



# PRODUCT SAFETY & LIABILITY



## REPORTER

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### Metoclopramide

#### **Supreme Court Takes Up Preemption Again, This Time in Generic Drug Labeling Dispute**

**F**ollowing preemption decisions in medical device, brand-name drug, and vaccine cases, the U.S. Supreme Court is now poised to determine the viability of failure-to-warn claims against makers of generic drugs, whose products account for the overwhelming majority of prescriptions filled in the United States (*Pliva Inc. v. Mensing*, U.S., No. 09-993, *brief filed 2/24/11*; *Actavis Elizabeth LLC v. Mensing*, U.S., No. 09-1039, *brief filed 2/24/11*; *Actavis Inc. v. Demahy*, U.S., No. 09-1501, *brief filed 2/24/11*).

Oral argument is scheduled for March 30.

On its own, the case is significant in part because of the sheer number of people who use generic drugs. Together with other preemption-related activity on the Supreme Court this term, the case is part of “an extraordinary time for preemption law,” Nicholas Wittner, professor of law at Michigan State University’s College of Law, told BNA in an interview. Wittner teaches product liability law and is an expert on preemption in product liability cases.

Already this term, the court decided *Williamson v. Mazda Motor of America Inc.*, an auto preemption case (39 PSLR 210, 2/28/11), ordered a state court to revisit a pro-preemption ruling in *Priester v. Ford Motor Co.* (39 PSLR 238, 3/7/11), involving auto glazing, decided the *Bruesewitz v. Wyeth* vaccine case (39 PSLR 212, 2/28/11), denied a petition for review in *McNeil PPC Inc. v. Valdes*, a case involving cold medication (39 PSLR 78, 1/24/11), and has a pending petition for review in *Farina v. Nokia Inc.*, a cell phone radiation preemption case, Wittner said. “Preemption has become an enormous issue on a variety of fronts. The court is paying tremendous attention.”

**Arguments of Parties, Amici.** In the next preemption case set for argument, generic drug manufacturers (petitioners) and their amici argued that distinctions in the law and regulations governing branded versus generic products, particularly a mandate that generic labels be the same as those for their branded counterparts, warrant preemption (39 PSLR 130, 2/7/11). And they contended that they operate on thin margins, and said state tort claims would burden the Food and Drug Administration and impose duties and costs on manufacturers that would undermine the goals of the Hatch-Waxman Amendments, which created an expedited approval process to make generic drugs more affordable (39 PSLR 182, 2/21/11).

But the injured plaintiffs (respondents) and their amici asserted that the impossibility and frustration-of-purpose implied preemption arguments failed against branded drug makers in *Wyeth v. Levine*, 555 U.S. \_\_\_ (2009) (37 PSLR 274, 3/9/09), which rejected preemption of failure-to-warn claims against branded drug makers absent “clear evidence” the FDA would have rejected the proposed label change. The petitioners maintained that neither argument overcomes the pre-sumption against preemption as applied in a generic drug case.

A pro-preemption decision would create a distinction between two classes of plaintiffs: those who used brand-name medication could pursue warning-based claims under *Levine*, while those who used generics would be barred from suing. That distinction would, itself, undermine the “sameness” requirements behind the Hatch-Waxman Amendments, some of the respondents’ amici argued.

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An estimated 70 percent of prescriptions in the United States are filled with generic drugs. The industry is expected to grow at an annual rate of more than 7.8 percent, according to an amicus brief by the American Medical Association and several state medical associations. Generic drugs generate \$60 billion in U.S. sales annually, according to an amicus brief by health care economists.

There are more than 1,000 cases pending in federal and state courts involving metoclopramide, the drug at issue in this case, according to manufacturer Actavis Inc.

**What’s at Stake?** “The question is whether, for the majority of prescriptions filled, consumers would be able to hold manufacturers responsible, and will manufacturers of the majority of drugs used have incentives to keep those drugs safe,” Adina Rosenbaum of Public Citizen told BNA. Public Citizen, together with the American Association of Retired Persons (AARP), submitted an amicus brief supporting respondents Gladys Mensing and Julie Demahy.

Bert W. Rein of Wiley Rein LLP in Washington, D.C., who represented Wyeth Inc. in the *Wyeth v. Levine* case, told BNA this case presents difficult questions. “It’s not easy to sort out the equities,” Rein said. “What’s going to be interesting is, will there be a rethinking of the balance between the need for a uniform label and the people who say the label isn’t good enough under state law?”

The Food, Drug, and Cosmetic Act “wasn’t written with the idea of multiple sellers of the same drug,” Rein said, noting that in *Levine*, the court did not consider a multi-seller situation.

Because new side effects and new information may become apparent years after approval, “The label can’t be a dead letter. There may be reasons to change the label,” Rein said. “The problem is you can’t have eight people changing the label. Managing the post-approval world is very difficult.”

Brian Wolfman, co-director of the Institute of Public Representation at Georgetown University Law Center, expressed concern over the dual system that would emerge from a pro-preemption decision. “If generic manufacturers are right, it ascribes to Congress an intent to have that asymmetry. No rational Congress would derive a system like that. Either both are liable or neither are liable. It’s too jarring to think you’d have a system where we’re trying to encourage generics and we have preemption on one side of the line and not the other.”

**Solicitor General to Participate.** The court has granted the U.S. Solicitor General’s motion to participate in oral argument. In amicus briefs filed in support of the respondents, the government staked a position against

categorical preemption of failure-to-warn claims, but disagreed with the courts below and with the respondents’ regulatory interpretation of how a generic manufacturer may get a drug label changed.

Rosenbaum said she expects the justices will be interested in what the government has to say, especially given the petitioners’ arguments that allowing state tort claims would burden the Food and Drug Administration.

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GEORGETOWN UNIVERSITY LAW CENTER

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The government argued in support of manufacturer Wyeth Inc. in the vaccine case *Bruesewitz v. Wyeth Inc.*, and observers told BNA afterward the court seemed particularly interested in hearing how government agencies handle vaccine research and safety issues.

While declining to predict the outcome of the generic drugs case, Rosenbaum said the court “should” hold there is no preemption here, based on the reasoning of *Wyeth v. Levine*: The court affirmed the presumption against preemption, and held manufacturers responsible for their labeling.

**Stronger Lineup Now Against Preemption?** Wittner offered some perspective, drawing on the recent *Williamson* decision as well as some previous preemption rulings. “Now, there is a stronger lineup against preemption” than there was when the court decided *Geier v. American Honda Motor Co.* (28 PSLR 464, 5/29/00), in which a 5-4 court ruled that conflict preemption principles barred claims that a car should have been equipped with an air bag. Justice Stephen Breyer wrote the majority opinion in *Geier*; retired Justice John Paul Stevens wrote the dissent.

“Now, you have justices who are either unfriendly to [implied] preemption or defer to the Solicitor General,” Wittner said. Justice Clarence Thomas has “antipathy” to frustration-of-purpose preemption, Justice Ruth Bader Ginsburg “rarely finds preemption,” and Justice Sonia M. Sotomayor is “skeptical” toward preemption, Wittner said. “We don’t know for certain” where Justice Elena Kagan stands on preemption, “but briefs filed while she was solicitor general suggest she frowns on implied preemption, and the Solicitor General’s office has been aggressive against preemption.”

Breyer, “who has assumed a prominent role on the court,” deferred to then-Solicitor General Kagan, who filed a brief for the government in support of the *Williamsons*, Wittner noted. Justice Anthony M. Kennedy can be a swing vote, and often votes with Breyer. And, “putting aside *Williamson*, Chief Justice John G. Roberts Jr., and Justices Samuel A. Alito Jr., and Antonin Scalia find preemption,” Wittner said.

Wittner also noted that the Obama administration is against preemption.

In *Wyeth v. Levine*, the vote was 6–3: Stevens wrote the majority opinion, joined by Kennedy, retired Justice David H. Souter, Ginsburg, and Breyer. Thomas concurred separately; critical of implied preemption. Alito authored the dissenting opinion, joined by Roberts and Scalia.

**Fifth, Eighth Circuits Allow Generic Drug Claims.** At issue are decisions from the U.S. Court of Appeals for the Fifth Circuit, *Demahy v. Actavis Inc.* (38 PSLR 40, 1/18/10); and the Eighth Circuit, *Mensing v. Pliva Inc.* (37 PSLR 1232, 12/7/09). First the Eighth Circuit, and then the Fifth Circuit, said federal law does not preempt failure-to-warn suits against generic drug companies.

The suits involve metoclopramide, a generic equivalent to the branded drug Reglan. Plaintiffs Julie Demahy and Gladys Mensing alleged they developed tardive dyskinesia, an involuntary movement disorder, after using metoclopramide for several years to treat gastroesophageal reflux. They claimed the defendants failed to warn about the risks of long-term use. Demahy used metoclopramide manufactured by Actavis Inc.; Mensing took medication made by Pliva Inc., Teva Pharmaceuticals USA Inc., UDL Laboratories Inc., and Actavis.

Both the Fifth and Eighth Circuits said the manufacturer could have effected a warning change, thereby complying with state and federal requirements. The Eighth Circuit said it need not resolve an ongoing dispute over whether generic companies could use the “changes being effected” or CBE provision, allowing a unilateral change, because they could have used other means. The Fifth Circuit said the CBE was permissible.

The Ninth Circuit also recently voiced its view on preemption of failure-to-warn claims involving generic drugs. In a case involving over-the-counter ibuprofen, the court said such claims are allowed (39 PSLR 105, 1/31/11). According to the Ninth Circuit, federal regulations allow generic manufacturers to use the CBE process and the prior approval supplement (PAS) process, and to ask the FDA to send Dear Doctor letters to health care professionals. A generic failure-to-warn case is pending in the Sixth Circuit.

A Supreme Court decision “may clarify some disputed specifics about how the generic scheme works,” Rosenbaum noted. But she said that for this case, the disagreement “doesn’t matter that much. The bottom line is, [the generic drug manufacturers] haven’t shown it was impossible to comply. At the very least, it seems everyone agrees they could have presented information to the FDA to get a label approved.”

Wolfman, who was one of the attorneys representing Diana Levine in the branded drug case that went to the Supreme Court, said “the more fundamental” point of the court’s decision in *Wyeth v. Levine* was not the availability of the CBE, but that “it was the basic obligation of any drug manufacturer to keep its label current, so the label isn’t false or misleading.”

**Amici Support Respondents.** Some 14 amici, including the United States, Rep. Henry Waxman (D-Calif.), law professors, health care economists, medical experts, and the National Council of State Legislatures, filed briefs supporting Demahy and Mensing.

According to the United States, FDA regulations require both branded and generic drug manufacturers alike to act upon new safety information that warrants added or strengthened warnings. Although the manu-

facturers could not use the CBE or PAS process to meet their federal duty, they nonetheless “should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised,” the government’s brief said.

A drug is misbranded under the federal Food, Drug, and Cosmetic Act if “its labeling [does not] bear [] \*\*\* adequate warnings \*\*\* against unsafe dosage or methods or duration of administration or application,” the brief said, citing 21 U.S.C. § 352 (f)(2).

This reflects the premise, noted in *Levine*, that a manufacturer bears responsibility for the content of its label at all times, the United States said. Under 21 C.F.R. § 201.57(e), a prescription drug’s label “shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.”

For preemption purposes, the question is whether the generic drugs that Mensing and Demahy took were misbranded under 21 U.S.C. 352(f)(2) and the standard of 21 C.F.R. 201.57(e). That approach reconciles the Hatch-Waxman Amendments’ “same as” requirement with the FDCA’s misbranding standard and FDA’s implementing regulation and fulfills Congress’ intention that failure-to-warn suits would provide compensation for consumers and motivate manufacturers to provide adequate warnings, the government said.

The cases should be allowed to proceed, according to the government.

**Public Health Issues: NCSL.** The National Conference of State Legislatures, the American Medical Association and several state medical associations, and a group of health care economists described some practical public health ramifications they said would follow a decision finding preemption.

According to the NCSL, the disparate liability schemes that would follow a pro-preemption ruling “would unsettle bedrock assumptions that have guided state law in this field for decades.” All the states have adopted carefully drawn policies on generic drug substitution, “which encourage and often require the dispensing of generic drugs except where the patient has a specific need for the brand drug.”

And generic drugs are required to be dispensed in various public health care programs, the NCSL observed. These policies have been a significant factor in the burgeoning demand for generic drugs, the NCSL said.

Out of candor to their citizens, states might opt to inform the public of the disparity that would follow a pro-preemption ruling, NCSL suggested. But it said a message that “[m]anufacturers of generic drugs cannot be liable for failure to warn of health risks associated with their products” could lead some patients—at least those financially able to do so—“to spurn generic drugs, undermining the policies of the Hatch-Waxman Act and state generic substitution laws alike.”

Moreover, some doctors may be deterred from prescribing generic drugs if they knew they could be on the hook alone if a generic drug caused a patient to suffer injury, NCSL said.

According to the brief, in the absence of any indication that Congress intended such a regime, the manufacturers advance arguments based on *Buckman v. Plaintiffs’ Legal Committee*, 531 U.S. 341 (2001), and

*Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981), to the effect that tort law duties of care are incompatible with the FDA's exercise of its statutory responsibilities.

But the claims here are plain tort claims, based on traditional state-law duties, not the "fraud-on-the-agency" claims at issue in *Buckman*. Moreover, the claims here, unlike the claims at issue in *Buckman* or *ArkLa*, do not entail any sort of collateral attack on the FDA's action or decision, NCLS said.

**Pharmacovigilance Responsibilities.** Addressing drug manufacturers' responsibilities of pharmacovigilance, the American Medical Association, as well as several state medical associations, observed that Canada and European Union countries expressly impose post-marketing risk-management duties on brand-name and generic manufacturers alike.

The statutory framework and case law "supports the notion of an affirmative duty owed by drug manufacturers in the United States—regardless of their position in line—to maintain the accuracy and adequacy of labels for products they sell," their brief urged.

**Later-Emerging Risks.** Several briefs pointed to examples of risks that did not become apparent until drugs had been available as generic products for many years.

These include the diet drug fenfluramine, which was introduced to the U.S. market in 1973 and withdrawn in late 1997, after two scientific articles brought to light significant cardiac and pulmonary side effects; and Terbutaline sulfate, which was approved in the 1970s as an asthma drug, and later evolved into a treatment for pre-term labor in obstetrics patients. As of Feb. 17, 2011, the drug must carry a black box warning because of post-marketing safety reports of heart problems and possible deaths, as well as a lack of data demonstrating effectiveness.

Terbutaline sulfate is only available in generic form; the brand name products have been discontinued by the companies that formerly made them, the medical associations said. Terbutaline, therefore, is a stark example of a drug with "no surveillance oversight" by the brand-name drug maker, the brief noted: For some one-third of all drugs, there is no longer a branded product available, according to the health care economists.

Metoclopramide, the drug at issue here, was first marketed as Reglan in 1979; the drug was available in generic form by the mid-1980s. As new risk information continued to emerge, the FDA ordered significant label changes for safety issues in 2004 and 2009, more than 25 years after its launch, amici said.

Dr. Christy Graves, who prescribed metoclopramide to Julie Demahy, said the actual risk of tardive dyskinesia from long-term use of the drug was at least 100 times higher than it was portrayed in the metoclopramide warnings in effect from 1985 through 2009. "Such information was readily available to generic manufacturers through the FDA's publicly available database of reported adverse drug reactions," Graves said in a brief. "All the generic manufacturers needed to do was monitor the medical literature for articles on their own drug and periodically check the FDA database for new reports relating to metoclopramide."

When the FDA finally considered the evidence of metoclopramide-induced TD in 2008-2009, it acted "decisively and urgently" to add a black box warning,

based on information that had been available for more than a decade, Graves said. "There is little need to speculate regarding the FDA's reaction to that same information had generic manufacturers submitted it earlier in connection with a proposed labeling change."

## Amici Line Up Behind Respondents

Full text of the Constitutional Accountability Center's brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8etnwf>.

Full text of the Graves brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8etnyh>.

Full text of the AAJ brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8etnzw>.

Full text of the Coalition Against Censorship brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8etp9j>.

Full text of the torts' professors brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eulzn>.

Full text of the AMA brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eum5c>.

Full text of the brief by the states is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eum69>.

Full text of the brief by the administrative law and civil procedure scholars is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eum7z>.

Full text of Rep. Henry A. Waxman's brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eum8z>.

Full text of the United States' brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8euma7>.

Full text of the brief by former New England Journal of Medicine editors is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eumcc>.

Full text of the brief by the National Council of State Legislatures is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eumdc>.

Full text of the health care economists' brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eumeh>.

Full text of the Public Justice/AARP brief is available at <http://op.bna.com/pslr.nsf/r?Open=jstg-8eumfe>.

Finally, several amici cited recent news about the analgesic Darvon. Darvon, known generically as propoxyphene, was approved in 1957. In November 2010, the FDA requested that all manufacturers of branded and generic products remove their products from the market after determining the risks of severe cardiac side ef-

fects outweighed the benefits of the drug. In 2007, some 21.3 million prescriptions were filled for the generic combination of propoxyphene and acetaminophen, AARP and Public Citizen said.

Jerome P. Kassirer, M.D., former Editor-in-Chief of *The New England Journal of Medicine*, and Paul D. Stolley, M.D., M.P.H., epidemiologist, public health expert, and former *NEJM* editorial board member, said only half of newly discovered serious adverse drug reactions are detected and documented within seven years after drug approval. Clinical trials typically study only a few hundred or a few thousand people, and only for six weeks to two years.

Federal law authorizes generic drug approval “when brand-name drugs’ legal protections end, not because their safety profile has been definitely established,” their brief said.

**Tort Claims Provide Incentives.** The Hatch-Waxman incentives were intended to provide a means to deliver drug products equally safe as, yet less expensive, than branded medication. States should not be foreclosed from enforcing failure-to-warn laws that provide needed incentives to generic drug manufacturers to report safety information to the FDA, the health care economists argued in their brief.

Acknowledging the petitioners’ point that branded manufacturers generally have greater access to their own unpublished drug-specific risk information than do generic manufacturers, the economists said, “The appropriate comparison is not between branded and generic manufacturers but between a product’s manufacturer and consumers.” State-law failure-to-warn litigation mitigates this information asymmetry by aligning the incentives of drug manufacturers and consumers.

The economists didn’t buy the theory that allowing state-law failure-to-warn litigation would cause a deluge of information that the FDA “neither wants nor needs.” The FDA is, after all, in the business of protecting the public’s health, the economists said. And history shows that manufacturers tend to under-report risk, not over-report it, they argued.

The economists also said the manufacturers’ amici incorrectly assume that the FDA is equipped to address all health risk issues without the aid of reporting incentives on drug manufacturers.

The economists also discounted the generic drug makers’ argument that because Congress meant their products to be affordable, it must have intended to exempt them from the economic burdens associated with production, including the cost of reporting available risk information. The generic industry remains subject to a wide range of laws that impose costs of doing busi-

ness, including state wage and hour laws, state discrimination laws, and state torts for negligent manufacture. “It has achieved success without exemption from those laws, and has demonstrated no real need for exemption from the claims at issue here,” the economists said.

**Public Citizen, AARP.** The AARP and Public Citizen recalled that at hearings on the Hatch-Waxman Amendments, generic drug industry representatives “recognized their continuing responsibility for their products after approval.”

Generic drug companies often are in the best position to take early action to address risks that come to light once the branded drug’s patent exclusivity period ends, because once generics are available, they often have the majority market share for the drug, according to the Public Citizen/AARP brief.

According to Public Citizen/AARP, the manufacturers argued that litigating a case on the merits may require speculation about how the FDA would have responded to their efforts to seek an enhanced warning. But in *Levine*, AARP and Public Citizen said, the court held that “absent clear evidence” that the FDA would not have approved a label change, it was not impossible for the manufacturer to comply with state and federal requirements. The court, therefore, recognized that state tort claims are not preempted because they might involve speculation about agency action, the brief argued.

**Waxman: No Intent to Preempt.** Rep. Henry A. Waxman, the architect of the Hatch-Waxman Amendments, affirmed that Congress did not intend categorically to preempt failure-to-warn claims against generic drug manufacturers.

Congress did include express preemption in legislation for medical devices in 1976 and for vaccines in 1986, the brief said. But the 1962 amendments to the FDCA, said, in part, that the amendments shall not be construed as invalidating any provision of state law “unless there is a direct and positive conflict between such amendments and such provisions of State law.”

The Supreme Court’s recent decision in *Bruesewitz v. Wyeth*, finding preemption of design defect claims against vaccine manufacturers, supports a finding of no preemption here, Waxman said. The *Bruesewitz* court expressed concern about preempting state claims when there was no federal remedy. In the vaccine cases, Congress established a no-fault compensation scheme. But no such scheme is in place for generic drugs, and there is no indication that Congress sought to displace traditional state-law tort remedies, he said.

BY JULIE A. STEINBERG