

screening, but the magnitude of overdiagnosis in the NLST (with a scan at baseline and annually for 2 additional years) doesn't appear to be large³ and is probably less than that with mammography and substantially less than that with prostate-specific antigen screening.

Finally, the guide emphasizes the most important message for smokers: not smoking is the best way to reduce your overall risk of dying prematurely and your risk of dying from smoking-related diseases.

In issuing this guide, the NCI aims to help shift communication about screening toward approaches grounded in information rather than persuasion. It does so at a time when a new screening test for lung cancer is being introduced into clinical practice and

a multisociety collaborative (including the American Cancer Society and the American College of Chest Physicians) has issued new clinical recommendations.

We hope that similar data summaries will be developed for other tests and interventions. The intent should be neither to persuade people to undergo screening nor to dissuade them from doing so, but to increase the awareness of screening's benefits and harms so as to encourage informed personal decisions.

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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 the manufacturers of metoclopramide for failing to properly warn physicians and patients about the risk of tardive dyskinesia caused by 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 version, and the Court found that it was "impossible" to hold generics manufacturers liable in state court for not updating their labels to integrate new warning information.¹ The Court's rationale was that these requirements were preempted by

legal requirements that generics manufacturers maintain labels identical to those of their brand-name counterparts.

Justice Clarence Thomas, writing for the five-to-four majority, noted that this decision could eliminate legal recourse for patients who were harmed by a generic drug. As predicted, after the *Pliva* ruling, dozens of failure-to-warn cases against generic-drug manufacturers were dismissed.² In response, a bipartisan group of lawmakers introduced legislation seeking to make generics manufacturers responsible for updating their labels just as brand-name drug companies are. The legislation remains under consideration in both the House and the Senate.

Liability issues surrounding generic drugs have been a point

of controversy in the United States since the emergence of a generic-drug industry in the 1960s. The earliest threats of liability for generic drugs were felt most keenly by pharmacists, not manufacturers. Initially, substituting drugs made by different manufacturers violated pharmacy codes of ethics and was explicitly illegal in most states. Yet to market a drug as a generic was to market it as substitutable — a fact that raised questions about the liability of the pharmacist in cases of injury from a medication that was selected not by a 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 a generic drug



Early Promotion of Liability Coverage Offered by Generic-Drug Manufacturers.

Advertisement by Lederle Standard Products, American Druggist, 1978.

unless they were specifically mandated by law to do so. In response, some generic-drug manufacturers offered liability insurance programs to pharmacists (see advertisement). The liability risk gave the manufacturers taking on such responsibility an incentive to ensure that the warnings on their labels remained up to date.

The Hatch–Waxman Act of 1984 changed this calculus. The statute permitted approval of generic drugs if they had the same active ingredient as the brand-name drug; they could then be sold using the same labeling information. Hatch–Waxman’s Abbreviated New Drug Application process linked generics’ claims of efficacy, safety, and harm to those in the label of the brand-name drug. As a result, the original manufacturer became the steward of the public warnings for a growing family of bioequivalent drugs. But after a generic drug is introduced, the producer of the brand-name version may stop manufacturing it, leaving a gap in responsibility for such labeling. Even if production continues, the brand-name manufacturer usually sharply reduces the resources committed to that product, including support of ongoing safety assessments. Al-

though some generic-drug firms have grown into sophisticated multinational corporations, few routinely conduct rigorous postmarketing safety evaluations. The growing number of generics manufacturers that now enter the marketplace after patent expiration — a direct result of the Hatch–Waxman Act — complicates the aggregation of adverse-event reports on which potential label changes would be based.

This dispersion of responsibility weakens the ability to define and report new potential risks that may surface after generic versions reach the market. Although black-box safety warnings are routinely added to drug labels after approval,³ they have occasionally been based on adverse-effects data that come to light only after there is generic competition, as was the case with metoclopramide (see table). In many cases, such safety information did not emerge because of vigilance by the manufacturer or the FDA, but owing to evolving litigation, publicly funded research, or studies of competing products.

Current legislative proposals to impose liability directly on generics manufacturers for discovering and reporting new adverse effects are unlikely to solve the

problem, and such an approach disregards the special position that generics hold in the pharmaceutical marketplace. Imposing vague liability and postmarketing surveillance responsibilities on large numbers of generic-drug manufacturers, many of them small companies that are ill-prepared to undertake such surveillance, may be ineffective in generating sufficient knowledge about drug safety and could make these products more expensive, creating a Catch-22.

A better solution would ensure vigilance for late-arising safety issues. A central repository of information on adverse drug events could be used to study late-arising side effects and to assess the need for changes to drug labels. This repository could be based at the FDA and managed by its Sentinel program, the Patient-Centered Outcomes Research Institute, or another organization with pharmacoepidemiology expertise. Such a database would make it possible to conduct more active oversight of the safety of generic drugs by assessing pooled adverse-event reports, which would lead to additional primary research as needed. The FDA would be responsible for overseeing the integration of new findings into a centrally written consensus label. With generic drugs now accounting for more than 75% of U.S. prescriptions, imposing even a minimal fee on each prescription would provide the revenue for an important investment in pharmacovigilance for late-arising safety issues. (The cost of systematic safety surveillance using modern pharmacoepidemiologic approaches and large electronic databases is modest.) It would also be more sensible than the current approach, in which so much research on the risks posed

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 yr	Major Events Contributing to Decision to Add BBW
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 com-

penensation 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.

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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