VIEWPOINT

High Costs of FDA Approval for Formerly Unapproved Marketed Drugs

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In May 2017, the US Food and Drug Administration (FDA) announced a Drug Competition Action Plan, designed to address competition and pricing in the generic market and improve access to prescription drugs.[1] One of FDA's stated goals is to reexamine "places where its rules—including standards and procedures related to generic drug approvals—are being used in ways that may create obstacles to generic access,"[1] instead of ensuring the vigorous competition Congress intended. In this Viewpoint, we examine FDA's 2006 Unapproved Drugs Initiative (UDI), designed to strengthen the agency's regulatory oversight related to unapproved marketed drugs. Using an illustrative example, we discuss this initiative's unintended consequences, as it appears to have created obstacles to generic drug access, likely increasing prescription drug costs.

The FDA estimates that in the United States, as many as several thousand drug products are marketed without FDA approval, many of which entered the market prior to the 1938 Federal Food, Drug and Cosmetic Act.[2] Examples of unapproved prescription drugs include nitroglycerin sublingual tablets, phenobarbital, prenatal vitamins, calcium gluconate injection, and sodium phosphate injection. The goal of the UDI was to remove unapproved drugs from the market, "without imposing undue burden on consumers, or unnecessarily disrupting the market." The FDA's final guidance stated that if a company obtained approval to market a product that other companies were marketing without approval, FDA would "more likely take enforcement action against remaining unapproved drugs." The first company to obtain approval would therefore have a period of "de facto market exclusivity" before other products obtained approval, providing "an incentive to firms to be the first to obtain approval to market a previously unapproved drug."[2]

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An increasing number of manufacturers have successfully obtained approval for formerly unapproved but marketed products, an example of which is intravenous vasopressin, used to increase blood pressure in adults with vasodilatory shock (eg, postcardiotomy and sepsis) who remain hypotensive despite fluids and catecholamines. The drug has been marketed in the United States for nearly a century.[3] On September 26, 2012, Par Pharmaceuticals submitted a New Drug Application to FDA for its intravenous vasopressin product under the name Vasostrict, relying on a review of published literature to characterize the clinical pharmacology, safety, and efficacy of the drug.[4] Thus, no new nonclinical pharmacology, toxicology, or human studies supported regulatory approval. On November 14, 2014, Par received FDA approval for Vasostrict, and on December 15, 2014, FDA instructed all other suppliers of unapproved intravenous vasopressin to stop manufacturing their products by January 30, 2015, leaving only Par with a marketed product.[3] Subsequently, the average wholesale price of intravenous vasopressin increased from $4.27 to $138.40 per vial in November 2016, a 3141% increase.[5] In 2013, when there were multiple competing suppliers, total sales from intravenous vasopressin approximated $4 million.[3] As of November 2016, Vasostrict achieved annualized sales of nearly $400 million.[6] As a result of the high cost, reports have surfaced of vasopressin being removed from code carts, making it unavailable in life-threatening situations.

This illustrative example is reinforced by a broader study. A recent examination of all prescription drugs targeted by the UDI between 2006 and 2015 demonstrated that the price of these drugs increased by a median of 37% after UDI regulatory action or approval.[7] Moreover, nearly 90% of drugs that received FDA approval through the UDI were supported by literature reviews or bioequivalence studies, not new clinical trial evidence, suggesting that the UDI is not motivating new studies of these old drugs. Notable examples of drug approvals for previously unapproved marketed therapies include Adrenalin (epinephrine) for the emergency treatment of allergic reactions, Akovaz (ephedrine sulfate injection) for anesthesia-induced hypotension, Bloxiverz (neostigmine methlysulfate) to reverse nondepolarizing neuromuscular blockade after surgery, Colcrys (colchicine) for the treatment of acute gout, and potassium chloride (oral solution) for hypokalemia.[5,7] All of these drugs have decades of use establishing safety and efficacy and do not have reasonable therapeutic substitutes, allowing for significant monopoly profits once unapproved marketed drug competitors are taken off the market. As an example, the price of neostigmine methylsulfate, a drug first synthesized more than 80 years ago, increased from $3.25 to $80.50 per vial as of November 2016, and cumulative sales of Bloxiverz since approval in 2013 were $238 million as of the third quarter of 2016.[5]

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Once a manufacturer obtains approval for a formerly unapproved marketed product, several hurdles may delay the entry of competitors. First, FDA approval of an Abbreviated New Drug Application (ANDA) for subsequent versions of the same drug takes an average of 24 to 36 months.[2] Second, pharmaceutical companies can prevent competitors' access to raw pharmaceutical product source material by signing exclusive dealing agreements with specialty chemical manufacturers. Generic competitors typically purchase the active pharmaceutical ingredient (API) from a chemical supplier and then combine the API with various excipients to produce the finished product. In the case of vasopressin, the only 3 chemical suppliers that have an active Drug Master File with FDA for the supply of its API in the United States have all signed exclusive agreements with Par.[3] Third, holders of New Drug Applications may list new patents claiming the approved drug product in FDA Orange Book. Consequently, any ANDA filer is subject to an automatic 30-month stay of marketing approval to permit litigation. Indeed, as the result of a new formulation patent for Vasostrict issued on June 28, 2016, Par expects exclusivity of the vasopressin market until at least 2019.[6] Fourth, in certain cases, the newly approved drug product may be eligible to receive statutory marketing exclusivity, such as under the Orphan Drug Act. Fifth, manufacturers may implement closed distribution systems, removing the drug product from regular wholesalers and pharmacies to prevent generic companies from accessing the necessary product to complete bioequivalence studies for ANDAs.

The UDI aims to ensure that all drugs are held to the same safety, efficacy, and quality standards, including investment in robust manufacturing processes, thereby lowering the risk for shortage. While FDA "welcomes manufacturers' sensitivity to pricing of these newly approved versions," the agency has no authority to directly regulate drug prices and does not factor costs into its regulatory decisions.[2]

The FDA has recently announced several policy measures designed to remove obstacles to new generic competition that are relevant to the UDI. First, FDA has posted a tentative list of branded drugs that have no listed patents or exclusivities and for which the agency has yet to approve a generic drug application, and the agency intends to prioritize its review of generic drug applications from this list.[1] However, the list does not appear to contain many prominent formerly unapproved marketed drugs targeted by the UDI, such as vasopressin. Second, FDA will also expedite the review of generic drug applications until there are 3 approved generics for a given drug product,[1] which could foster quicker entry of generics to drugs approved through the UDI.

Several additional reforms might be considered to mitigate the harms of monopoly price increases that have resulted from the UDI. First, FDA should better coordinate with the Federal Trade Commission in identifying and publicizing anticompetitive practices that delay generic entry, such as closed market distribution systems or restrictive-API contracts with chemical manufacturers. Second, to better contextualize the price increases on formerly unapproved, marketed drugs, the federal government should require pharmaceutical companies to disclose development expenditures required to achieve approval through the UDI. Third, to encourage voluntary compliance with the UDI, the federal government could provide prespecified, fixed monetary payments to reimburse the development of formerly unapproved drugs. The implications of de facto market exclusivity for previously unapproved marketed drugs can be substantial for pharmacies, hospitals, insurers, government agencies, and patients. Ultimately, although FDA's goal of strengthening regulatory oversight related to unapproved drugs is laudable, monopolies carry societal harms, and the current system appears to lead to rewards out of proportion to manufacturer investment.

ARTICLE INFORMATION

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