doing our patients a disservice. In focus groups related to his research, he's found that patients are far more open than the medical community is to questioning ethical boundaries. "The idea that we as physicians have the moral imperative to make these decisions on our own is an outdated idea," Montgomery told me.

In Canada, some patients are already taking part in such decisions. When Ms. J., a 46-year-old Canadian nurse with ALS, elected to proceed with MAID and organ donation last July, the prospect that even in death she could give back to others gave her a sense of control and solace, says her husband, Mr. J. Before she died, Ms. J., who directed one of her kidneys to a friend, was given a little information about the other people in whom her organs would live on. Mr. J. believes that this knowledge allowed her to focus on something positive going into the MAID procedure, and he says it eased his grief after she died. "It's not as if she's gone and that's it," Mr. J. said. "We know someone else's life is being made better." Ms. J. chose to die knowing that, too.

An audio interview with Dr. Joshua Mezrich is available at NEJM.org

Disclosure forms provided by the author are available at NEJM.org.

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Abuses of FDA Regulatory Procedures — The Case of Suboxone

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Only about 20% of the more than 2 million Americans with an opioid use disorder (OUD) receive treatment in a given year, much of which is not evidence-based.[1] Buprenorphine, one of several medications used to treat OUD, substantially reduces the risk of overdose and can be delivered in office-based settings.[2,3] Various barriers impede widespread access to buprenorphine, however, including federal requirements that clinicians obtain a waiver to prescribe it.[3] In addition, high prices for brand-name buprenorphine formulations strain the budgets of public programs, which cover a disproportionately large share of people with OUD. In 2017, Medicare and Medicaid were responsible for 32% of the $2.58 billion in prescription buprenorphine sales. The bulk of these sales was for Suboxone, a patent-protected buprenorphine–naloxone sublingual film made by Reckitt Benckiser Pharmaceuticals (now separated from its former parent company and known as Indivior).

In the profitable buprenorphine market, Reckitt Benckiser exploited various Food and Drug Administration (FDA) regulatory procedures to impede entry of generic competitors and maintain elevated prices. By securing potentially undeserved orphan-drug status for its buprenorphine products, manipulating the availability of such products, filing questionable citizen petitions, and engaging in abuses of the FDA Risk Evaluation and Mitigation Strategy (REMS) plan to attenuate safety risks associated with buprenorphine products, the company earned at least $1 billion in extra profits.[4] These actions contributed to a recent $1.4 billion settlement between Reckitt Benckiser's former parent company and the federal government. Indivior continues to be the subject of related criminal allegations.

Although combination buprenorphine–naloxone products have a favorable safety profile and are critical for treating OUD,[3] the Suboxone tale is alarming. First, by arguing that its Subutex (buprenorphine) and Suboxone (buprenorphine–naloxone) tablets wouldn't recoup their costs of development, Reckitt Benckiser secured an orphan-drug designation from the FDA and 7 years of marketing exclusivity for these products.[5] Indivior leveraged this designation when seeking approval for its injectable buprenorphine product Sublocade in 2017. Responding to pressure from generics manufacturers, the FDA ulti-

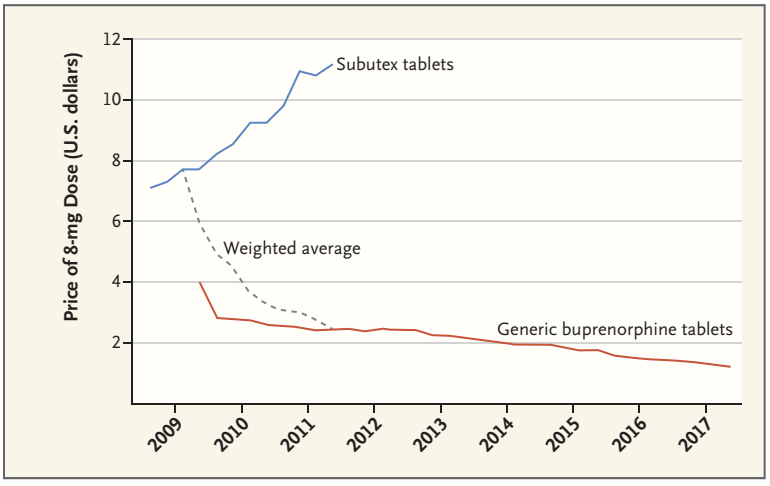
mately revoked buprenorphine's orphan-drug designation owing to the substantial profits generated by these products.[5]

Second, with expiration of exclusivity status for Subutex and Suboxone tablets approaching, Reckitt Benckiser took steps in 2009 to block market entry of generic versions. The company "product hopped" from its tablet formulations to its new Suboxone film formulation, introduced in 2010. This move involved raising prices on tablets and then removing Subutex tablets from the market — making it impossible for pharmacists to substitute lower-priced generic buprenorphine-only tablets, as is otherwise permitted or required by state laws.

The company also filed a "sham" citizen petition to formally request that the FDA take administrative action against manufacturers of generic buprenorphine tablets. Members of the public can file citizen petitions requesting that the FDA take certain regulatory action. Reckitt Benckiser's petition claimed that tablet buprenorphine formulations packaged in bottles posed a greater risk of overdose for children than Suboxone films sold in unit-dose, child-resistant packaging. The FDA ultimately denied this petition, finding that the REMS program for buprenorphine products adequately mitigated harms to children, and referred the petition to the Federal Trade Commission as an anticompetitive action. Then, Reckitt Benckiser refused to cooperate with prospective generics manufacturers in developing a single shared REMS plan for combined buprenorphine–naloxone tablets.[4] Generics manufacturers were therefore compelled to apply for a waiver to have their own REMS plan to facilitate marketing approval. These actions extended Reckitt Benckiser's dominance of the buprenorphine market.

Reckitt Benckiser subsequently engaged in further regulatory manipulation to extend its market exclusivity. In 2012, the company announced its intention to remove Suboxone tablets from the market. Its sister company, MonoSol Rx, filed a second citizen petition asking the FDA to reject any application for generic versions of buprenorphine–naloxone film that didn't "reference" Suboxone film's drug application (thereby requiring generics to have evidence of bioequivalence to Suboxone film). In 2016, attorneys general in 36 states sued Reckitt Benckiser for violating antitrust laws by illegally product hopping to extend its Suboxone monopoly. The lawsuit was dismissed in late 2018, largely because the court couldn't find Indivior responsible for actions taken when Reckitt Benckiser was under a different parent company. In 2019, federal prosecutors in Virginia filed criminal charges against Indivior for fraud and conspiracy related to its claims that Suboxone film is safer and less prone to abuse than generic versions.

The example of Subutex tablets can be used to estimate potential savings that would result from introducing generics into the Suboxone film market. Subutex tablets were first subject to generic competition in late 2009 and were removed from the market in 2011 (see graph). Within a year after a generic buprenorphine tablet entered the market, its price was estimated to be 37% lower than the price of Subutex at the



Prices for Subutex and Generic Buprenorphine and the Product Average.

Data are from the IQVIA transactional data warehouse of buprenorphine sales by product for 2009 to 2017. The Subutex price was calculated by taking the dollar volume of sales in each quarter and dividing it by the quantity of sales expressed in 8-mg–equivalent tablets sold in each quarter. A similar calculation was made for generic buprenorphine tablets in each quarter. The dashed line representing the weighted average is the volume-weighted average price for the period when both products were on the market. We then conducted a regression analysis of the effect of the loss of exclusivity on the price of buprenorphine tablets that includes both the Subutex and the generic prices. The regression models estimated demonstrate a price reduction of roughly 37% attributable to generic competition.

time the generic was launched. So the introduction of a generic buprenorphine–naloxone film in 2017 to compete with Suboxone film, which garnered $1.90 billion in sales that year, might have saved approximately $703 million overall and $203 million for Medicaid alone.

Suboxone provides just one example of the kinds of abuses that are common in prescription-drug markets.[4] Congress could modify regulatory procedures to directly address these problems. The recent passage of the CREATES Act represents one meaningful step toward curbing abuse, but it is not sufficient. This law empowers generics developers to sue a patent holder that fails to provide sufficient quantities of the brand-name product on reasonable terms to allow them to conduct bioequivalence testing, and clarifies that providing such samples doesn't violate REMS requirements. It also establishes a separate REMS-approval process for companies that file generic-drug applications to avoid delays caused by negotiations with brand-name manufacturers over a shared REMS plan.

Congress could also reform the Orphan Drug Act to prohibit "grandfathering" of orphan drugs and require the FDA to base qualifying economic-recoupment determinations for orphan drugs on unbiased sales projections and to revoke designations if revenues exceed projected sales. To the FDA's credit, it intends soon to carefully review and possibly revoke the orphan designation for combination buprenorphine–naloxone, after previously revoking buprenorphine's orphan designation.[5]

To address product hopping, we suggest that Congress modernize the Hatch–Waxman Act, which provides the framework for FDA regulation of generic-drug entry and for extensions of market exclusivity that are granted when products are reformulated. For example, legislation could define a period before the loss of product exclusivity (e.g., 1 year) and a similar period after generic entry during which new formulations of the existing product wouldn't be granted market exclusivity. This policy would have reduced Reckitt Benckiser's incentive to introduce Suboxone film shortly before the exclusivity for its tablets expired.

Finally, Congress could further modify filing procedures for citizen petitions. Modifications could include empowering the FDA to penalize sham filings under an objective standard, rather than having to refer these cases to the Federal Trade Commission; requiring that petitions be filed within a year after a generics manufacturer files a new drug application, which would reduce the number of petitions filed just before a generic is eligible for approval; prohibiting companies from marketing products they have questioned in a citizen petition; and lowering the statutory threshold required for the FDA to summarily deny citizen petitions filed for the purpose of delaying entry of generic competitors. These steps would have deterred Reckitt Benckiser from filing its initial citizen petition shortly before the exclusivity for its tablet formulations expired and from questioning the safety of products akin to its own. They might also have empowered the FDA to deny Reckitt Benckiser's petitions more rapidly. Although these policy actions alone wouldn't completely solve the problem of high drug prices and other access barriers, they could contribute meaningfully toward making generic versions of lifesavings drugs more quickly available at affordable prices.

Disclosure forms provided by the authors are available at NEJM.org.

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