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Risk, responsibility, and generic drugs

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In 2011, the Supreme Court reviewed PLIVA v. Mensing, a consolidation of two cases in which patients sued manufacturers of the drug metoclopramide for failing to properly warn about the risk of tardive dyskinesia with its long-term use. A few years before, the Court had ruled that brand-name drug manufacturers had a duty to update their labels as new safety information became available, even without formal approval from the Food and Drug Administration (FDA). However, in PLIVA the drug was a generic, and the Court found that it was “impossible” to hold generic manufacturers liable in state court for not individually updating their labels to integrate new warning information.¹ The Court's rationale was that these state-imposed requirements were preempted by federal statutory language directing generic manufacturers to maintain labels identical to their brand-name counterparts (brand-name manufacturers operated under no such mandate).

Justice Clarence Thomas, for the 5-to-4 majority, wrote that this outcome could eliminate a legal option for patients who were harmed by a generic drug. As predicted, following the PLIVA ruling, dozens of failure-to-warn cases against generic drug manufacturers were dismissed.² In response, a bipartisan group of congressmen introduced legislation seeking to make generic manufacturers liable for not updating their label, similar to brand-name companies. The legislation remains under consideration at both the House and Senate.

Liability issues surrounding generic drugs have been a point of controversy in the US since the emergence of a generic drug industry in the 1960s. The earliest threats of generic liability were felt most keenly by pharmacists, not manufacturers. The act of substituting drugs made by different manufacturers violated pharmacy codes of ethics and was explicitly illegal in most states. Yet to market a drug as generic was to market it as substitutable—a process that raised questions about the liability of the pharmacist in cases of injury from a medication selected not by physician but by the dispensing druggist.

As a result, even when most states reversed course and passed laws in the 1970s and 1980s that permitted substitution, pharmacists generally chose not to fill prescriptions with generic drugs unless specifically mandated by law. In response, some generic manufacturers offered liability insurance programs to pharmacists (see Figure). Generic manufacturers taking on

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such responsibility were incentivized to ensure that the warnings on their labels remained up-to-date.

The Hatch-Waxman Act of 1984, however, changed the calculus by permitting generic drugs to be approved on the basis of having the same active ingredient and to be sold under the same labeling information as the brand-name drug. Hatch-Waxman's abbreviated new drug application process tethered generics' claims of efficacy, safety, and harm to those described on the original label. As a result, the original manufacturer became the steward of the public warnings for a growing family of bioequivalent drugs. However, after a generic is introduced, the brand-name producer may stop manufacturing its product, leaving a gap in responsibility for labeling. Even if production continues, the brand-name manufacturer will drastically reduce the resources committed to that product, including support of safety assessments.

This dispersion of label responsibility weakens the development and reporting of new risk issues that may surface after generic versions reach the market. While black box safety warnings are routinely added to drugs after their approval,³ for a number of drugs—including metoclopramide—these warnings were related to data on adverse effects that came to light only after these drugs faced generic competition (see Table). In many cases, the safety information did not emerge due to vigilance by the manufacturer or the FDA, but out of evolving litigation, publicly funded research, or studies of competing products.

However, current legislative proposals to impose liability directly on generic manufacturers disregard the special position they now hold in the pharmaceutical marketplace. While some generic companies are sophisticated multinational firms, few are presently equipped to conduct rigorous post-market safety evaluations. The numerous generic manufacturers that now enter the marketplace after patent expiration—a direct result of the Hatch-Waxman Act—also complicate the aggregation of adverse event reports on which potential label changes would be based. Therefore, imposing vague liability and post-marketing surveillance responsibilities on individual generic manufacturers may be ineffective in generating knowledge about drug safety and could make these products more expensive. This creates a Catch-22: direct liability of generic producers would result in increased prices, potentially reducing the cost-savings to patients and payors that form the rationale for encouraging generic substitution in the first place.

A better solution would address both the need for low-cost generic drug producers after brand-name patent expiration as well as the need to maintain vigilance for late-arising safety issues. First, it would be useful to create a central repository that could study late-arising side effects and assess the need for prescription drug label changes. This function could be based in the FDA, the Patient-Centered Outcomes Research Institute, or other organizations with pharmacoepidemiology expertise. The goal would be to conduct more active oversight of generic drug safety by assessing pooled adverse event reports and then engaging additional primary research as needed. FDA would be responsible for overseeing the integration of new findings into a centrally-written consensus label. With generic drugs now making up over 75% of prescriptions, imposing even a minimal fee on each prescription would provide an important investment in pharmacovigilance for late-arising safety issues,

and the cost of systematic safety surveillance with modern pharmacoepidemiologic approaches using large electronic databases is not great. It would also be a more sensible alternative to the current situation in which so much research on risks of approved drugs is funded by the manufacturers, which can lead to problematic collection, analysis, and reporting of safety data.⁴ Finally, this approach would be in keeping with a stronger, better managed role for FDA in monitoring drug side effects, as manifested by its increasingly important Sentinel system of proactive safety surveillance.

A similar approach could also be used to pool funds to compensate patients injured by adverse events emerging after a drug lost its market exclusivity. Such a system could be structured like the vaccine market. To ensure a continued vaccine supply in the face of liability exposure of vaccine manufacturers, Congress in 1986 created a no-fault compensation system paid out of taxes levied on each dose of vaccine. Patients could qualify for the generic compensation program by demonstrating that they were harmed by a side effect from a generic drug that was not properly addressed in the label. Generic manufacturers that joined the program would bear additional liability only if their labels did not match the consensus version.⁵

At present, it is clearly unfair to injured patients that their rights to reparations can vary based on whether they received a brand-name or generic version of the same drug, a choice that may have been fully out of their control. Left unchecked, the PLIVA decision also reduces incentives for generic companies to perform pharmacovigilance and monitor late-emerging safety risks related to the products they sell. Consideration of how questions of generic liability 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 to monitor and document drug safety and protect patients.

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References

1. Glantz LH, Annas GJ. Impossible? Outlawing state safety laws for generic drugs. *New England Journal of Medicine*. 2011; 365(8):681–683. [PubMed: 21830958]
2. Thomas, K. *NY Times*. Mar 20. 2012 Generic drugs proving resistant to damage suits.
3. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new Black Box Warnings and withdrawals for prescription medications. *JAMA*. 2002; 287(17):2215–2220. [PubMed: 11980521]
4. Madigan D, Sigelman DW, Mayer JW, Furberg CD, Avorn J. Underreporting of cardiovascular events in the rofecoxib Alzheimer disease studies. *American Heart Journal*. (in press). 10.1016/j.ahj.2012.05.002
5. Lacayo, IC. Plaintiffs get around Mensing with failure-to-update drug label claims. *Product Liability Monitor*. Mar 15. 2012 Available at: <http://product-liability.weil.com/mass-tort/plaintiffs-get-around-mensing-with-failure-to-update-drug-label-claims/#ixzz217tGLcAo>

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CHAIN STORE ADD/DRUG EDITION, SEPTEMBER 1978

Figure.

Early promotion of liability coverage offered by generic manufacturers

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Table 1

Table Examples of drugs with Black Box Warnings (BBW) added during generic period

Drug name	Drug approval year	BBW content	Latency between approval and BBW (yrs)	Major events contributing to decision to add BBW
Promethazine	1955	Severe tissue injury, gangrene	54	Litigation
Indomethacin	1965	Cardiovascular mortality	40	Results from randomized trials of cyclooxygenase-2 inhibitors
Haloperidol	1967	Increased mortality in elderly patients with dementia-related psychosis	41	Canadian and US government- sponsored observational studies
Droperidol	1970	QT 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	1985	Tardive dyskinesia	24	Litigation
Fluoxetine	1987	Suicidality in children and adolescents	17	Litigation that revealed suppressed clinical trial findings