Strategies that delay or prevent the timely availability of affordable generic drugs in the United States

Gregory H. Jones,[1] Michael A. Carrier,[2] Richard T. Silver,[3] and Hagop Kantarjian[1,4]

[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [2]Rutgers Law School, Camden, NJ; [3]Weill Cornell Medical Center, New York, NY; and [4]Baker Institute, Rice University, Houston, TX

High cancer drug prices are influenced by the availability of generic cancer drugs in a timely manner. Several strategies have been used to delay the availability of affordable generic drugs into the United States and world markets. These include reverse payment or pay-for-delay patent settlements, authorized generics, product hopping, lobbying against cross-border drug importation, buying out the competition, and others. In this forum, we detail these strategies and how they can be prevented. (*Blood*. 2016;127(11):1398-1402)

Introduction

Health care costs, specifically prescription drug prices, have created a significant barrier to the economic well-being of patients in the United States and around the world. With 75% of Americans >50 years old taking prescription medication in 2013, the United States spent nearly 40% more per capita on pharmaceuticals than the next closest country, Canada.[1] Approximately 1 in 5 Americans do not fill prescriptions because of prohibitive cost[2]; <1 in 10 Canadians, Germans, and Australians experience this problem.[3] As we discuss in this article, brand-name drug companies have engaged in strategies that have delayed or prevented the availability of generic drugs, thereby increasing the price paid by patients, governments, and insurance companies.

Generic drugs: importance and issues

The introduction of generic drugs saved the US health system nearly $1.5 trillion between 2004 and 2013.[4] The timely availability of generic cancer drugs, for example, increases affordability for many patients with cancer. Many drugs are priced at monopoly levels and are protected by patents that last 20 years from the date the application is filed with the US Patent and Trademark Office.[5]

In 1984, the US Congress passed the Drug Price Competition and Patent Term Restoration Act (typically referred to as the Hatch-Waxman Act).[6,7] The act outlines the process for generic manufacturers to file an abbreviated new drug application for approval of a generic drug by the US Food and Drug Administration (FDA). Congress encouraged competition and lower prices by allowing generic manufacturers to rely on the safety and effectiveness studies of brand companies and to experiment on drugs during the patent term. Congress also encouraged patent challenges by giving the first company to file an abbreviated new drug application (claiming that the patent on a particular drug is invalid or not infringed) 180 days of exclusive rights to market the drug as the generic alternative to the branded drug.[7] At the same time, the act benefited brand firms by providing for patent term extensions, periods of market exclusivity not based on patents (eg, for drugs with new active ingredients), and an automatic 30-month stay of FDA approval (similar to a preliminary injunction) for patent holders that sue generics.[7]

Patent challenges are important given the questionable validity of many patents at the center of pay-for-delay settlements, with 1 study finding that (1) 89% of patents in settled litigation are "secondary patents" covering ancillary aspects of drug innovation (such as formulation or composition) rather than the active ingredient, and (2) the brand firm is far less likely to win on these secondary patents (32%) than it is on active ingredient patents (92%).[8] In enacting the Hatch-Waxman Act, Congress sought to ensure the provision of "low-cost, generic drugs for millions of Americans" and stated that generic competition would "do more to contain the cost of elderly care than perhaps anything else this Congress has passed."[9] Unfortunately, the act has been exploited by brand and generic companies that mutually benefit from settlement, as the brand company can pay the generic company to extend its patent monopoly, while the generic company receives guaranteed compensation.

Because of the large revenues provided by sales of brand-name drugs, and to fulfill their fiduciary duty toward investors, brand-name drug companies have developed, over the years, multiple strategies to extend the lifetime of patented drugs and to delay the availability of generics. These include reverse payment or "pay-for-delay" patent settlements, "authorized generics" (AGs), "product hopping," buying out the competition, and others. What do these strategies mean and how do they distort and delay the availability of generics?

Reverse payment or pay-for-delay patent settlements

In "pay-for-delay" settlements, patent holders agree to pay potential generic competitors that challenge the patent of the brand company to delay entry into the market. "Reverse payment" refers to the fact that the patent company pays the generic company, with the payment moving in the opposite direction than what would be ordinarily expected in patent

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litigation (with a potential infringer typically paying the patent holder to enter the market). In the past decade, it has become increasingly common for pharmaceutical companies to pay would-be competitors to delay entering the market, thereby securing a longer period of exclusivity. In return for lucrative payments that may even exceed the profits the generic competitor would have earned if it had entered the market, the generic firm agrees to delay entry and not contest the patent (eg, claiming that it is not valid or not infringed by the generic drug). These settlements have been criticized as anticompetitive and contrary to the public interest.[7-24]

A hypothetical example to understand this transaction is as follows: suppose the annual sales of the brand-name drug in the United States are $1 billion, and the generic company wishes to enter the market and sell the generic drug at 10% of the patented drug price (annual sales $100 million). The brand-name company could pay the generic company $100 million not to enter the market while still generating $1 billion in revenues over the next year. Both companies profit in revenues, but those revenues are lost to our health care system, force higher patient out-of-pocket expenses, and push the patented drug out of reach for many patients who cannot afford it and thus could die of cancer progression.

The Federal Trade Commission (FTC) estimates that pay-for-delay settlements cost taxpayers, insurance companies, and consumers ~$3.5 billion per year.[11] In the landmark case of *FTC v. Actavis*, the Supreme Court concluded that pay-for-delay settlements "tend to have significant adverse effects on competition" and could violate the antitrust laws.[15] The California Supreme Court found that a nearly $400 million payment to block access to an affordable version of the antibiotic ciprofloxacin (which prevented access to a generic version for nearly 7 years) similarly could violate the antitrust laws.[16]

Numerous examples have shown how pay-for-delay settlements have increased costs to consumers by billions of dollars. The brand company Cephalon reached settlements with 4 generic manufacturers to delay the release of generic versions of Provigil until 2012. For a collective compensation of >$300 million, Cephalon entered into settlements that, as its CEO conceded, provided "six more years of patent protection," which was "$4 billion in sales that no one expected."[17,18] In 2015, the FTC's 7-year lawsuit against Cephalon (now Teva) was settled for $1.2 billion, the largest settlement ever secured by the FTC.[19] In another recent case, in an agreement with the generic company Sun Pharmaceuticals, Novartis delayed the availability of generic imatinib that would compete with its leukemia drug Gleevec for 7 months beyond the end of the term of the compound patent, from July 2015 until February 2016. Because the price of imatinib increased from $26 000/y in 2001 to $132 000/y in 2014, a 6-month delay is equivalent to a revenue stream from patent extension of at least 2 years at the launch price (the initial price in 2001).[20] The danger of this strategy derives from the mutual financial benefit to both brand and generic producers at the expense of patients and our health care system.[21] This issue is still pressing today. Even though the Supreme Court in *Actavis* found that the settlements could violate the antitrust laws, some courts since then have excessively constricted antitrust liability by holding that only payments in the form of cash present antitrust issues[22] or that plaintiffs must show extraordinary levels of detail in their complaints.[23,24]

AGs

AGs are drugs produced by brand pharmaceutical companies or in collaboration with other companies and marketed under a different label, at "generic prices." In this scenario, the patent companies either produce their own AGs or provide intellectual property to generic companies to allow them to enter the market earlier than others.[25,26] As interpreted by the courts, the Hatch-Waxman Act allows brand companies to produce their own AG versions of a drug during the first-filing generic's 180-day exclusivity period.[27] The FTC estimates that the introduction of AG versions during the 180-day period results in a 4% to 8% short-term reduction in consumer retail prices and a 14% to 17% reduction in wholesale prices.[25] Although this short-term reduction in price is welcome, the threat of AG creation can serve as a coercive tool because the introduction of AG competition reduces first-filer revenues by (on average) 40% to 52% during the exclusivity period, and by 53% to 62% in the 30 months following the period.[26] Although the ultimate net effect of the introduction of AGs on consumer welfare is not entirely clear, what is clear is that pay-for-delay settlements today often include payment in the form of brand companies' promises not to introduce AGs that would compete with true generics. Settlements with no-AG clauses have involved some of the most popular drugs, including the attention-deficit-hyperactivity-disorder drug Adderall XR, the antidepressant Effexor XR, the acid-reflux drug Nexium, and the clot-preventing Plavix.[28] Brand companies' promises not to introduce AGs are extremely valuable to the generics. In fact, these settlements can be viewed as a form of market division, with the generic company agreeing to delay entering the market (prolonging the brand's monopoly) and the brand company agreeing not to introduce an AG during the first-filing generic's exclusivity period, creating a generic monopoly.[29]

Product hopping

Product hopping, also called "forced switching" or "evergreening," involves a brand-name company switching the market for a drug, prior to its patent expiration date, to a reformulated version that has a later-expiring patent, but which offers little or no therapeutic advantages. The newer version, for example, could have a slightly different tablet or capsule dose or a slow-release formulation (given once a day rather than twice daily). In conjunction with this change, the company spends heavily to convince doctors and/or patients to switch to the new drug and may even withdraw the (often profitable) older drug from the market before its patent expiration date. When the generic version of the drug becomes available, pharmacists cannot substitute it for the new (branded) version because state laws allow drug substitution only if the dosage strength and other characteristics remain the same.[30-38]

For instance, over more than a decade, Abbott Laboratories produced several bioequivalent formations of fenofibrate, already in generic form. Through a complex switching approach involving the sequential launch of branded reformulations (not superior to the first-generation product) and patent litigations to delay the approval of the generics, the maneuvers were estimated to cost the US health care system ~$700 million a year.[32] Historically, when patients are forced to switch from a drug with a near-to-expire patent to the new formulation, only 10% to 20% go back to the generic once it becomes available.[33]

As another example of product hopping, Actavis attempted to remove an older version of Namenda, a $1.5-billion drug used to treat Alzheimer's disease, with a "new and improved" version (taken once daily instead of twice daily) that was protected by a patent until 2029. This product hopping scheme would have led to consumers "pay[ing] almost $300 million more," third-party payors "pay[ing] almost $1.4 billion more," and Medicare and its beneficiaries paying "a minimum of $6 billion over the next ten years." Although the New York Attorney General obtained an injunction that prevented Actavis from removing the older version from market, other courts have allowed product hopping schemes to continue. For example, 1 court ignored the crucial

role played by state automatic substitution laws, asserting that the generic's "[s]pending some of its revenue on advertising would have lessened [its] now-increased profits" but complaining that the generic "chose not to do so," which led it to be "a 'victim' of its own business strategy, not Defendants' 'predatory' conduct."[34-39]

Combining several forms of conduct, drug companies sometimes have used product hopping together with settlements. In particular, by delaying generic entry, a settlement can give the brand firm the opportunity to switch the market to the new product. By the time the generic enters, years later, the market will have already been switched, with the generic unable to take advantage of automatic substitution under state laws. One example is the Cephalon case discussed previously. Cephalon used the period of delayed generic entry to switch the market from the old sleep-disorder drug Provigil (increasing the price 74%) to the new drug Nuvigil (heavily promoting the drug).[31]

Lobbying against cross-border drug importation

Several studies have shown that the price of identical brand-name drugs around the world can be as low as 20% to 50% of the price in the United States.[40] In addition to the different prices, because of the different strategies and lobbying pressures in the United States, certain generic drugs can become available outside the United States at significantly earlier times than inside the country. For example, in 2014, the brand drug imatinib was priced at $132 000 for 1 year of treatment in the United States. At the same time, its price in Canada was only $38 000 per year of therapy. Today, there are >18 generic versions of imatinib available worldwide, including 3 in Canada since 2013. The price of the generic imatinib in Ontario (which cannot exceed >25% of the brand-name drug price by law) is only $8800.[40]

To obtain affordable medications, some patients will seek to import drugs from other countries for personal use. There is a strong and clear indication that international online pharmacies are equally as safe as domestic ones, and that the importation of drugs is safe.[41,42] Nonetheless, Section 708 of the FDA Safety and Innovation Act facilitates the destruction of legal, imported drugs for individual use that are valued at $2500 or less "in the interest of public safety." This discourages patients from seeking the same drugs in cheaper markets. Allowing cross-border importation of drugs would improve market forces and increase pressure for more affordable drug prices. Such legislation has been proposed by Senators Amy Klobuchar and John McCain.[42] This would be a clear advantage when a drug company like Turing Pharmaceuticals (discussed later) increases the price of pyrimethamine in the United States overnight from $13.50 to $750, while the same drug (under a different company) remains at the same old price in Canada.

Lobbying, advertising, or buying out the competition

Even past the 20-year expiration of patents, companies can still rely on lobbying, branding, and aggressive advertising to produce profit. From 1998 to 2013, pharmaceutical lobbying interests were 42% larger than the second highest-paying industry (health insurance). The $2.7 billion effort made up more than half of all health care lobbying expenditures and almost equaled the combined contributions of Big Oil ($1.3 billion) and the defense industry ($1.5 billion).[38] An even greater financial commitment is made to advertising. The United States and New Zealand are the only 2 countries that allow prescription medications to be advertised on television. In 2012, nearly $3.5 billion was invested in the United States in pharmaceutical marketing.[38] For every dollar spent on research, an average of >$2 (sometimes up to $19) is spent on marketing.[38] Nine out of 10 large pharmaceutical companies spend more on marketing than on research and development.[43]

Finally, a recent trend in strategies that suppress access to generics involves drug companies' simply buying out competitor companies and increasing the prices of drugs several fold overnight.[44] Nothing changes in regard to the drug structure, properties, source of raw materials, laboratory work, human testing, or more expensive infrastructures. The only change is the owner of the drug. A recent example is Turing Pharmaceuticals acquiring pyrimethamine (Daraprim, a 62-year-old drug used to treat toxoplasmosis) as the sole US manufacturer, and raising the price of a tablet from $13.50 to $750.[45] A spokesperson for Valeant, a Canadian company notorious for this approach (it increased drug prices by at least 20% >120 times since 2011), explains it as follows: "Our duty to our shareholders is to maximize the value of the drugs."[44] But "value" here means what the market can bear, not the real value to patients. Valeant's approach of buying generic drugs and raising prices excessively has been recently highlighted as an extreme but increasing trend in drug companies' strategies.[46] Of note, in 2014, Valeant spent only 3% of sales on research and development but paid its top 5 executives 1.5% of sales.[47] Such marketing strategies unfortunately appear to have become a general trend: abandoning the dual mission of social corporate responsibility to both help patients and make profit in favor of a mission to maximize profits at any cost. We have moved far past the famous statement of George Merck, past president of Merck Company, that "medicine is for the people" and "not for the profits."[48]

Strategies to delay the availability of affordable generics is a global problem

The issues discussed in this forum are not limited to the United States.

The European Commission (EC or commission) has examined settlements. It published a pharmaceutical sector inquiry in 2009 that concentrated on "practices which companies may use to block or delay generic competition as well as to block or delay the development of competing [brand] products."[49] The report found that 22% of settlements from 2000 to 2008 involved payments from the brand to the generic firm and a restriction on generic entry.[49] Since that time, the inquiry has been followed up by 5 monitoring exercises that generally found a reduction in pay-for-delay settlements. The most recent, published in 2014, found a reduction of settlements involving payment for delayed entry to 8%.[50]

In addition to the monitoring exercises, the EC has also targeted individual companies. In June 2013, the commission announced that it would fine Lundbeck (roughly) €94 million and generic firms €52 million for violating Article 101 of the Treaty on the Functioning of the European Union for agreeing "to delay the market entry of cheaper generic versions of Lundbeck's branded citalopram, a blockbuster antidepressant."[51] In January 2015, the EC published a nonconfidential version of this decision in which it made clear that the agreements constituted an "infringement by object" because they "were by their very nature injurious to the proper functioning of normal competition."[52] The commission also found that the agreements prohibited entry and "contained a transfer of value"; that they "did not resolve any patent dispute" but "postponed the issue raised by potential generic market entry"; and that the agreements "obtained results for Lundbeck that [it] could not have achieved by enforcing its process patents before the national courts."[52]

In a second case, in July 2014, the EC fined Servier and generic rivals €427 million for settlements that delayed generic entry of perindopril, a blockbuster blood pressure medicine.[53] The EC stated that "between 2005 and 2007, virtually each time a generic company came close to entering the market, Servier and the company in question settled the challenge."[53] In July 2015, the EC released a nonconfidential version of the decision and concluded that "Servier sought protection against generic entry by concluding five patent settlement agreements with the (most) advanced generic contenders" that "consisted of significant payments, or other inducements, to the generic companies, and the obligation for them not to challenge Servier's patents and not to enter the market (directly or indirectly) for a number of years."[54]

Other countries also are starting to consider these settlement issues. In September 2014, the Canadian Competition Bureau released a paper entitled "Patent Litigation Settlement Agreements: A Canadian Perspective."[55] In it, the bureau explained the difference between the regulatory regimes in Canada and the United States, such as "(1) the lack of a notification system in Canada, (2) the absence in Canada of a 180-day period of exclusivity for the first generic to challenge a brand's patent, (3) particularities of [Canada's Patented Medicine Notice of Compliance Regulations (PM(NOC))] prohibition proceedings, and (4) the potential for generics to receive damages from brands in Canada."[55] The bureau concluded that these differences do not "diminish the role of competition analysis in reviewing potentially anticompetitive settlements."[55] It stated that it would consider applying both civil and (for a more limited category of behavior) criminal liability to reverse-payment settlements.[55] Similar procedures examining reverse-payment settlements and imposing penalties were reported in Korea and other countries.[56,57]

Europe has also considered the issues related to product hopping. In 2010, the European General Court upheld an EC finding that AstraZeneca had abused its dominant position by blocking and delaying market access to the generic version of the ulcer medication Losec. The Court found that AstraZeneca gave misleading information to patent offices so it could get a supplemental protection certificate, which provided an additional period of patent protection.[58] The court found that AstraZeneca deregistered capsule marketing authorizations to "delay and make more difficult" the marketing of generics.[58]

A second example of product hopping is provided by the case involving Gaviscon, a drug used to treat heartburn and acid reflux. In 2011, the UK Office of Fair Trading found that Reckitt Benckiser abused a dominant position. Reckitt Benckiser's objective was to "delay for as long as possible the introduction of a generic name" and to "replace/cannibalise all current . . . sales" with "the new patent protected variant."[59] The UK office concluded that the company withdrawal of a profitable medicine was not "competition on the merits" but "tended to restrict competition or was capable of having that effect."[59]

In short, issues related to the strategies to delay the entry of affordable generics are a global, not a regional problem.

Conclusions

Profit at the expense of long-term utility to society seems to be a theme consistent with each of the brand drug company strategies aimed at delaying, preventing, and suppressing the timely availability of affordable generic drugs in the United States. The pharmaceutical industry takes advantage of the complexity presented by the intersection of the patent laws, the antitrust laws, the Hatch-Waxman Act, and state drug product selection laws. The trend of high drug prices has recently "infected" generic companies that now appear to raise prices on old generic drugs to exorbitant levels without any of the old justifications (cost of research, cost benefit), simply because they can, in a drug market that seems to approach monopolistic levels. Patients, physicians, and health care experts should be vigilant and cognizant of these prevailing strategies that delay the availability of affordable generic drugs and should advocate for measures to lower drug prices (discussed elsewhere).[40,60,61]

Corrective measures may be different in the United States and the rest of the world depending on existing laws. Some solutions in the United States include: (1) allowing Medicare to negotiate drug prices; (2) developing mechanisms to propose a "just" or fair price for drugs depending on the treatment "value"; (3) monitoring and penalizing pay-for-delay strategies that are anticompetitive (discussed earlier); (4) allowing transportation of drugs across the borders for personal use; (5) monitoring potential buyouts by generic companies to establish monopolies for drugs in small markets and increase prices beyond reasonable levels and without proper justifications (as in the extreme examples cited with Turing, Valiant, and others); (6) facilitating the steps, procedures, and costs associated with the introduction of generics and encouraging the presence of multiple (rather than few) generic companies; (7) considering (as in Canada) reasonable price boundaries for generics to encourage competition and to prevent price gouging; (8) asking drug companies to become more transparent about the cost of research and development in justifying the prices asked for particular drugs; (9) challenging weak patents at the Patent and Trademark Office; and (10) other solutions tailored to emerging problems. Globally, several of the previously mentioned solutions apply, with the additional factor of stronger government interventions, monitoring, and penalties for anticompetitive behaviors as discussed with several examples from Europe, Canada, Korea, and other nations.[49-59] The essence of these measures is simple: reduce the cost of drugs and improve patient access and treatment security.

Authorship

Contribution: All authors have designed the research, provided analytical tools, analyzed data, and wrote the manuscript.

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Correspondence: Hagop Kantarjian, Department of Leukemia, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0428, Houston, TX 77030; e-mail: hkantarjian@mdanderson.org.

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