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A Look At The Legality Behind Daraprim's Price Spike

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Turing Pharmaceuticals AG and its controversial CEO Martin Shkreli recently made headlines when Turing raised the price of its antiprotozal drug Daraprim (pyrimethamine) from $13.50 to $750 per tablet.[1] The price increase received significant media attention.

Here, we evaluate Turing's Daraprim price hike from a legal perspective, including an analysis of the mechanisms used to balance innovation and drug pricing in the U.S., and their degree of application, if any, to the drug's recent price hike.

Balancing Drug Prices and Innovation

The United States has traditionally incentivized drug development innovation. Patents and the U.S. Food and Drug Administration's regulatory exclusivities allow an innovator to enjoy a protected U.S. market for a finite period of time. The market protection provided by these exclusivities helps innovators to recoup their research costs and make profits which, in part, are used to fund new research.

Conversely, after the expiration of patents and market exclusivities, generic drugs can enter the marketplace. Generic drugs can ultimately cost 80 percent less than the branded drug.[2] Accordingly, U.S. laws (e.g., the Hatch-Waxman Act and Biologic Price Competition and Innovation Act of 2009) attempt to strike a balance by providing market incentives to innovators to bring new medicines to market in exchange for making generic drugs available to patients at a greatly reduced cost. Thus, a first mechanism for balancing innovation and drug prices are the laws that establish generic drug competition.

There Is Currently No Generic Equivalent for Daraprim

Daraprim was first approved by the FDA on Jan. 23, 1953.[3] Through a chain of title that included GlaxoSmithKline PLC, Amedra Pharmaceuticals LLC and Impax Laboratories Inc., Turing acquired the rights of Daraprim in August 2015. Daraprim is a reference listed drug in the FDA's Orange Book[4] and no generic version of the drug is currently available.[5]

One reason no generic may be available is the small number of patients who take Daraprim. The U.S. market for Daraprim is estimated to be about 2,000 patients. The relatively small number of patients,

coupled with a modest price of $17.50 per pill for the brand product (which a generic would likely lower), do not create a significant financial incentive for a generic market entry.

Another potential reason why a generic is not currently available is the presence of a restricted distribution program.[6] According to press coverage, Turing, the sole U.S. supplier of Daraprim, acquired exclusive rights from Impax Laboratories in August 2015. Prior to the acquisition, Impax subsidiary Amedra Pharmaceuticals LLC, the then-manufacturer of Daraprim, implemented a restricted distribution program.[7] Restricted distribution programs are often put in place when required by the FDA as part of a risk evaluation and mitigation strategy ("REMS"). REMS help to mitigate a drug's risk profile by various means, including controlling drug access to ensure that only educated physicians prescribe the drug to patients that actually need it.

Amedra's restricted distribution program does not appear to be associated with an approved REMS, and therefore it appears to have been a self-implemented restricted distribution.[8] While restricted distribution can make drugs safer, restricted distribution programs in some circumstances could also make it tougher for generics to enter the market. In order to receive FDA approval, a generic manufacturer must show that its drug is bioequivalent to the marketed drug.

Restricted distribution programs potentially could make it more difficult to get sufficient quantities of the marketed drug to perform these bioequivalence studies. Thus, as a result of the restricted distribution program, a generic competitor — seeing the opportunity to make profits by entering the marketplace after Turing's price hike — might have a harder time developing the required data package to support approval. Restricted distribution programs in the context of REMS have been evaluated under the antitrust laws,[9] and restricted distribution absent a REMS likewise potentially could raise antitrust issues.

Antitrust Laws Do Not Address Daraprim's Price Increase

Some might also ask whether the antitrust laws have a role to play for Turing's price increase itself. Cries of price gouging are often heard from Congress and other public actors for similar large price increases in other industries. However, unilateral price increases alone — when not done by agreement or through collusion with competitors — are almost never actionable under U.S. antitrust law. As long as Turing acted alone in raising Daraprim's price, it would be highly unlikely to face any antitrust claim or criminal antitrust penalties.

Impact of Pharmacy Benefit Management on the Price of Daraprim

Another mechanism that affects drug prices in the United States is the work done by pharmacy benefit managers ("PBMs"). PBMs manage drug benefits for as much as 57 percent of U.S. patients.[10] While not directly involved in the drug supply chain, PMBs work with third-party payers to manage some consumer drug prices and purchases by defining:

- what drugs will be paid for;
- consumers' out-of-pocket cost for a drug; and
- the amount that a pharmacy receives for selling a drug.[11]

For some drugs, PBMs use formularies to negotiate drug price discounts with drug manufacturers. These discounts may be granted in return for a drug being included in a formulary (and for excluding

manufacturers of competing drugs from the formulary). PBMs also negotiate rebates from manufacturers on drugs included in the formulary. The rebates, like inclusion in the formulary, are contractual. These contracted rebates often allow PBMs to keep a portion of the rebate in return for their negotiating with drug manufacturers and developing a formulary.

PBMs, at least in the near future, will be constrained in their bargaining with Turing because the company is the only approved U.S. supplier for Daraprim. Thus, PBMs will not be able to play one manufacturer against another for inclusion in their formularies. PBMs may be able, however, to still negotiate some form of a discount by threatening to exclude Daraprim from a formulary. This is not without risk, however, as failure to include Daraprim, in the absence of alternatives, may give rise to patient lawsuits against their plans and their PBMs.

Impact of Government Purchasers on the Price of Daraprim

Federal and state governments also influence the balance of innovation and drug prices in certain circumstances. For example, federal rules require that states pay the lower of:

- the estimated acquisition cost of a drug; or
- the usual or customary charge to the public.

Manufacturers who want to have their drugs covered by Medicaid also must provide rebates to state Medicaid programs.

Other federal requirements include the Section 340B drug pricing program for certain nonprofit entities and the U.S. Department of Veterans Affairs' Federal Supply Schedule program. All of these programs could blunt at least some of Daraprim's price increase for Medicaid recipients, community health centers and the VA.

Public Opinion Impact on the Price of Daraprim

A final mechanism to balance innovation and drug pricing is public opinion, and the threat of pharmaceutical price legislation. This mechanism appears to have ultimately caused Turing to announce it would roll back Daraprim's price increase. Public outcry, and a positive response of politicians to that outcry, can be effective in balancing drug benefit and cost.[12]

Conclusion

Turing appears to have identified a path to maintain market exclusivity for its small molecule drug. The press has deemed the level of its price increase to be controversial. Moreover, this situation is unusual in that mechanisms which generally help to balance drug benefits and costs (e.g., finite exclusivities, generic competition, PBMs and government purchasing) were not immediately applicable for a number of reasons. And, while a generic could step in, no generic has yet come to market. Even so, public outcry, and the threat of pharmaceutical price legislation, appear to have convinced Turing to actually consider rolling back its price increase.

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[1] H. Malcom and L. Szabo, "Turing pharma CEO recedes from public after backtracking on drug price hike", *USA Today*, Sept. 24, 2015; available electronically at:http://www.usatoday.com/story/money/business/2015/09/23/turing-pharmaceuticals-ceo-martin-shkreli-will-lower-price-of-Daraprim/72670124/, last accessed Sept. 28, 2015.

[2] "Facts about Generic Drugs", *FDA*, June 19, 2015; available electronically at:http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm, last accessed Sept. 28, 2015.

[3] *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist, *FDA*, last accessed Sept. 28, 2015.

[4] *See* http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=008578&TABLE1=OB_Rx, FDA, last accessed Sept. 28, 2015.

[5] *See, e.g.*, "Daraprim", *Drugs.com*, available electronically at: http://www.drugs.com/pro/daraprim.html; *see also*:http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM183605.pdf, *FDA*, both last accessed Sept. 28, 2015.

[6] *See, e.g.*, M. V. Mahoney, "New Pyrimethamine Dispensing Program: What Pharmacists Should Know", *Pharmacy Times*, July 17, 2015, available electronically at:http://www.pharmacytimes.com/contributor/monica-v-golik-mahoney-pharmd-bcps-aq-id/2015/07/new-pyrimethamine-dispensing-program-what-pharmacists-should-know, last accessed Sept. 28, 2015.

[7] *Id*. In the restricted distribution program, inpatient providers were required to set up an account with the Daraprim Direct program and place orders directly with the manufacturer. Patient prescriptions

were filled by Walgreens Specialty Pharmacy and delivered to the patient's home address.

[8] *See, e.g.*, "Approved Risk Evaluation and Mitigation Strategies (REMS)", and files therein, *FDA*, available electronically at:http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page, last accessed Sept. 28, 2015.

[9] *See, e.g.*, Oral Opinion, *Mylan Pharmaceuticals Inc. v. Celgene Corp*., No. 2:13-cv-02094-ES (D.N.J. Dec. 22, 2014).

[10] *See, e.g.*, "Follow the Pill: Understanding the U.S. Commercial Pharmaceutical Supply Chain", The Health Strategies Consultancy LLC, 2005, available electronically at:http://avalere.com/research/docs/Follow_the_Pill.pdf, last accessed Sept. 28, 2015.

[11] *Id*.

[12] Other mechanisms, like drug reimportation and manufacturer patient assistance programs, are not addressed in this article because they have limited applicability.