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Why Are Some Generic Drugs Skyrocketing In Price?

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In our economy for medicines, the dual principles of market-based rewards that attract entrepreneurship and deep value once patents have lapsed are longstanding features of our system. The competition between branded and generic drug makers has enabled remarkable advances in science, and vibrant competition on price.

The compromises struck in the Hatch-Waxman legislation decades ago, have endured even as the market has changed. Generic drug makers have grown more sophisticated at challenging patents and unlocking new value for consumers. At the same time branded drug makers -- recognizing this competition -- have moved into new areas of science where resulting products are more specialized, unique, and beneficial. The competitive interplay between branded and generic firms, and the benefits that it affords, grows more relevant as the industries continue to evolve.

Recently, questions have been raised whether this competitive landscape is giving way to new economic features that erode some of the original intent of Hatch-Waxman. Market observers have made note of the substantial price increases observed with a select number of drugs, even though these medicines have been long subject to generic price competition. Yet in observing these cases, there is no

one discernable feature, or policy shortcoming, that explains the events. In each case, there are some unique features that led cost of goods to rise, or competition to temporarily erode. At the same time, market-wide generic drug prices continue to decline when you look across all of the drugs. So what is one to conclude?

America indeed has a challenge when it comes to the original compact that gave us a vibrant market for low-priced generic drugs. But it is largely not revealed by the anecdotal cases where a select number of drugs have undergone exorbitant price increases. These situations stem from unique circumstances, many of which will be hard to solve through policy alone because the situations are exceptional, and more likely than not, temporary, as market dynamics work to correct themselves.

On the contrary, a more pervasive and concerning trend relates to market challenges and policies that are slowly raising overall generic cost of goods. Some of these policies are borne of appropriate compromises. Others are not as well thought out. While focusing on the anecdotal cases where some prices have undergone sharp increase, Congress should also take note of the broader underlying trends.

While generic drug prices, on the whole, continue to decline, that is by no means a sure thing. If this deflation eventually reverses, it won't be as a consequence of the small number of cases where select drugs underwent substantial price increases. It will likely be a result of more pervasive increases in industry wide COGS.

Overall Generic Prices Continue To Fall

The increasing use of generic medications has helped mitigate growth of health care spending in the U.S. over the last decade. According to a recent report by the Government Accountability Office, on average, the retail price of a generic drug is 75% lower than the retail price of a brand-name drug.ⁱ ⁱⁱ Until the early 2000s, drug spending was one of the fastest growing components of healthcare spending. However, since that time, the rate of increase has declined each year. These reductions are attributable, in part, to the greater use of generic drugs and more competition between generic drug makers that lowers the cost of generic drugs.

That same GAO report condensed a series of studies conducted for Generic Pharmaceutical Association by IMS Health that estimated the total savings generic substitution provided to the overall U.S. health care system. The studies looked at the 12-year period 1999 through 2010.ⁱⁱⁱ These reports found that during this period, generic substitution saved the U.S. health care system more than \$1 trillion. In 2010 alone, generic substitution generated more than \$157 billion in savings.^{iv}

These studies, however, don't answer the question before us today: What is happening to the prices of individual generic drugs. Here again, the news is encouraging. Data reported in the Express Scripts Prescription Price Index show

that generic drug prices have been halved since 2008.^v Thompson Reuters reported that generic dose prices in certain markets, especially in the United States, “have gone into a downward spiral, squeezing margins for generic dose companies and often for API manufacturers as well. Contributing to this pricing pressure are an increase in the number of generic dose players, availability of low-cost active ingredient from India and China, incumbents’ desire to maintain market share.”^{vi}

This doesn’t negate the fact that the price of select number of generic drugs has gone up, in some cases substantially. This has put pressure on some pharmacies and consumers. There are concerns that it could be the start of a broader trend. But it is important to note that the prices of generic drugs are constantly fluctuating. When shortages of certain drugs or active ingredients exist, or manufacturers exit the market (leaving less competition for the sale of specific medicines) prices rise. When the maximum allowable cost limits that pharmacies agree to in their contracts don’t keep pace with rising generic acquisition costs, these cost increases can squeeze pharmacies’ profits. Over time, the MACs will catch up, and pharmacies often benefit when this same phenomenon works in reverse. Once prices start declining again, pharmacies benefit because higher reimbursement lags behind the lower acquisition costs. In the cases of the drugs that underwent price increases, the higher prices serve to attract additional generic competitors, and costs decline.

Indeed, some of the articles pertaining to the rising cost of some generic drugs seem to prove out this point in trying to make the opposite case, that generic prices are going up more sharply and unexpectedly than in the past. For example, the Wall Street Journal recently noted, in one such article, that pharmacies are paying more money for 37% of all generics than they did in the previous quarter. But that would imply that they paid the same or less for the other 63% of generic drugs. This would seem to follow a basic rule of thumb that, at any time, about a third of generic prices are going up, a third are staying the same, and a third are declining. This is the dynamic long observed in this highly competitive market.^{vii} During an August 5th conference call to discuss financial results, CVS Health President and CEO Larry Merlo appeared to dismiss the notion that a broader generic inflation is underway. “While the cost of goods inflation does exist on some generic items, it is not material in the context of our overall purchasing volume and again was generally within our expectations,” he told investors. “On balance, the deflationary nature of the generic pharmaceutical market remains intact and overall, our pharmacy margins’ increase this quarter for multiple reasons were in line with our expectations.”

But recently, the cost increases appear to be larger and more frequent, attracting notice. Yet there is no data to suggest that this is part of a broader trend. In fact, as I noted, the aggregate data points to the opposite conclusion. Over any time period, there are always subsets of drugs that undergo substantial price increases as a result of many factors, often related to disruptions in raw materials. However, as I will conclude later, there is reason to be concerned that the cost of goods for generic drugs, more generally, could rise if we are not careful in how we implement some

new policies. That's true even if, for now at least, it would appear that in the aggregate, brisk competition continues to hold down overall generic drug costs.

What Do The Big Price Hikes Tell Us?

Notwithstanding the favorable trends, some lawmakers have noted that there are examples where some generic drugs have undergone substantial price increases. A key question is whether there are common, underlying reasons for these price increases. Whether these anecdotes point to a larger failure of policy or markets?

Consider first, the ten drugs that have been recently cited by lawmakers from both the House and Senate as examples where old generic medicines underwent substantial price increases over the last two years. These ten drugs include doxycycline hyclate, albuterol sulfate, glycopyrrolate, divalproex, pravastatin, neostigmine, benzapril/hydrochlorothiazide, isuprel, nitropress, and digoxin.

Yet in looking at the circumstances surrounding the price rises, these drugs don't lend to any consistent, shared observations. In many cases, the active pharmaceutical ingredient used to manufacture a drug was in shortage because of plant closures. This was the case with doxycycline and perhaps some of the sterile, parenteral drugs included in this list. Some drugs have seen their use decline as a consequence of patient preference for other competing generic medicines in the same class. As a consequence, manufacturers have not maintained production of the less popular alternatives. This has the effect of creating temporary shortages. This appears to be the case, for example, with pravastatin sodium.

In some cases, there are temporarily fewer competitors in the market for certain generics as companies exited for business or regulatory reasons. This appears to be the case with digoxin. In the case of digoxin, as of January this year, there were two companies actively manufacturing and marketing the drug -- Lannett and Impax. In January, Covis Pharmaceuticals also entered the market. One of the key events was the elimination of one of the manufactures of the API for Digoxin as a result of tightened FDA oversight of that manufacturing facility. In this case, the company (Westwood) had to curtail its supply of both API as well as its own, tableted version of the drug. It's worth noting that Digoxin is also difficult to formulate, especially at low dosage forms.^{viii} Once a category is split between just two or three manufactures, it will follow that price will temporarily rise as competition declines.

How do we know this? It is well documented that significant generic drug price breaks of about 40% off the cost of the branded alternative are not achieved until there are at least four generic companies competing to manufacture the same drug. Prices don't fall to a sustainable and low equilibrium of about 20% of the cost of the branded drug until about seven manufactures enter the market. Moreover, the often-cited statistic that a generic drug is priced at just 10% of the cost of its

branded alternative (or less) is not achieved until there are about 15 generic manufactures competing to market one particular generic medicine.^{ix} It should follow suit that, if the market is competitive, these same economic principles will work in reverse. As generic manufacturers come in and out of the market for certain drugs, when competition falls, prices will rise until new firms enter the market. This is one of the principles that makes this market competitive, and self-correcting.

A critical question is whether the market for generic drugs is still self-correcting, or have other forces impeded the entry of new generic competitors into some of these categories. It has been said that generic drug mergers have reduced the number of generic manufacturers. While it's true that big generic companies have gotten larger, the market for generic drug makers is still vibrant. It is marked by literally thousands of different generic drug manufactures globally. But is the U.S. market still highly accessible to these companies? Is it still relatively straightforward, and inexpensive, to enter the market with a generic drug? In some cases, policies pursued by the U.S. have raised the cost of market entry for new generic manufacturers. This could reduce competition, and raise prices in the long run.

Concerns For The Future Of Generic Pricing

There are some gathering signs that the underlying cost structure in the generic drug industry is indeed rising, in a manner that could raise barriers to entry and increase the cost of goods in the long run. I believe we should focus more attention on this challenge. One factor is rising COGS in the generic drug industry. Some of this is driven by input costs. For example, commodities are part of the raw ingredient of certain drugs. On a broader scale, in most cases the single costliest input into the manufacturing of active pharmaceutical ingredients is the energy costs. As the price of energy has gone up in recent years, so will the underlying cost of the API.

Another reason is regulatory costs. In recent years, FDA has increased its oversight of generic manufacturing. The merits of FDA's oversight are beyond dispute. The balance struck between safety and access by FDA's sometimes-abrupt imposition of these new standards is beyond the scope of this discussion. But the fact remains that new standards were sometimes imposed with little notice or accomodation, leading to plant closures while facilities were remediated. Product shortages resulted. It's reasonable to ask whether, in cases where there was no imminent risk, facilities could have been remediated under close FDA supervision while they continued to produce key medicines, reducing the likelihood of shortages. This, however, has not been the policy. The bottom line is that COGS in this sector have gone up as a result. The higher manufacturing costs, and the tighter scrutiny applied to new manufacturing facilities, have increased the entry costs for new generic drugs and generic drug makers. How much costs have risen is difficult to fully quantify.

Competition is also diminished because FDA continues to be plagued by a backlog of generic applications. While generic drug user fees were intended to work this backlog off, it has actually increased. Moreover, FDA is now issuing refuse to receive letters, basically telling some generic sponsors that the agency won't even file their applications because of deficiencies. In some cases, these deficiencies are largely clerical in nature. By refusing to receive certain generic applications, it could have the effect of understating the actual functional backlog of generic approvals. A key question is how many of the generic drugs being cited for taking large price increases are faced with competition that now sits in FDA's backlog?

Generic manufacturers are also facing higher costs as a result of increased product liability risks as a result of "failure to warn" claims that they are being exposed to for the first time. A new regulation FDA crafted, in part with this understanding and purpose in mind, will impose on generic manufacturers a requirement to unilaterally change their labels without FDA review and approval—which they are currently prohibited from doing. By placing this burden on generic drug makers, the effect of FDA's new regulation would expose generic firms to the same large torts that are targeted to branded drug firms. The action may undermine some of the key public health benefits that generic drugs provide by substantially raising the industry's costs, in the process reducing access to low cost generic medicines.^x

The generic drug makers are also subject to user fees for the first time. These fees will help underwrite the investments needed to make sure the efficiency of FDA's generic drug approval process continues to improve. Nonetheless, the direct costs of these fees raise the barriers to generic entry, raise the cost of goods, and are ultimately passed on to consumers. These fees are not trivial. They include an application fee of \$58,730 for each ANDA, a \$29,370 fee for each new prior approval supplement (PAS) to an approved ANDA, a one time \$26,720 fee for the drug master files, a \$41,926 annual fee for domestic API Facilities, a \$56,926 annual fee for foreign generic drug API Facilities, a \$247,717 Annual fee for domestic finished dosage form facilities, and a \$262,717 annual fee for foreign FDF facilities.^{xi}

In addition to these user fees, generic manufacturers face some other fees. For one thing, many generic applications are not filed under the generic ANDA pathway, which falls under 505(j); but under another pathway referred to as 505(B)2. When a generic application is filed under 505(b) it faces full, branded drug user fees (which are much higher than generic drug user fees). Moreover, these drugs are also subject to the drug fees created under the Affordable Care Act as a way to close the Medicare Part D "doughnut hole." This was the gap in drug coverage that seniors experienced as their drug costs fell in between the lower and upper boundary of coverage limits. The ACA said only that these fees would apply to drugs approved under 505B, which ends up including generic applications filed under 505(b)2.

Other, expenses are getting loaded onto the generic drug supply chain. While each may be small, they start to add up. For example, under new regulations, generic companies are required to do many more validation batches before they file ANDAs.

Even shipping costs have increased. And a growing number of drugs need to be stored at more precise temperatures (an area of increased enforcement by FDA).

One of the central tenets of the generic drug framework was the idea that there would be low barriers to entry. Generic manufacturers have long faced substantially lower entry costs when compared with branded counterparts. Historically, enrolling a single patient in a BE/BA study as part of the ANDA required for a generic filing, on average, about \$1,000. Today, the average cost per subject ranges closer to \$5,000-\$6,000. In most cases, a BE/BA trial would enroll fewer than 50 patients to satisfy the requirements of the ANDA. Even that number has risen.

In addition, it had long been said that filing a generic application would cost about \$1 million, and a branded or specialty drug would become subject to generic competition once it reached \$10 million in revenue. It goes without saying that this \$10 million “rule of thumb” figure is substantially higher now. Recent data suggests that bringing a generic drug to the market can cost up to \$5 million per filing for a section viii filing, and another \$5-\$15 million for a paragraph IV filing. The amount of revenue or scripts a category must generate, before it attracts robust generic competition, has also increased beyond that \$10 million figure. That is another factor behind some of the very large price increases we have seen with a select number of older, generic drugs. For example, in 2014 the total sales of the generic doxycycline formulations that have been called into question were about \$6.9 million.^{xiii} These drugs, while expensive on a per pill basis, do not generate sufficient aggregate revenue to offset the investment needed to attract many competitors. That is why the market has not corrected more quickly in some of these cases.

The fact is that generic companies lose money on many of their offerings. They try and maintain a broad portfolio because it helps them contract and meet customer demand. So they continue to manufacture generic drugs even when they break even, or worse, sustain losses. But entering a category where they know they will lose money from the outset is another matter. These are not public utilities, notwithstanding the fact that they provide an important public benefit by delivering substantial value to consumers. At the end of the day, they need to remain profitable to continue to provide those benefits. Firms will take price increases in circumstances where the market will enable profits. This helps offset all of the situations where other circumstances create losses. The rising cost of entry increases the hurdle rate that must be offset for companies to enter new categories.

Consumers have an expectation in recent years that healthcare costs should start to level off or even decline. They have been promised as much in recent policy debates. And they have been conditioned to expect low prices when it comes to their old, generic medicines. So they are rightly concerned when prices on some old drugs undergo substantial increases, even if these costs aren't passed directly onto them. They don't follow the day-to-day headlines concerning supply shortages, manufacturing snafus, or the like. All they see are their bills.

The underlying cost pressures inside the generic drug industry are indeed changing. There is a risk that increased barriers to entry, increased cost of goods, and increased cost of regulatory scrutiny and manufacturing, can coalesce to lower the competition that this sector has long enjoyed, and the savings consumers have long appreciated. The anecdotal cases of substantial price increases that plague a subset of drug categories are concerning, but don't themselves point to any uniform trends. Instead, it is the underlying cost pressure that should merit our policy attention.

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ⁱ GAO-12-371R Savings from Generic Drug Use <http://www.gao.gov/assets/590/588064.pdf>

ⁱⁱ CBO, "Effects of Using Generic Drugs on Medicare's Prescription Drug Spending," September 2010.

ⁱⁱⁱ GPhA, Savings: An Economic Analysis of Generic Drug Usage in the U.S. (September 2011); GPhA, Savings Achieved through the Use of Generic Pharmaceuticals, 2000-2009 (July 2010); GPhA, Economic Analysis: Generic Pharmaceuticals 1999-2008—\$734 Billion in Health Care Savings (May 2009).

^{iv} GPhA, Savings: An Economic Analysis of Generic Drug Usage in the U.S. (September 2011)

^v Express Scripts. "Express Scripts Prescription Price Index." Drug Trend Report. (2014).

^{vi} Industrial Pharmacy, September 2006, Issue 11 http://thomsonreuters.com/business-unit/science/pdf/ls/pharma/challenges_generics.pdf

^{vii} Ed Silverman. To the moon: will rising prices for some generic drugs never end? The Wall Street Journal, November 14, 2014 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1381504/>

^{ix} U.S. Food and Drug Administration, Generic Competition and Drug Prices.

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm>

^x Scott Gottlieb, Alex Brill, and Robert W. Pollock. Proposed FDA generic drug regulation: Higher prices, no public health benefit, American Enterprise Institute Health Policy Outlook. March 12, 2014 <http://www.aei.org/publication/proposed-fda-generic-drug-regulation-higher-prices-no-public-health-benefit/>

^{xi} David Lennarz. FDA Updates Generic Drug User Fee Rates, FDA News. August 4, 2014. <http://fda-news.registrarcorp.com/2014/08/fda-generic-drug-user-fee/>

^{xii} Gross Doxycycline Hyclate Sales by Calendar Year per IMS: 2012, \$13,105,912; 2013, \$10,975,295; 2014, \$6,937,065