Premier's Roadmap For a Healthier Drug Market

PROBLEM

Our nation's healthcare system has experienced an alarming increase in drug prices for a range of products vital to patient care. In recent years, the frequency and impact of drug pricing spikes has risen to critical levels and is threatening patients' access to life-saving treatments, as well as adding to burgeoning healthcare spending. In fact, prescription drug costs is a key driver in healthcare spending growth in the U.S., outpacing other healthcare sectors.[1] The increase in spending on drugs in the inpatient hospital setting is particularly alarming, rising an average of 23.4 percent annually.[2]

These skyrocketing price spikes are harming patients, payers, providers, hospitals and the government. Exorbitant price increases have caused problems for health systems, which operate on a fixed Medicare payment level, and are putting a great burden on patients, who are often held hostage to paying high costs of drugs for which there are no less costly alternatives.

Dramatic drug price increases are often the fallout of competitive failures that allow monopoly players to raise prices at will, often by hundreds or thousands of percentage points – creating wildly expensive medications and added costs without true added value. Many of the drugs that lack competition and are experiencing dramatic price spikes are essential to patient care and include those used to treat common conditions like arthritis, asthma and abnormal cholesterol and in life-saving emergency cases.

The FDA continues to face a significant backlog of generic drug applications, with more than 4,000 applications pending[3] and average approval times reaching three or more years. This long wait time stifles the ability of manufacturers who seek to introduce competition in the generic market.

Fueling this lack of competition are failures in the marketplace that allow some pharmaceutical manufacturers to prevent or slow the introduction of more affordable alternatives to brand-name drugs for American consumers or that boost prices for drugs that have been in the market for decades. These anticompetitive actions cost consumers billions in higher drug costs every year.

RECOMMENDATIONS

A wealth of research and Premier analytics show that competition in the pharmaceutical marketplace brings down prices. Competition from generic drugs, in particular, has saved the U.S. healthcare system $1.46 trillion from 2005 to 2015.[4] According to the FDA, drug prices drop to roughly 52 percent of brand-name drug prices with two manufacturers producing a generic product, 44 percent with three manufacturers and 13 percent with 15 manufacturers.[5] This dynamic is reflected in the fact that 88 percent of dispensed prescriptions are for generic drugs, yet they account for only 28 percent of total drug spending. But in order to increase the competitive forces, more players are needed.

Congress and the administration can take steps that will help lower costs and increase competition in the healthcare marketplace by:

- Reducing the enormous backlog of generic drug approvals at FDA and expanding FDA's authority to expedite review and approval for new generic drugs;
- Enacting the Creating and Restoring Equal Access to Equivalent Samples ("CREATES") Act and the Fair Access for Safe and Timely ("FAST") Generics Act, which offer a common sense solution to prevent a few manufacturers from restricting generic manufacturers' access to product samples needed for bioequivalence testing for FDA generic drug approval;

- Enacting the “Preserve Access to Affordable Generics Act,” which will help put an end to pay-for-delay deals that extend brand name drugs marketing exclusivity at the expense of consumers;
- Ensuring access to biosimilars;
- Preserving the intent of the Orphan Drug status by extending it only to true orphan drugs that are developed to treat rare diseases;
- Differentiating between true breakthrough drugs vs. changes designed to manipulate the system;
- Removing the roadblocks that citizen petitions have erected against generic competition;
- Ensuring safe, decades-old drugs are still available to consumers at reasonable prices; and
- Ensuring that drugs and biological products are labeled so that providers and patients have consistent information on brand and generic drugs for their safe and effective use.

[1]Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group data. Sean P. Keehan, Devin A. Stone, John A. Poisal, Gigi A. Cuckler, Andrea M. Sisko, Sheila D. Smith, Andrew J. Madison, Christian J. Wolfe and Joseph M. Lizonitz. National Health Expenditure Projections, 2016-25: Price Increases, Aging Push Sector To 20 Percent Of Economy; Health Affairs published online February 15, 2017. http://content.healthaffairs.org/content/early/2017/02/14/hlthaff.2016.1627.
[2] Annual increase between 2013 and 2015. NORC at the University of Chicago. Trends in Hospital Inpatient Drug Costs: Issues and Challenges. October 11, 2016.
[3] FDA: The Generic Drug Review Dashboard
[4] Testimony of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Before the United States House of Representatives, Committee on Energy and Commerce Subcommittee. HealthQuintilesIMS Institute
[5] https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm129385.htm

June 2017

Reduce Backlog of Generic Applications

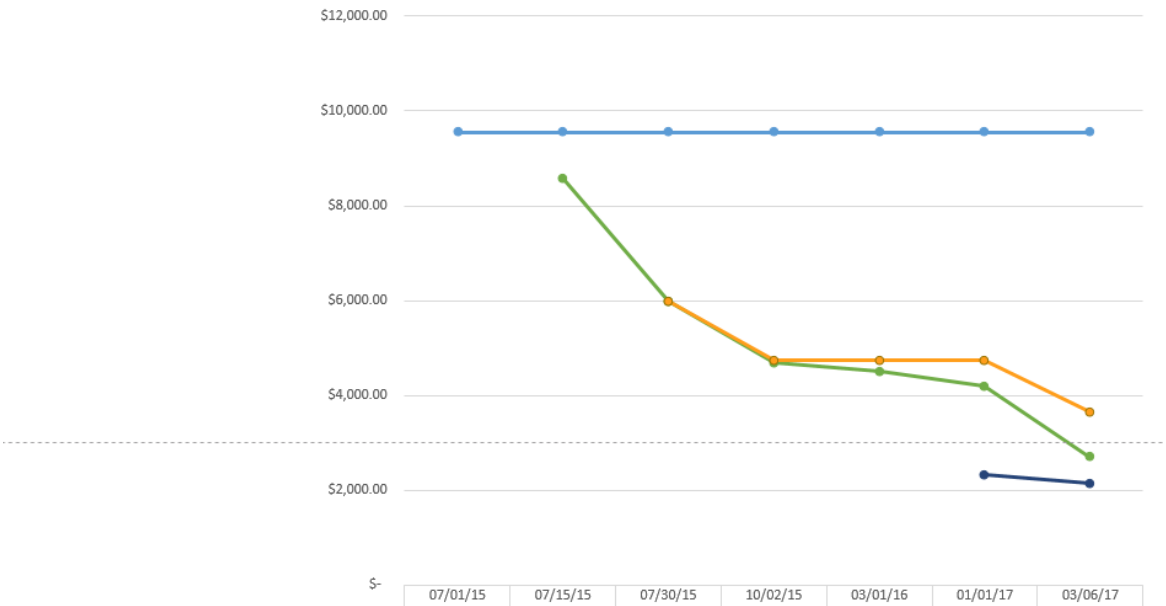
PROBLEM

The Food and Drug Administration (FDA) continues to face a significant backlog of generic drug applications that are currently under review by the agency pending potential approval. As of Jan. 1, 2017, the FDA generic drug review dashboard reported that the total original Abbreviated New Drug Applications (ANDA) workload activity for unapproved applications was 4,205. Due to the backlog at the FDA Office of Generic Drugs, it typically takes three to four years for a drug to enter the application process to become approved by the FDA.

Because of the length of time in approving new entrants to the market, many sole source drugs are left unchallenged in the market, thereby creating a defacto monopoly. Usually these drugs have had their R&D costs recouped many years earlier, and often by a prior manufacturer that initially launched the drug on the market. Yet, some manufacturers are capitalizing on these competitive failures, raising prices—sometimes by hundreds or thousands of percentage points. These skyrocketing price spikes are harming patients, payers, providers, hospitals and the government.

A wealth of research and Premier analytics show that competition in the pharmaceutical marketplace brings down prices. Competition from generic drugs, in particular, has saved the U.S. healthcare system $1.46 trillion from 2005 to 2015.[1] According to the FDA, drug prices drop to roughly 52 percent of brand-name drug prices with two manufacturers producing a generic product, 44 percent with three manufacturers and 13 percent with 15 manufacturers.[2]

As an example, Bivalirudin, a blood thinner agent used during angioplasty to prevent blood clots, experienced a dramatic reduction in pricing when two other generic competitors entered the market. While the brand name drug, Angiomax, stayed at a consistent price of $9,557, the first generic drug was priced $1,500 less than the brand drug, then dropped another $2,500 when the second generic drug entered the market, then fell another $1,500 over the course of the year. With the third generic drug in the market, the generic drug is now $7,500 less than the brand drug.



	07/01/15	07/15/15	07/30/15	10/02/15	03/01/16	01/01/17	03/06/17
MEDICINES COMPANY, THE ANGIOMAX VIAL 250MG	$9,557.00	$9,557.00	$9,557.00	$9,557.00	$9,557.00	$9,557.00	$9,557.00
SANDOZ INC. BIVALIRUDIN VIAL 250MG		$8,592.70	$6,000.00	$4,698.00	$4,500.00	$4,200.00	$2,700.00
HOSPIRA BIVALIRUDIN VIAL 250MG			$6,000.00	$4,753.00	$4,753.00	$4,753.00	$3,642.00
FRESENIUS KABI BIVALIRUDIN VIAL 250MG						$2,327.50	$2,140.00

*Pricing reflects 10 pack pricing

RECOMMENDATIONS

FDA should prioritize the review of generic drug applications when a lack of competition exists in the market. By facilitating the entry of new entrants to the market, FDA will spur competition and help address significant increases in drug prices that have occurred in the generic market. Premier supports S. 1115 included in the Generic Drug User Fee Amendment (GDUFA II) during the Senate Health, Education, Labor and Pensions and House Energy and Commerce Committee markup. This legislation requires FDA to publish a list of generic drugs where there are three or fewer competitors in the market, and allows manufacturers to request expedited review for generic drug applications in these cases. The legislation also sets a clear timeframe for the FDA to act on facility inspections after an applicant has notified FDA that they have taken necessary actions to resolve an identified issue will go far to keep existing manufacturers in the market.

Congress should include S. 1115, the "Making Pharmaceutical Markets More Competitive Act," introduced by Senators Collins (R-ME), McCaskill (R-MO), Cotton (R-AR) and Franken (D-MN) as part of the final GDUFA II package.

[1] Testimony of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Before the United States House of Representatives, Committee on Energy and Commerce Subcommittee. HealthQuintilesIMS Institute
[2] https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm129385.htm

Prohibiting Generic Manufacturers Access to Pharmaceuticals for Product Evaluation Required as Part of FDA Approval Process

PROBLEM

Since the Hatch-Waxman Act of 1984, generic manufacturing companies have safely and effectively purchased branded drugs to conduct bioequivalent tests needed for the FDA generic drug approval process. Competition from generic drugs has saved the healthcare system $1.46 trillion over the past decade and $227 billion in 2015 alone. However, in recent years, some brand manufacturers have started to deny generic manufacturers access to samples of their drug products, thereby extending their market exclusivity well beyond the law's intent.

The Senate Special Committee on Aging report, "The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S, Health Care System," cited how Turing Pharmaceuticals was restricting Daraprim's distribution thereby not allowing generic manufacturers access to samples needed for bioequivalence testing for FDA approval. First, some manufacturers have sought to establish overly narrow networks of distribution, and in doing so, effectively restrict the purchase of samples by generic manufacturers. This is problematic because generic manufacturers must demonstrate bioequivalence as part of their application for FDA approval and without reference samples to compare against, such evaluation is not possible. Additionally, some manufacturers inappropriately use the FDA's Risk Evaluation and Mitigation Strategy (REMS) program to also keep reference samples from generic manufacturers. When these tactics are employed, brand name manufacturers inappropriately delay access to products for testing and therefore slow the market entry of any competitor. The impact of this behavior raises prices for all stakeholders.

Without access to brand-name samples, generic and biosimilar approvals are not possible to pursue, which has the net effect of denying patients access to more affordable alternatives. These restricted access programs that prevent generic competition cost the healthcare system $5.4 billion annually, including $1.8 billion to the federal government. Equally alarming, as companies expand this practice to biosimilars, such anti-competitive behavior could result in approximately $140 million in lost savings for every $1 billion in biologics sales.

While certain restrictive networks and REMS programs are appropriate to ensure safe handling of fragile drug products and ensure proper use by patients, many of these restricted distribution setups are implemented completely independently from FDA mandates, and exist solely to limit control of who purchases the product for competitive purposes. Generic and biosimilar manufacturers seeking access to samples for bioequivalence testing should always be able to access them. In recognition of the importance of access, the FDA and Congress have recognized and sought to curb these practices, but have not taken any final steps to address the problem.

The Senate passed legislation in 2012 at FDA's request to address the abuse by some manufacturers. The legislative fix was included in the prescription drug user fee reauthorization but later taken out before becoming law. Lawmakers also discussed including the language in the 21st Century Cures bill to address the growing problem of access to pharmaceutical samples for bioequivalence testing, but ultimately did not. Most recently, the House Oversight and Investigations Committee held a March 2017 hearing entitled, "Examining the Impact of Voluntary Restricted Distribution Systems in the Pharmaceutical Supply Chain" and heard from FDA, hospitals and manufactures regarding the abuse of narrow distribution networks and the REMS program in preventing access to samples.

RECOMMENDATION

Congress should enact the following legislation this year to prevent a few manufacturers from using narrow networks and the FDA's REMS process to limit competition in the marketplace. The Congressional Budget Office estimated that recently introduced legislation would save the federal budget $3.3 billion and additional saving in the private market.

- H.R. 2015, “Fair Access for Safe and Timely (FAST) Generics Act of 2017” introduced April 6 by Rep. McKinley (R-WA) and Rep. Welch (D-VT)

- H.R. 2212/S. 974, “Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act,” introduced April 27, by Reps. Tom Marino (R-PA) and David Cicilline (D-RI) and Sens. Patrick Leahy, (D-VT), Chuck Grassley (R-IA), Mike Lee (R- UT) and Amy Klobuchar (D-MN), Tom Cotton (R-AR), Sheldon Whitehouse (D-RI) John McCain (R-AZ) Richard Blumenthal (D-CT) Susan Collins (R-ME) Claire McCaskill (D-MO), Dick Durbin (D-IL), and Diane Feinstein (D-CA).

The REMS legislation would close loopholes and address the most common abuses of REMS and non-REMS restrictive access programs. Specifically, these bills would:

- Put a stop to anticompetitive practices by prohibiting companies from restricting or interfering with eligible generic and biosimilar product developers’ access to covered products.
- Promote safety and addresses public health safety concerns by ensuring that companies seeking access to product samples have safety protections in place.
- Create a clear process to obtain product samples by setting forth tailored legal requirements for a pathway to short-circuit delay tactics and procedures regarding the acquisition of covered products by generic and biosimilar product developers at commercially reasonable prices.

[1]Testimony of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Before the United States House of Representatives, Committee on Energy and Commerce Subcommittee. HealthQuintilesIMS Institute
[2]2014 analysis by Matrix Global Advisors

Pay-For-Delay: When Drug Companies Agree Not to Compete

PROBLEM

Some brand drug manufacturers have been able to sidestep competition by offering patent settlements that pay generic companies not to bring lower-cost alternatives to their branded product to market. These are voluntary settlements of patent litigation where a generic company agrees to refrain from marketing its own generic product for a specific period of time in return for compensation from the branded company. A 2013 Federal Trade Commission (FTC) study[1] reported that these anticompetitive deals cost consumers and taxpayers $3.5 billion in higher drug costs every year.

Since 2001, the FTC has filed a number of lawsuits against brand and generic drug manufacturers to stop these deals. However, even with some success by FTC, the practice continues and additional congressional action is needed.

The "Medicare Prescription Drug, Improvement and Modernization Act" required manufacturers to file their agreements over patent disputes with the FTC. In the latest review of these agreements, the FTC found that:

- 21 final settlements potentially involve pay for delay because they contain both explicit compensation from a brand manufacturer to a generic manufacturer and a restriction on the generic manufacturer's ability to market its product in competition with the branded product.

- 11 of these were "first-flier" generics – i.e. those generic producers who were the first to file abbreviated new drug applications (ANDAs) on the litigated product and, at the time of settlement, were potentially eligible for 180 days of generic market exclusivity under the Hatch-Waxman Act.

Typically, the first generic sells for 20 to 30 percent discount off of the branded price, and 85 to 90 percent when multiple generic competitors are in the market. When drug companies agree not to compete, consumers lose.

RECOMMENDATION

Congress should enact S. 124, the "Preserve Access to Affordable Generics Act," introduced by Sens. Amy Klobuchar (D-MN) and Charles Grassley (R-IA) to eliminate agreements between brand and generic manufactures to delay generics in the market.

Under the legislation, an agreement will be presumed to have anticompetitive effects if a generic ANDA filer receives anything of value, including an exclusive license, agrees to limit or forgo research, development, manufacturing, marketing or sales of the ANDA product for any period of time. The manufacturers will need to show that the agreement is not anti-competitive with the FTC.

[1] Agreements Filed with the Federal Trade Commission under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Overview of Agreements Filed in Fiscal Year 2012: A Report by the Bureau of Competition - https://www.ftc.gov/reports/agreements-filed-federal-trade-commission-under-medicare-prescription-drug-improvement

Ensuring Access to Biosimilars

PROBLEM

Biologics are medicines that are derived from living cells that providers in our health systems use to treat patients with many serious and life-threatening conditions. Biologics are among the most expensive drugs on the market and are consuming a dramatically rising share of drug spending in the U.S. In fact, the eight most expensive Medicare Part B drugs in 2010 were all biologics – accounting for $8.3 billion, or nearly 43 percent of all Part B drug spending.[1] The introduction into the market of biosimilars—which are biological products that are highly similar to brand name biologics—will increase patients' access to critical therapies and has been estimated to save between $42 billion and $250 billion over 10 years.

The ability to safely substitute FDA-approved biosimilars for innovator biologics will be critical to realizing full cost-savings and access potential of biosimilars. On Jan. 17, 2017, the FDA issued draft guidance titled "Considerations for Demonstrating Interchangeability with a Reference Product." The guidance would require an applicant seeking an interchangeable designation to rely on switching studies exclusively using U.S.-licensed reference products. There is no scientifically justifiable distinction between reference products acquired in the U.S. and those licensed in other comparable markets. This requirement will create significant burden on biosimilar manufacturers pursuing switching studies, who can often acquire equivalent samples of reference products from other highly regulated markets at much lower costs. Requiring switching studies to rely on more expensive, U.S.-licensed reference product samples over less costly samples from other markets, without any real clinical difference between the two will simply create additional, unnecessary barriers to entry for biosimilar developers.

RECOMMENDATION

The Food and Drug Administration (FDA) and Congress should ensure that the pathway to market for biosimilars prioritizes patient access and safety and encourages development of these cost-saving medicines. As FDA works on finalizing its guidance for biosimilar interchangeability, Premier offers the following recommendations:

- As an overarching principle, FDA should permit a designation of biosimilarity parallel to granting an interchangeability designation if the applicant seeks both. Any applications which demonstrate that the product can be expected to produce "the same clinical results as the reference product in any given patient," as required by statute should be deemed interchangeable.

- The guidance's totality of evidence approach will provide FDA the flexibility necessary to evaluate biologic products as appropriate including structural complexity, toxicity, and immunogenicity risk. The FDA should be able to adjust its review standards to account for the high level of complexity and variability in these products.

- The extrapolation of data should be considered adequate to demonstrate interchangeability for some or all of the conditions of use of the reference product, subject to sufficient scientific justification. An interchangeability pathway that requires switching studies for each condition of use of the reference product would place an undue burden on sponsors and delay demonstration of interchangeability.

[1] U.S. Government Accountability Office. "Information on Highest- Expenditure Part B Drugs," Testimony Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives. June 28, 2013.

Limitations on Orphan Drug Status

PROBLEM

Enacted in 1983, the Orphan Drug Act established new incentives for manufacturers to invest in developing drugs to treat rare diseases. Orphan drug status applies to drugs and biologics that are intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., and is expressly for those manufacturers that are not expected to recover the costs of developing and marketing the drug. Orphan drug status allows for a special FDA approval pathway and seven years of exclusivity on the orphan product as well as additional tax benefits, even if the drug is not ultimately approved. The program has been successful in bringing new therapies to small patient populations. In 2014, 41 percent of FDA approvals were for orphan drugs.

However, concerns have been raised about the potential abuse of the program by manufacturers that only apply for a single treatment indication narrow enough to qualify for the orphan drug qualification, but then the drug is used on a broader basis for other indications once launched on the market. In addition, FDA previously has denied orphan status based on "medical plausibility" criteria. This means that if the drug can be used more broadly for indications other than the orphan indication, then FDA can deny orphan status. In recent years, the FDA has employed the "medical plausibility" criteria much less frequently than in prior years. Manufacturers have also taken drugs that have been on the market for a long time for broader patient populations and sought/obtained orphan status for different, qualifying conditions under the FDA orphan drug program.

In a 2015 commentary published in the *American Journal of Clinical Oncology*, Dr. Martin Makary at Johns Hopkins University School of Medicine focused on cancer drugs including Rituzimab, which was originally approved to treat lymphoma, a disease that affects 14,000 patients a year. Now, under different trade names, the drug also treats arthritis which affects 1.3 million people. It is the number one selling drug approved as an orphan drug and the 12th all-time best selling drug in the U.S. which generated $3.7 billion in domestic sales in 2014. Another analysis by Evaluate Pharma for Kaiser Health News in Sept. 2016 found that seven of the 10 best-selling drugs in the country were orphan drugs.

Congressional leaders have also raised concerns about reports that some manufacturers might be taking advantage of the orphan drug approval process to maximize profits. On March 3, 2017, Senators Orrin Hatch (R-UT), Charles Grassley (R-IA) and Tom Cotton (R-AR) sent a letter to the U.S. Government Accountability Office (GAO) requesting information to assist with their review of the orphan drug program, including information on:

- All drugs applying for orphan drug status, approved and denied;
- Any indications for the drug other than the orphan designation;
- Whether FDA's Office of Orphan Products Development (OOPD) evaluation criteria is consistent across reviewers;
- Whether the Orphan Drug Act is still incentivizing product development for diseases with fewer than 200,000 affected individual as intended; and
- Any regulatory or legislative changes that may be needed in order to preserve the intent of this vital law.

RECOMMENDATION

- Congress should finish its review of the Orphan Drug Program and assess what action are needed to address any potential abuses.
- Congress could consider limiting the orphan status to "new" drugs on the market vs. allowing companies to seek orphan indications for older existing drugs.
- Congress should review the change in FDA's interpretation of "medical plausibility" standard over the years. Orphan status now is often granted knowing there is a reasonable likelihood that the drugs may be used for other indications beyond its orphan target population.

Evergreening/Product Hopping

PROBLEM

"Evergreening" is a way branded manufacturers extend coveted patent and market exclusivity protections, thereby deferring generic competition, by seeking approval for a "new" product that is essentially the same as the original product. If a branded patent is scheduled to expire, and there are no generics on the market, one technique to delay generic competition is for the brand to obtain new patent protection by devising a new formulation such as extended release (ER), once-a-day vs. two times a day administration, or new drug delivery modality. By modifying the formulation, the manufacturer essentially creates a new product launch with its related patent and market exclusivity protections. When this product is released, brand manufacturers often pull the older version from the market leaving no opportunity for generic manufacturers to obtain samples of the previous formulation to use for their bioequivalence studies required for FDA approval.

By not allowing access to the older reference listed drug (RLD), the manufacturer strategically removes the option of another manufacturer producing the older, and potentially cheaper, product for bioequivalence against that older formulation. While some updated versions of a drug may be beneficial, patients need options in choosing medications. As an example, Abbott pulled an older version of the drug Tricor from the market before the patent expired, forcing the conversion to the new drug just before the generic could enter the market. The drug helps control cholesterol and the newer version did not require it to be taken with food. This brand name drug was almost a billion-dollar a year drug, and by removing the old brand and not allowing the generic to enter the market, consumer choice was limited to only the higher priced drug. In 2008 Abbott settled a court case with generic manufacturers that claimed the practice was anti-competitive.

In January 2017, FDA issued a draft guidance (Referencing Approved Drug Products in ANDA Submissions), seeking to address part of this issue by allowing discontinued drugs, which were not withdrawn based on concerns about safety or efficacy, to be used as the reference listed drug for generic manufacturers in their abbreviated new drug application (ANDA) submission for bioequivalence testing required to support the approval of the ANDA.

RECOMMENDATION

- If brand name manufacturers choose to discontinue a drug even though it has no known safety/efficacy concerns, the FDA should continue to allow for its use in bioequivalence studies as the RLD for a generic drug application. This would ultimately increase competition in the market and provide more choice to consumers as is proposed in the draft guidance.

- Congress should review the regulatory process which allows manufacturers to keep extending their market exclusivity for a drug that is essentially the same. Congress should by legislation, or letter, request review of this "evergreening" practice, and related practices involving "product hopping," by the Federal Trade Commission or by the U.S. Government Accountability Office (e.g., approval of new NDAs for reformulated drug for the same medical condition in advance of generic approval of older drug). Evergreening undermines the spirit of the Hatch-Waxman law. The FTC or GAO request should also provide any regulatory or legislative changes that may be needed in order to preserve the intent of this vital law.

Citizens Petition

PROBLEM

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask the agency to take any form of action related to a pending application for generic drug approval. When used properly, and submitted early in the process, a citizen petition can bring important information to FDA's attention such as suggesting a particular method for demonstrating the bioequivalence of a proposed generic product to the referenced listed drug. However, when petitions are filed with no real merit, they delay generic drug entry into the market, and in doing so, stymiey competition. When such anticompetitive behavior is employed, the inappropriate use of citizen petitions leaves the brand manufacturers extended exclusivity, which was never part of Congressional intent.

To help limit the delay of generic drug competition, Congress enacted legislation in 2007 to require FDA to issue a rule on petitions within 180 days of filing and then reduced the timeframe to 150 days in 2012. However, without additional resources for multiple departments within FDA to process and respond to each request, the filing of petitions by manufacturers without merit has continued to slow FDA's approval process, even though most have been denied. In fact, an analysis by Michael Carrier, a Rutgers University School of Law professor found that brand manufactures filed 92 percent of the citizen petitions between 2011 and 2015, and nine out of 10 were denied. In FDA's report to Congress in July 2016, the agency noted that it continues to be concerned that petitions are intended primarily to delay the approval of competing drug products, and not for their intended purpose of raising valid scientific issues.

In November 2016, FDA amended the regulations on citizen petitions[1] to underscore that petitions submitted late in the generic drug application review process and that do not raise valid scientific and/or legal issues may have the effect of improperly delaying the approval of an application. In these cases, FDA clarified that its goal would be not to delay approval of pending generic or biosimilar drugs because of such petitions, unless that delay is necessary to protect the public's health.

Despite these actions taken by Congress and the FDA, abuses persist. In one recent case the Federal Trade Commission (FTC) charged Shine ViroPharma, a company that has used 24 citizen petitions over one antibiotic, with violating antitrust laws. The FTC complaint alleges that because of ViroPharma's actions, consumers and other purchasers have paid hundreds of millions more for their medications.

RECOMMENDATIONS

Congress and the FDA should take the following steps to discourage manufacturers from overusing and abusing the Citizen Petition process:

- Greater transparency is needed in this process. Petitions should be filed directly by the principals (e.g. manufacturers) and not by law firms or consultants that mask the identity of the principal.

- Appropriate penalties should be established for frequently failed petitions by manufacturers that FDA determines to be primarily dilatory with insufficient substantive basis.

- Congress should by letter or legislation request a review of the citizen petition process by the U.S. General Accountability Office or the FTC. The request should also provide any regulatory or legislative changes that may be needed in order to preserve the intent of the citizen petition.

[1] Amendments to the Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets became effective January 9, 2017.

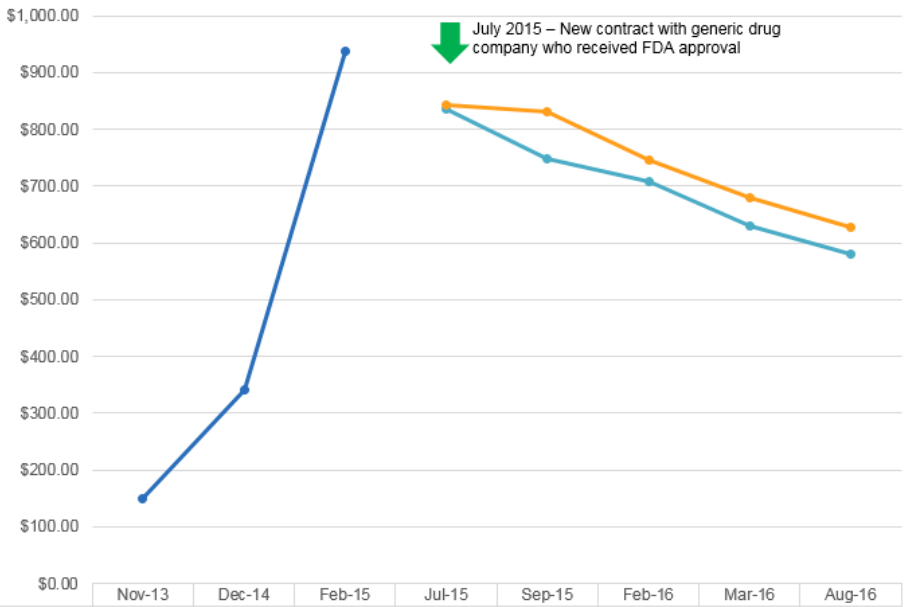
FDA Approval Process for Older Medications

PROBLEM

FDA authority to approve drugs was initiated in 1938 by the *Federal Food, Drug & Cosmetic Act* (FFDCA), which required that new drugs marketed in the U.S. submit a New Drug Application (NDA) to FDA for labeling for safe use. In 1962, the act was further amended to require NDAs to include proof of safety and efficacy through medical research. Because of the disparity in the FDA approval standards between 1938 and 1962, Congress also required that drugs approved in that time frame be reviewed again based on the updated safety and efficacy requirements. FDA carries out these requirements through a process called the Drug Efficacy Study Implementation (DESI). FDA later also included pre-1938 drugs in the review as well as in an initiative called the "Prescription Drug Wrap-Up."

In 2006, FDA announced a new drug safety initiative to remove unapproved drugs from the market and to further encourage the manufacturers of unapproved products to obtain the required evidence and submit marketing applications for these drugs. The requirements were outlined in the *Marketed Unapproved drugs-Compliance Policy Guide*. At that time FDA estimated there were still over 3,000 medications in the market that were unapproved. In 2011, FDA updated its Compliance Policy Guide and said it would evaluate the potential for market disruption should an abrupt reduction in supply result from FDA action requiring other manufacturers of the same drug to exit the market once a NDA was approved. However, providers and consumers have experienced significant price spikes as an unintended consequence of this process.

When manufacturers of these older drugs are forced to leave the market (e.g., guaifenesin, levothyroxine, digoxin, morphine, colchicine, etc.), providers have experienced significant drug price increases due to the lack of competition. For example, Neostigmine was priced at $33 (for 10 vials of 10mg/mL) in 2009. The new "brand" Bloxiverz, approved by FDA in the same package size, jumped to $150 in 2013 and continued to experience price increases up to $938.12 by 2015 when other manufacturers of these older unapproved drugs were forced to leave the market. While not anywhere near where it was prior to the removal of other manufacturers in the market, the price dropped to $580.90 in 2015 with two other manufacturers entering the market.



	Nov-13	Dec-14	Feb-15	Jul-15	Sep-15	Feb-16	Mar-16	Aug-16
BLOXIVERZ 0.5MG/ML, 1MG/ML	$150.00	$340.10	$938.12					
NEOSTIGMINE METHYLSULFATE 0.5MG/ML				$835.76	$748.80	$707.80	$631.00	$580.90
NEOSTIGMINE METHYLSULFATE 1MG/ML				$844.20	$832.00	$745.00	$680.00	$627.50

While FDA's efforts to obtain safety and efficacy data on all drugs in the marketplace is laudable, many of these drugs have a long history of safety and efficacy. Because of their length of time on the market, most of these products have maintained relatively low prices. The disruption to the marketplace when other products are forced to exit as a result of FDA's policy should not be underestimated.

RECOMMENDATIONS

Premier recommends options for changing the process at FDA to allow more notice for manufacturers and providers regarding FDA action on these older drugs when immediate removal from the market is not necessary. Specifically:

- FDA should announce in the *Federal Register* the first NDA approval for an older medication that is currently manufactured by other companies.
- FDA should then allow for 18 to 24 months after that notice before requiring current manufactures to exit the market. This would give providers, purchasers and consumers time to engage with manufacturers on their decision-making regarding seeking FDA approval of a competing drug to the NDA.
- User fees should be lowered or removed altogether in order to not discourage generic manufacturers from filing an NDA for these older drugs. NDA costs vary greatly based on the extent of new human clinical research required to prove safety and efficacy. If a 505(b)(2) route is selected, the sponsor can use published clinical data and minimize new data required. That cost can range from $500,000 to $2-3 million. A full 505(b)(1) NDA can cost $10-$50 million to conduct required studies and prepare the application. It can take 10-12 years in this development cycle to test, prepare, file and gain approval.

Generic Drug Labeling

PROBLEM

The labeling for approved drugs and biological products provide healthcare professionals and patients with information needed for the safe and effective use of the product. Under current law, generic drugs are required to have the same label as the brand counterparts to ensure the same information on scientifically equivalent drugs and biological products is available to health professionals and patients. Brand manufacturers have the responsibility to update the label with any new safety information with simultaneous review by the FDA, and generic drugs must similarly update their labels as well. In 2013, the FDA issued a proposed rule, Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products; 0910-AG94, which would undermine the "sameness" principle and ensure that brand and their related generic products have identical information on their respective labels. The guidance would permit generic manufacturers to change the label with any new safety information, as well.

If finalized, the rule will permit multiple, different versions of labels for therapeutically equivalent products. While providers appreciate FDA's goal of having the drug label updated as quickly as possible, having multiple labels for essentially the same product will confuse providers and patients, leading to less generic products used and creating unnecessary costs in the caring of patients. This is evidenced by a survey of prescribers by the National Coalition on Healthcare and the Generic Pharmaceutical Association that found:

- 81 percent thought FDA approval should be required before any safety label information is changed;
- 75 percent thought patients would be confused by different labels for the same medication and almost 80 percent said multiple labels would be confusing for themselves; and
- 60 percent said that their willingness to prescribe generic drugs would change if the labels were different.

RECOMMENDATIONS

- FDA should withdraw the proposed rule due to multiple concerns raised in the provider community over the effect it could have in provider prescribing and patients trust in generic drugs.

- If FDA does move forward on its proposal to change the current process for updating drug labels, both brand and generic manufacturers could send to FDA any data needed to update the labels, and ensure a consistent label across brand and generic bioequivalent products. In April 2016, Premier along with 14 other healthcare and supply chain organizations sent a letter to FDA expressing continued concern regarding the proposed rule allowing different labels on the same product. In the letter, we shared that we believe FDA is best positioned to review new safety information for multi-source products and serve as the centralized authority for labeling changes. This alternative to the proposed rule meets the shared public health goal of ensuring the safety and efficacy of pharmaceutical products.