Recent estimates show that allowing Medicare Part D to negotiate prices could save $15 to $16 billion per year (94). The ACP strongly reaffirms this position.

Medicaid faces unique challenges in paying for high-priced drugs without imposing unnecessary burdens on patients and physicians. In 2014, the National Association of Medicaid Directors sent a letter to House and Senate leaders outlining the increased cost to their programs and difficulties with Sovaldi, including a lack of meaningful supplemental rebates on the drug, the conflict between the large upfront cost of the drug and Medicaid funding cycles, the frequent transition of patients on and off public insurance programs, and the lack of clinical data on the use of Sovaldi in patients with comorbidities that may alter the effectiveness of the drug (95). The group proposed looking into various federal interventions, including enhancing federal match rates for “curative” specialty drugs, mandating additional rebates from a manufacturer, and allowing Medicaid programs to “utilize cost-effectiveness research to identify whether or not a particular drug will be included in the program’s formulary by granting Medicaid the flexibility to exclude products that are found to not be cost-effective” (95).

The Bipartisan Budget Act of 2015 included a provision that would increase rebates from drug manufac-
The issue of single-source drugs primarily pertains to market and may be generic or single-source drugs. A review of generic drug price increases by the Office of the Inspector General found that between 1991 and 2004, 35% of the top 200 generic drugs would be eligible for a rebate and the Medicaid program would have received a total of $966 million in additional rebates (96).

The ACP has previously supported reimportation of drugs manufactured in the United States and exported for sale in other countries if the FDA can ensure the safety of the suppliers of such drugs. Under current law, drugs may only be reimported to the manufacturer of the drug in the United States, not to individuals or pharmacies. Difficulties the FDA has noted about reimported drugs include their safety, efficacy, and concentration as well as the lack of sufficient resources to ensure their safety (97).

Drugs exported to foreign countries are subject to any pricing regulations that country’s government imposes (98). This may result in a lower price for a drug in the foreign country than in the United States. Quon and colleagues (99) examined the difference in brand-name drug pricing between Canadian Internet pharmacies and U.S. chain pharmacies and determined a potential savings of approximately 24% on brand-name medications. However, these savings can be variable, based on the fluctuating nature of drug pricing.

The ACP continues to support consideration of the reimportation of drugs, especially sole-source generic drugs, provided that their safety can be reasonably assured by regulators, as part of larger efforts to control the cost of prescription drugs. The ACP believes it should be a closed system, with participating pharmacies and suppliers required to meet FDA standards; have a tightly controlled and documented supply chain; not include controlled substances, biologics, or products that are infused or injected; and include adequate resources for inspections of facilities and enforcement of U.S. requirements, among others. The ACP acknowledges that drug importation is not a long-term solution to the high price of prescription medication, and there are various safety concerns about the reimportation of prescription drugs. Yet, we continue to support a careful evaluation of how existing federal importation standards may be used to encourage the reimportation of drugs to the United States, and how existing technology and recent legislative initiatives may assist in safeguarding the supply chain against counterfeiting or contamination.

It is important that policies addressing the increase in prescription drug prices cover not only new entrants to the market, but also drugs that have been on the market and may be generic or single-source drugs. The issue of single-source drugs primarily pertains to the generic market, or to drugs used to treat rare diseases with small populations. In the generic market, where drugs are reproduced inexpensively and there are relatively low profit margins, the elimination or consolidation of 1 or 2 manufacturers might have a huge effect on the production of generic drugs, potentially driving up the cost for payers and patients. In the case of Daraprim, the drug was inexpensive to produce and had a relatively low toxicity, underscoring why the dramatic price increase was so glaring.

Addressing the issue of sole-source drugs will require examination of the economic and noneconomic factors driving this trend. At the core of developing a competitive marketplace is the ability to identify and bring new therapies to market. Pharmaceutical companies spend billions of dollars each year on research that is abandoned or fails, but there are potential uses for these drugs that could be explored. The government is developing programs that would encourage companies to take drugs that have failed and find new uses for them.

The Accelerating Medicines Partnership (AMP), and the Discovering New Therapeutic Uses for Existing Molecules Initiative, also known as “New Therapeutic Uses,” are public-private partnerships among the U.S. government, pharmaceutical companies, and some nonprofit organizations to test new therapeutic uses for drugs and determine how to use the existing drug development pipeline in a more efficient way. The AMP was launched in February 2014 with projects in Alzheimer disease, type 2 diabetes, rheumatoid arthritis, and lupus. All partners in the AMP have agreed to make the data and analyses from the project publicly accessible to the biomedical community (100).

The New Therapeutic Uses program “helps re-engineer the research pipeline using an innovative strategy to identify new uses for assets that have undergone significant research and development by industry, including safety testing in humans” (101). One of the pilot projects found that a compound originally developed as a cancer therapy could be used to treat Alzheimer disease; because of the previous testing that had been done, investigators were able to initiate human testing within 3 months, whereas it could take as long as a decade to reach that stage under the traditional pathway (102). The AMP and New Therapeutic Uses initiatives are limited to certain disease groups currently, but may expand. The success of these programs could translate to a broader number of diseases or treatments, including diseases that have been ignored or therapies that have been allowed to be discontinued.

4. ACP opposes extending market or data exclusivity periods beyond the current exclusivities granted to small-molecule, generic, orphan, and biologic drugs. ACP supports robust oversight and enforcement of re-
strictions on product-hopping, evergreening, and pay-for-delay practices as a way to increase marketability and availability of competitor products.

Pharmaceutical companies claim that long exclusivity periods are needed to support innovation and allow a return on their investment and promote future innovation. Marketing exclusivity is granted by the FDA upon approval, during which a competitor, typically a generic drug, is prohibited from being marketed. Data exclusivity prohibits a competitor company from using the data collected by an originator company to gain approval of their drug.

In the case of biosimilars, the high cost of developing and conducting trials undermines the potential cost-savings to the manufacturer if they are required to collect new data. Congress approved a 12-year data exclusivity period for biologics under the Affordable Care Act, although some have noted that this amount of time is unnecessary (103). The President’s fiscal year 2016 budget called for a reduction in data exclusivity for biologics from 12 years to 7 years in addition to prohibiting product-hopping or evergreening; in these practices, companies prevent generic competition from entering the market by making small adjustments to a drug with no real therapeutic value that grant the company longer patent protection, or they remove the drug from the market, forcing patients to switch to a reformulated version of the same drug (104). The two proposals would save the federal government an estimated $16 billion over 10 years, including in Medicare and Medicaid (105).

Although providing for intellectual property protection is important to encourage innovation and introduction of medical advancements in the U.S. market, a 12-year period may not be wholly necessary. In 2009, the Federal Trade Commission (FTC) issued a report stating that a 12- to 14-year exclusivity period is unnecessary to promote innovation by biologic manufacturing companies, noting that “FOBs [follow-on biologics] are unlikely to introduce their products at price discounts beyond 10 to 30 percent. Moreover, FOBs are likely to have difficulty rapidly growing their market shares as compared to generic small-molecule drugs products. Indeed, projections are that branded biologic drugs are likely to maintain their first-mover advantages by retaining 70 to 90 percent of their market share years after FOB entry” (106).

Data exclusivity provisions were also a major issue when negotiating the Trans-Pacific Partnership (TPP). The TPP, a trade agreement between the United States and 11 other countries, establishes a 5-year mandatory minimum period of data protection and does not explicitly state a maximum (107). The agreement recognizes that the field of biologics is still generally new and included a provision that after 10 years, those party to the agreement or the commission may choose to re-view the provision and make changes to this time frame relative to the nature of the biologic and biosimilar markets (108). Although these provisions may be beneficial for U.S. patients by speeding the availability of lower-cost biosimilars to market, some public health organizations, including Doctors Without Borders, are concerned about the economic ramifications on TPP member countries that do not provide any data exclusivity for biologic drugs or provide for shorter terms (109). A survey of data exclusivity laws worldwide by the International Federation of Pharmaceutical Manufacturers & Associations found that of the countries with data exclusivity laws, the United States is the only one that provides 12-year data exclusivity for biologics (110). The TPP must be ratified by Congress in order to go into effect.

In 2014, the FDA issued draft guidance clarifying that the 12-year exclusivity does not apply to altered versions of already marketed biologics with a new “indications, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength” (111). This may combat the product-hopping that has become increasingly common in the traditional drug market. In 2013, the FTC filed an amicus brief opposing product-hopping, noting, “The potential for anticompetitive product redesign is particularly acute in the pharmaceutical industry” (112). Preventing lower-cost generic or biosimilar competitor drugs from entering the market only seeks to delay reductions in revenue for the parent company of a brand-name drug and may be detrimental to patients if the changes do not provide any measurable or meaningful benefit.

There are also concerns that pay-for-delay practices are keeping lower cost drugs out of the market. Pay-for-delay, also known as “reverse payment settlement,” is a patent settlement strategy in which a patent holder pays a generic manufacturer to keep a potential generic drug off the market for a certain period. The number of pay-for-delay agreements increased from 3 in 2005 to 19 in 2009, after court decisions upheld the legality of such agreements, which prohibit generic drugs from entering the market on average nearly 17 months longer than agreements without compensation (113). In 2013, the Supreme Court ruled that although pay-for-delay agreements are not presumptively illegal, the FTC cannot be prevented from initiating legal action in regard to such agreements (114).

It is estimated that pay-for-delay agreements will cost $35 billion between 2010 and 2020. The Congressional Budget Office estimated that enacting legislation restricting pay-for-delay settlements would cut the federal deficit by $4.8 billion over 10 years (115). Proponents of pay-for-delay agreements assert that they cut short potentially lengthy and costly legal proceedings and may guarantee the entry of generics to the market (116).
It is important that pay-for-delay settlements are not exploited as a tool to keep the prices of certain drugs artificially high when suitable generic substitutes are prepared to come to market. Robust oversight of pay-for-delay agreements by the appropriate federal agencies is a cornerstone to assessing whether these agreements are valid or potentially in violation of antitrust statutes.

5. ACP supports research into novel approaches that would further value-based decision making and encourages research into policies that would tie price to innovations and clinical value. Consider the following options:

a. Value frameworks;
b. Bundled payments;
c. Indication-specific pricing;
d. Evidence-based benefit designs that include explicit consideration of the pricing, cost, value, and comparative effectiveness of prescription medications included in a health plan’s benefit package.

With the great attention being paid to the price of drugs, determining how to assess the value of a drug, which patients may benefit the most from a certain drug, and the economic value of a drug has charged the conversation. Novel pilot programs have been launched, including the American Society of Clinical Oncology’s (ASCO’s) conceptual value framework and the Memorial Sloan Kettering Drug Abacus. The ASCO framework attempts to address relative value of new cancer therapies compared with established treatments factors, including cost, benefit, and toxicity. The Drug Abacus is a patient-led evaluation tool to measure the value of 54 new cancer drugs approved since 2001. Understanding that value means different things to different people, the Abacus takes into consideration measures of efficacy, toxicity, novelty, research and development, disease rarity, population health burden, and other factors.

In addition to these 2 initiatives, the American College of Cardiology and the American Heart Association, the Institute for Clinical and Economic Review, and the National Comprehensive Cancer Network have introduced programs to help patients understand the value of new therapies. An overview of these programs by Neumann and Cohen (118) notes that they will require additional refinement.

In 2015, the Center for Medicare & Medicaid Innovation (CMMI) announced the Oncology Care Model, a payment and service delivery model set to launch in 2016. Under this bundled payment model, oncologists who spend less than a benchmark figure on Medicare beneficiaries undergoing chemotherapy over a 6-month period will receive incentives; participating clinicians will also receive $160 per month per beneficiary (119). The approach may encourage the use of older, lower-priced drugs before newer, more expensive treatments with similar benefit and in turn affect drug utilization. This shift to paying for value as opposed to the number of services provided mirrors other similar shifts toward a evidence- and value-based system of health care. As these approaches are piloted and implemented, it is important to address such issues as patient preference and variability. Physicians should be included as part of the development and evaluation of these frameworks and programs to identify potential challenges and reflect the needs of the patient populations they treat.

The variability of disease and how patients react to medications makes indication-specific pricing potentially beneficial for such diseases as cancer. A study examining the improvement in survival for several cancer drugs found great variation (120). Paclitaxel holds indications for metastatic breast cancer, non-small-cell lung cancer, and pancreatic cancer. Data show that the drug improved median survival in patients with breast cancer by 0.18 year, but only 0.08 year in those with non-small-lung cancer, with similar treatment costs for each indication (120). Express Scripts has announced that they plan to work with pharmaceutical companies and develop an indication-based formulary for certain cancer drugs in 2016 (121).

As large parts of the greater health care system are embracing this value-based concept, it has been underrepresented in benefit design. With the rising prices of drugs, some are turning to methods of incorporating value into benefit frameworks. Analysts have advocated for hybrid models of novel and traditional approaches to benefit design that may bridge the divide between providing patients with the drugs they need with the high cost of these drugs, such as an integration of the medical and pharmacy benefit to keep all specialty drugs under 1 benefit (122). Payers have been hesitant to be assertive in managing spending on specialty medications because of the sensitivities involved; many of these drugs are key to living a normal, healthy life, and payers may face backlash if they institute aggressive payment strategies (123).

Innovative benefit designs can include incentives that vary by service, type of patient condition, or income (124). Evidence-based benefit design has also been advocated as a way to reduce health care costs and would be in line with the movement toward evidence-based medicine. Policies that encourage value-based benefit design can help consumers make educated choices about prescription drugs and keep costs low. Value-based benefit design uses financial incentives to increase health care quality and decrease cost by reducing barriers to maintain and improve health (125). The state of Washington has saved $20 to $30 million per year since instituting an evidence-based prescription drug program across state-administered health programs (31). Least-costly-
alternative standards may also help in controlling costs by setting a single price for a group of similar drugs and requiring consumers and patients choosing the higher-cost drug to pay the difference out of pocket (31). Another analysis measured the effect of a value-based benefit design in diabetes medications. The study found that a reduction in the copayment for diabetes medications resulted in a 30% reduction in non-adherent patients (126).

With the advent of personalized medicine and treatments in a variety of conditions from common medical conditions to chronic disease, a one-size-fits-all approach to benefit design may not be the best to address high health care costs.

6. ACP believes payers that use tiered or restrictive formularies must ensure that patient cost-sharing for specialty drugs are not set at a level that imposes a substantial economic barrier to enrollees obtaining needed medications, especially for enrollees with lower incomes. Health plans should operate in a way consistent with ACP policy on formularies and pharmacy benefit management.

Drug formularies divide prescription drugs into 4 or 5 tiers with varying levels of fixed prices (copayments) for all drugs in each tier, with the exception of the highest tier. The highest tier, typically the specialty tier, is subject to either the highest copayment or coinsurance in which the patient pays a percentage of the cost of the treatment. There has been a shift toward prescription drug plans with coinsurance in the top 2 tiers, typically the specialty tier and a nonpreferred brand tier that has no restrictions on which drugs can be placed on the tier. This can lead to higher coinsurance rates than that of the specialty tier (127). Usually, only the specialty tier has been subject to cost-sharing; all other tiers have copayments. A lawsuit recently filed against four insurers in Florida alleged discrimination against patients with HIV/AIDS for placing all HIV/AIDS drugs, including generics, in the specialty tier, which requires high levels of patient cost-sharing (128).

When health plans are faced with rising costs associated with high-priced drugs, they often look to increased cost-sharing, utilization management, or tiered formularies that place all drugs of a certain class into the highest tier, putting patients at risk for not being able to access or afford the medications they need or adhere to drug regimens properly. It is notable that an analysis by Avalere Health showed, for the first time, that all Medicare Part D prescription drug plans will use a specialty tier (128). An analysis of coverage for specialty rheumatoid arthritis drugs in Medicare Part D found that between 81% and 100% of patients were required to pay a coinsurance percentage—averaging about 30%, or between $2712 and $2774—before reaching the catastrophic phase of coverage. More than 1 in 4 Medicare beneficiaries use these disease-modifying antirheumatic drugs, and spending on them has risen sharply for Medicare Part D (129).

Increased coinsurance for all drugs in a certain class is seen with other patient populations with high drug costs, such as cancer. A 2010 study found that oncology patients taking prescription medications with an out-of-pocket cost higher than $200 were at least 3 times more likely to choose not to fill their prescriptions than those with out-of-pocket costs of $100 or less (130). Medication adherence—particularly for persons taking specialty medications, who also tend to have other health issues—is important to reducing overall health care costs. If plans want to realize these reduced costs, they need to ensure that their patients are able to complete their medication cycles as prescribed (131).

The ACP acknowledges that there are limited ways in which pharmacy benefit managers and health plans can negotiate costs, including the use of formulary inclusion or exclusion of certain medications. However, in the case of some drugs for which there are no other treatment alternatives, this negotiating power is diminished, although the therapeutic benefit of the drug is not. The Affordable Care Act instituted out-of-pocket maximums for insured and self-insured plans starting in January 2014. The out-of-pocket maximums ($6600 for an individual and $13 200 for a family plan) may alleviate some cost-sharing issues, but they may still be burdensome and prohibitive for some individuals and families. Rebates, coupons, and copayment assistance programs may also help reduce out-of-pocket costs but should not be considered a long-term solution.

The ACP has a comprehensive policy on formulary benefit design, including:

ACP opposes any formulary that may operate to the detriment of patient care, such as those developed primarily to control costs.

Decisions about which drugs are chosen for formulary inclusion should be based on the drug’s effectiveness, safety, and ease of administration rather than solely based on cost.

ACP recommends that pharmacy and therapeutic committees be representative of, and have the support of, the medical staffs that will utilize the formulary.

The full text of ACP’s formulary and pharmacy benefit management policies can be found in Appendix 2 (available at www.annals.org).

It has been suggested that in some cases, health plans place certain drugs in the higher classes of their formulary to deter patients from choosing those health plans and ending up with a sicker pool of patients, or to draw prospective consumers to their plan with low premiums only for those consumers to find that the drug formulary does not cover their drugs or places their drugs in higher-cost tiers. A survey showed that adults are willing to pay higher insurance premiums for better
coverage of specialty drugs; this would suggest that people assume their insurance plan will cover these drugs with less cost-sharing (132).

Not only do increased out-of-pocket costs for patients result in poorer medication adherence, but research also shows that increasing patients’ share of out-of-pocket costs is ineffective for controlling costs. A study found that for each 10% increase in cost-sharing, prescription drug spending decreases by 2% to 6%, depending on the drug and the patient’s condition (133). Patient cost-sharing incentives that work for traditional drugs typically only work for a small class of specialty drugs for which close substitutes exist; when there are no other alternatives and a specialty drug is placed in the highest formulary tier, patients have no other option but to pay the high cost for the drug (126). In this case, increases in cost-sharing would probably result in smaller decreases in drug spending. Traditional tiered programs are also less effective for specialty drugs, because manufacturer coupon programs pay the patient’s share of the cost of the medication for a certain period, overcoming the copayment incentive to use cheaper drugs (123).

7. ACP believes that biosimilar drug policy should aim to limit patient confusion between originator and biosimilar products and ensure safe use of the biosimilar product in order to promote the integration of biosimilar use into clinical practice.

Now that the first biosimilar has been approved for marketing in the United States, unresolved policy issues need to be addressed to ensure safe use of approved biosimilars and maximum utilization of biosimilars by patients and physicians. The ACP encourages the use of lower-cost alternatives when available, and recently released clinical practice guidelines promoting the use of generic medications when appropriate. The guidelines acknowledged that perception regarding safety may affect the prescribing practices of the physician (134). The relatively new nature of biosimilar introduction into the U.S. market represents an opportunity for physicians to understand the relative safety and efficacy of biosimilars and establish reasoned prescribing practices for biosimilars.

One of main issues has to do with the substitution of biosimilars for originator biologic products. Not all biosimilars will be considered interchangeable, and the indications for a biosimilar may differ from those of an originator product. The only approved biosimilar, Zarxio (filgrastim-sndz), a bone marrow stimulant, was granted approval for all indications of the originator product Neupogen (filgrastim), although only 1 indication was studied before its approval.

There are conflicting issues regarding the naming and labeling of biosimilars. The BPCA did not contain any provisions on the naming of biosimilar drugs, and some were concerned that too-similar naming may cause confusion, undermine the use of the reference or biosimilar product, and create issues between parent companies of reference products and the biosimilar manufacturers. In August 2015, the FDA issued the draft guidance “Nonproprietary Naming of Biological Products; Draft Guidance for Industry,” which proposes that biosimilars use the nonproprietary substance name with an FDA-designated suffix (135). This hybrid approach aims to reduce medication errors and increase patient safety by preventing inadvertent substitutions on noninterchangeable products (136).

The issues of substitution and naming pose challenges to establishing a strong base for biosimilar use. When substituting a generic drug for a brand-name drug, the pharmacist and physician can be confident in the chemical composition of the drug; to gain FDA approval, the generic substitute must be chemically identical to the brand-name product. However, the sensitivity of biosimilars to minor differences in their composition, manufacturing, and handling can result in variability compared with the originator product, and patients cannot assume that they will have the same reaction to the biosimilar as to the originator product. Thus, it is imperative that policies are in place to ensure physicians are consulted and notified of any biosimilar substitution. Pharmaceutical substitution laws are passed on a state-by-state basis (137). Currently, only 16 states have passed biosimilar substitution laws, and 14 require pharmacies to notify the physician of substitution. Ten states require patient notification of pharmacist substitution (138).

Conclusion

Through development and evolution of prescription drugs, tremendous progress has been made in the treatment of disease. However, these therapies are only as effective as a patient’s ability to access needed medications. Much has been said about the idea of getting the right drug to the right patient for the right indication at the right price. This philosophy highlights the need for comprehensive efforts to implement meaningful policies that link price, value, innovation, and access. We must start by identifying why drugs are priced the way they are, supporting extensive research efforts into innovative and value-based systems, and improving access to getting prescription drugs to the market and into the hands of the patients who need them most.

APPENDIX 2: ACP POLICY ON FORMULARIES AND PHARMACY BENEFIT MANAGEMENT

Formularies

1. ACP opposes any formulary that may operate to the detriment of patient care, such as those developed primarily to control costs.
2. Decisions about which drugs are chosen for formulary inclusion should be based upon the drug’s effectiveness, safety, and ease of administration rather than solely based on cost.

3. Evaluation of physician prescribing patterns (i.e., drug utilization review) should give priority to the effectiveness, and safety and ease of administration of the drugs prescribed rather than solely based on costs.

4. ACP recommends that financial incentive arrangements should be linked to cost-effective practices rather than formulary compliance.

5. ACP opposes financial arrangements that place the physician’s financial interest in conflict with his or her patient’s well-being.

6. ACP recommends that formularies should be constructed so that physicians have the option of prescribing drugs that are not on the formulary (based on objective data to support a justifiable, medically indicated cause) without cumbersome prior authorization requirements.

7. ACP recommends that a patient information program be instituted by managed care plans to make patients aware of formulary utilization and any associated costs such as co-pays.

8. Patient formulary education should include how the formulary functions, and a discussion of how co-payment and/or deductible requirements may affect their pharmacy benefit.

9. ACP supports prompt prior notification to patients and physicians when formularies are changed or discontinued.

10. ACP recommends such notification be given within a specified time period, not fewer than ninety (90) days prior to change implementation.

11. Formularies should be approved on a regional basis by a professionally qualified body which includes practicing physicians using that formulary.

12. ACP recommends that Pharmacy &Therapeutic (P&T) Committees be representative of, and have the support of, the medical staffs that will utilize the formulary.

13. ACP supports industry moves to develop technology to make formularies more accessible and easier to utilize. ACP recommends physician input in designing, and pre-testing of, these technologies.

14. ACP supports continued government and industry studies of the impact of formularies on patient care. ACP recommends that CMS and states develop annual report-cards on the impact of formularies on beneficiaries enrolled in Medicare managed care plans.

15. Prescribing patterns should be influenced primarily through educating physicians on safety and efficacy. Cost should be a determinant only when safety and efficacy are equal among specific drug choices.

**Pharmacy Benefit Management**

1. ACP supports government regulation and industry self-regulation of Pharmacy Benefit Managers (PBMs). ACP particularly supports close government oversight of mergers between PBMs and pharmaceutical manufacturers.

2. ACP supports the disclosure to patients, physicians, and insurers of the financial relationships between PBM companies, pharmacists, and pharmaceutical manufacturers.

3. ACP supports requiring that PBM organizations’ requests to alter medication regimes should occur only when such requests are based on objective data supported by peer reviewed medical literature and which undergo review and approval of associated managed care plans’/MBHOs’ P & T Committees.

4. ACP supports requiring that, with a patient’s consent, PBM organizations be required to provide treating physicians with all available information about the patient’s medication history. (BoR 00, reaffirmed BoR 11)

**Web-Only References**


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