Examples of Drugs with Black-Box Warnings (BBW) Added after Generic Versions Entered the Market. *

Drug	Year of Approval	BBW Content	Time between Approval and BBW	Major Events Contributing to Decision to Add BBW
			yr	
Promethazine†	1956	Severe tissue injury, gangrene	53	Litigation
Indomethacin	1965	Death from cardiovascular causes	40	Results from randomized trials of cyclooxygenase-2 inhibitors
Haloperidol	1967	Increased mortality among elderly patients with dementia-related psychosis	41	Canadian and U.S. government-sponsored observational studies
Droperidol	1970	QT-segment prolongation, torsades de pointes	31	Accumulated spontaneous reports
Disopyramide	1977	Increased mortality with class IC antiarrhythmics	19	Results from NIH-funded trial of other antiarrhythmics
Metoclopramide	1980	Tardive dyskinesia	29	Litigation
Fluoxetine	1987	Suicidality in children and adolescents	17	Litigation that revealed suppressed clinical-trial findings

* NIH denotes National Institutes of Health.
† The warning applies to the injectable form of promethazine only.

by approved drugs is funded by the manufacturers — a situation that can lead to problems with the collection, analysis, and reporting of safety data.[4] Finally, this alternative approach would be in keeping with a stronger, better-managed role for the FDA in monitoring drug side effects.

A similar approach could also be used to create a fund for compensating patients injured by adverse events that are recognized only after a brand-name drug has lost its market exclusivity. Such a system could be structured like the one for vaccine-related injuries: to ensure a continued vaccine supply in the face of the liability exposure of vaccine manufacturers, Congress in 1986 created a no-fault system in which injured parties received compensation from a fund created by levying a small fee on each dose of vaccine administered. In the case of generic drugs, patients could qualify for similar compensation by demonstrating that they had been harmed by a generic-drug side effect that was not properly addressed in the label. Generics manufacturers that joined the program would bear additional liability only if their labels did not match the consensus version.[5]

It is unfair to patients injured by unanticipated adverse drug effects for their right to reparations to depend on whether they received a brand-name or generic version of the same medication, a choice that may have been entirely out of their control. The existing *Pliva* decision also removes incentives for generic-drug companies to perform pharmacovigilance and monitor late-emerging safety risks related to the products they make. Consideration of how questions of liability for generic drugs came to shape the industry — and our ability to think of drugs as generically interchangeable at all — can help us better achieve a low-cost, high-quality generic drug supply without suspending responsibility for studying and documenting drug safety and protecting patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMp1208781

A Shift on "Pay for Delay" — Reopening Doors for Pharmaceutical Competition?

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In 1989, the pharmaceutical company Schering-Plough patented the controlled-release coating on a sustained-release potassium chloride tablet called K-Dur. In 1995, Upsher-Smith, a generic-drug manufacturer, sought approval from the Food and Drug Administration (FDA) to market a

generic version of the tablet, claiming that its product would not infringe Schering's patent because of differences in the coating's chemical composition. A second generics manufacturer, ESI Lederle, made a similar filing with the FDA later that year. In response, Schering filed infringement lawsuits against both generics firms, and both lawsuits were settled out of court. In its settlement, Upsher agreed not to market its product until September 1, 2001, and to grant Schering licenses to market several other Upsher products. Schering paid Upsher more than $60 million. ESI agreed not to market its product until January 1, 2004, and received $15 million from Schering.[1]

In July 2012, however, both agreements were called into question by the U.S. Court of Appeals for the Third Circuit, which broke with other recent court decisions by presuming that "pay-for-delay" agreements — whereby brand-name pharmaceutical companies pay generics manufacturers to delay marketing their generic versions of drugs ("reverse payments") — are anticompetitive. Other circuit courts had deemed these deals legal, as long as generics manufacturers were not paid to refrain from marketing a drug after the brand-name manufacturer's patents expired.

Pay-for-delay agreements arise in the context of the 1984 Hatch–Waxman Act, which created a truncated approval process for generic drugs. To market a drug in the United States, a manufacturer must file a New Drug Application with the FDA, which includes data on safety and efficacy. Hatch–Waxman allows generics manufacturers to instead file an Abbreviated New Drug Application (ANDA), which relies on the safety and efficacy data submitted by the brand-name manufacturer.

As part of its ANDA, a generics manufacturer must certify that its marketing of a drug does not infringe any lawful patent; if a relevant patent exists, the applicant asserts either that it's invalid or that it will not be infringed by the generic product — and in such a case must inform all patent holders of its claims. Patent holders then have the opportunity to sue the generics manufacturer for infringement.

In some cases, patent holders who want neither to sacrifice market exclusivity nor to engage in expensive litigation offer to pay challengers to delay marketing a competing product until at least part of the patent period has elapsed. These agreements, however, raise concerns under the Sherman Antitrust Act, which prohibits intercompany agreements that unreasonably interfere with competition. Typically, a payment to induce a competitor to refrain from entering a particular market clearly violates the Sherman Act. But payments by patent holders present a thornier question, since patents give their holders rights to exclusively market the patented products.

The first two courts that considered pay-for-delay agreements were dubious of their legality. In 2001 and 2003, respectively, the D.C. and Sixth Circuit Courts of Appeals considered an agreement by pharmaceutical company Hoechst Marion Roussel (HMR) to pay generics manufacturer Andrx Pharmaceuticals $40 million per year from the time Andrx's generic version of the calcium-channel blocker Cardizem (diltiazem) received FDA approval until Andrx began marketing its product or was found liable for patent infringement.[2,3] Because another Hatch–Waxman provision gave Andrx (the first generics manufacturer to file an ANDA for diltiazem) a 180-day window of exclusivity from the time it received FDA approval, the agreement temporarily eliminated all HMR's competition. Both circuit courts viewed this agreement as an illegitimate attempt to preserve monopolistic conditions.

But subsequent courts took a different view, focusing on patent holders' right to exclude competitors from the market. According to rulings that the Eleventh, Second, and Federal Circuit Courts issued in 2003 to 2008, patent holders could make agreements with prospective competitors to get them to refrain from competing, because patents confer the right to stop competitors from marketing the products to which the patents apply. This conclusion meant that pay-for-delay agreements were not subject to antitrust scrutiny, so long as the delay didn't extend beyond the patent-protection period.

The Second Circuit recognized that patent holders with the least-sound patents might benefit the most from its ruling, because they would retain patents that courts would otherwise invalidate.[4] The availability of pay-for-delay agreements, however, encouraged settlement, and the court was willing to accept the retention of some weak patents in the interest of judicial economy.

In considering the K-Dur agreement, the Third Circuit returned to the earlier judicial skepticism regarding such arrangements. The Eleventh Circuit had already considered a Federal Trade Commission (FTC) challenge to the K-Dur

agreement and found it legal.[5] The Third Circuit disagreed, arguing that these agreements should be presumed to be anticompetitive unless there was evidence that their purpose was not anticompetitive or that they had procompetitive effects.[1]

The court noted that Congress intended Hatch–Waxman to increase competition between brand-name and generics manufacturers in order to lower drug prices for consumers. Though Hatch–Waxman is silent on the legality of pay-for-delay agreements, allowing these agreements frustrates the Act's central procompetitive purpose, since challenges settled in that way simply divide monopoly profits between patent holders and their potential competitors. Consumers continue to pay higher prices because they're still forced to buy only from the patent holder, so the agreements have the anticompetitive effect of protecting monopoly pricing.

The FTC filed for Supreme Court review of the Eleventh Circuit Court case in which the K-Dur agreement was deemed acceptable. The FTC's petition was opposed by the solicitor general because the circuit courts had agreed on the legality of pay-for-delay. The fact that the Third Circuit has now disagreed makes it more likely that the agreements' status will ultimately be decided by the Supreme Court. Indeed, the solicitor general reversed position in October, filing a brief (regarding a different case) asking the Supreme Court to restrict pay-for-delay agreements.

More immediately, the Third Circuit's decision casts a shadow of uncertainty on the legality of pay for delay. By extending the reasoning used in cases dealing with the exploitation of Hatch–Waxman's 180-day exclusivity window — wherein courts emphasized that patent holders' attempts to pay competitors to preserve monopolistic conditions may violate antitrust laws — in order to invalidate pay-for-delay agreements generally, the court substantially broadened the scope of concern about their use. Pharmaceutical companies headquartered in Pennsylvania, Delaware, and New Jersey, all covered by the Third Circuit, are already limited by the court's decision.

As courts appeared increasingly friendly to pay-for-delay agreements, their use increased. In 2005, only 3 settlement agreements included reverse payments; by 2008, there were 19, according to the FTC. The Third Circuit decision may dampen enthusiasm for pay-for-delay arrangements even outside the court's official geographic domain, diminishing the incentives for both patent holders and generics companies to settle these disputes. Patent disputes may be more likely to proceed to court, and generics may reach the market faster, which would result in lower prices and potentially reduce the annual cost to consumers of pay-for-delay agreements — a figure that the FTC currently estimates at $3.5 billion. On the flip side, this limitation on settlement options may drive up litigation costs, which may be passed on to consumers.

Either way, the Third Circuit decision provides a weighty counterbalance to others, offering an analysis that emphasizes the anticompetitive effects of pay-for-delay agreements over both the rights of patent holders to exclude competitors by any means they choose and the judicial interest in promoting settlement. It may well affect the relationship between generic and brand-name pharmaceutical manufacturers, the degree of competition in the pharmaceutical market, and the prices we pay for drugs.

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From Patton Boggs, Washington, DC.

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4. *In re Tamoxifen Citrate Antitrust Litig.,* 466 F.3d.
5. *Schering-Plough Corp. v. FTC,* 402 F.3d 1056 (11th Cir. 2005).

DOI: 10.1056/NEJMp1209693

Growing Pains for the Medicare Hospice Benefit

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For 30 years, the Medicare hospice benefit has played a key role in shaping end-of-life care in the United States. Authorized by the Tax Equity and Fiscal Responsibility Act of 1982, the benefit was meant to improve the dying experience for terminally ill beneficiaries and to reduce the inten-