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CHEST

The Vexing Voyage of Vasopressin

The Consequences of Granting Market Exclusivity to Unapproved Drugs

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As the COVID-19 pandemic raged in 2020, vasopressin, a century-old drug to treat patients with critical illness with vasodilatory shock, was among the 10 most expensive drugs for hospitals.[1] Why did hospitals and the US health care system pay so much for this drug? Because the US Food and Drug Administration (FDA) did not formally approve vasopressin until April 2014, and Par Pharmaceutical leveraged their drug approval to dominate the market and raise the drug's price by 5,400% from 2010 to 2020 (Fig 1). The vasopressin approval was part of the FDA's Unapproved Drugs Initiative (UDI), an effort to regulate products that have remained on the market since before Congress granted the FDA authority to evaluate drug safety and effectiveness. The story of vasopressin calls attention to the perils of granting market exclusivity as a regulatory incentive, demonstrates the consequences of weak US drug patent standards, and highlights the need to reform the UDI.

The Unapproved Drugs Initiative

When Congress enacted the Food, Drug, and Cosmetic Act in 1938 to require premarket safety testing and FDA evaluation of new drugs, it exempted products that were already on the market. This allowed many older drugs, which included vasopressin, to remain available without formal FDA review of safety and (starting in 1962) effectiveness. The exemption for pre-1938 drugs applied only if they maintained the same composition and labeling; the FDA believes that no unapproved drugs on the market today fall under this exemption. However, the FDA has needed to balance the goals to regulating these products and ensure safety and effectiveness with the risk of disrupting availability to patients.

In 2006, the FDA established the UDI to address the estimated thousands of unapproved drug products remaining on the US market. The UDI incentivized manufacturers to voluntarily seek approval by promising to clear other unapproved versions off the market after a 1-year grace period. This effectively provided the first manufacturer to gain approval with temporary market exclusivity until another company earned approval, a process that could take $\geq$ 1 year.

According to the FDA, the UDI served two goals: improving regulatory oversight of unapproved drugs and incentivizing the generation of new safety and effectiveness evidence. Over the subsequent 2 decades, dozens of products were approved via the UDI, 90% of which were approved without new clinical data.[2]

The Vexing Voyage of Vasopressin

The effect of a pituitary substance on raising BP was first discovered in the late 19th century, and the peptide vasopressin was isolated and marketed in the US in 1928 to treat vasodilatory shock. Over the next century, vasopressin was made by several firms, but none sought FDA approval until JHP Pharmaceuticals (later acquired by Par Pharmaceutical) submitted a review of the literature (but no new clinical trials testing safety or effectiveness) in 2012.[3] Shortly after the FDA approved Par Pharmaceutical's version (Vasostrict) in 2014, the agency ordered other vasopressin manufacturers to cease production. Par Pharmaceutical initiated a strategy to defend its newfound market exclusivity.

A Patent Thicket

As of January 2022, Par Pharmaceutical had listed 14 patents that protect its formulation of the century-old drug with the FDA, the last of which expires in 2035.

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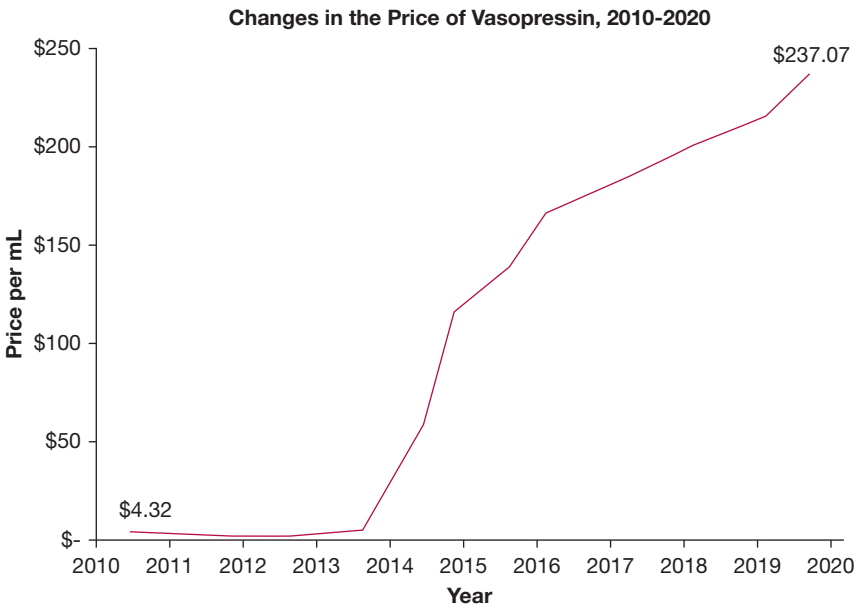
Figure 1 – *Changes in the price of vasopressin.*



Simply by obtaining these patents and listing them with the FDA, Par Pharmaceutical was eligible for 30 months of exclusivity under the Hatch-Waxman Act while generic challenges were underway. Most recently, Par Pharmaceutical obtained two patents based on a pharmacokinetic study completed in April 2021; these data were submitted to the FDA to amend the product's labeling. Par Pharmaceutical also filed at least one citizen petition to oppose the approval of generics. In December 2021, the FDA rejected the company's petition, referring Par Pharmaceutical's activities to the Federal Trade Commission for possible anticompetitive behavior.

Compounding the Problem

When other companies sought to sell compounded versions of vasopressin that could be reconstituted by local pharmacies, Par Pharmaceutical fought to block these efforts. In January 2017, the FDA proposed allowing compounding of vasopressin because of "clinical need." After Par Pharmaceutical sued the agency in response, however, the FDA reconsidered and determined that such a need did not exist.[4] A company interested in compounding the drug, Athenex Pharma Solutions, then sued the FDA. A judge upheld the agency's determination in 2019, disallowing the compounding of vasopressin and protecting Par Pharmaceutical's market exclusivity.[4]

Market Exclusivity Ends

Despite Par Pharmaceutical's efforts to further delay competition, in September 2021 a federal court ruled that Eagle Pharmaceuticals' generic version of vasopressin would not infringe on Par Pharmaceutical's patents. The FDA approved Eagle's abbreviated new drug application in December 2021, ending Par Pharmaceutical's market exclusivity. American Regent launched a second competitor in February 2022.

Par Pharmaceutical's 8-year control over the vasopressin market coincided with the COVID-19 crisis, when demand for vasopressin and other medications for patients with critical illness with COVID-19 spiked.[5] Vasopressin cost US hospitals nearly $600 million in 2020,[1] and rising prices caused some hospitals to implement barriers to patient access. Despite the sudden rise in cost, however, use of vasopressin to treat patients with critical illness continued to climb.[6]

Fixing the Unapproved Drugs Initiative

The 8-year market exclusivity period and high prices for vasopressin are the latest example of problematic collateral effects of the UDI's implementation. The UDI has decreased competition, increased prices, and led to shortages for numerous drugs that were approved under the program, including the antigout drug colchicine.[2,5] Among 21 UDI-approved drugs, 52% had $\geq$ 3 years of exclusivity, and prices typically remained elevated after 5 years.[5] The current structure of the UDI provides excessive rewards for minor manufacturer investments, generates unnecessary health care costs, and compromises access to needed medicines.

Policymakers should mitigate these harms and devise alternative plans to handle remaining unapproved drugs. One strategy would be for the FDA or other public health agencies (eg, the National Institutes of Health) to fund evidence reviews and, if needed, clinical trials to evaluate the safety and effectiveness of remaining unapproved drugs, which could be used to support approval of all versions and avoid disrupting competition. This could be modeled after the FDA's Orphan Products Grants Program, an initiative that supports rare diseases research. Beyond supporting the minimum safety and effectiveness standards needed for FDA approval, this approach could incentivize clinically useful comparative effectiveness studies, such as comparing vasopressin with other classes of vasopressors.

Additionally, manufacturers of drugs that are approved under the UDI should not be able to list patents with the FDA without making a clear demonstration that the patent covers a product formulation that offers added clinical benefit, because these products' active ingredients and other properties are typically decades old. The US Patent and Trademark Office should also be more judicious in awarding patents for these products.

Market exclusivity may no longer be an effective means to encourage voluntary data submission, because $>$ 80% of the 134 unapproved drugs marketed in 2020 were made by one or two manufacturers.[7] More tailored methods of encouraging manufacturers of unapproved drugs to undergo formal reviews include waiving user fees for new drug applications or providing additional tax breaks for research or manufacturing upgrades.

The FDA needs to reform the Unapproved Drugs Initiative to protect patients and the health system from the dangerous collateral effects of undue market exclusivity periods. High costs and limited access should not be the price patients have to pay to ensure that decades-old unapproved drugs are brought under the FDA's regulatory umbrella.

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