Pharmaceutical Safety Is Not Served By Federal Supremacy

by Thomas N. Tiedt

The Supreme Court is due to decide a case, *Wyeth v. Levine*, that may have far-reaching implications for patient welfare.

Because Congress has not expressly preempted pharmaceutical litigation, Wyeth is seeking the judicial remedy usually argued before trial and appellate courts by pharmaceutical industry defendants: unless the Food and Drug Administration (FDA) has determined that an approved prescription drug product is unsafe, mislabeled, defective or fraudulently marketed, marketers of FDA-approved prescription drugs should be immunized from product liability and failure-to-warn litigation. And because a Supreme Court ruling favoring Wyeth provides potential legal precedent, diverse industries support Wyeth's petition (e.g., Black & Decker, Boeing, BP America, Caterpillar, Estee Lauder, Ford Motor Company, General Electric Company, Microsoft, Panasonic and R. J. Reynolds Tobacco Company).[1]

If the Supreme Court rules in favor of Wyeth and against pharmaceutical litigation the historical balance between federal and state power will be dramatically altered.

The stakes are enormous and may presage the most significant change in product safety jurisprudence in history. Historically serving as the first responder to serious drug risks, benefiting patients as well as drug safety public policy, lawsuits from patients and other plaintiffs (e.g., agencies administering Medicare and Medicaid, municipalities, pension plans, group health cooperatives, insurance companies, state attorneys general, investors) have involved serious safety issues largely ignored by FDA until critical masses of litigation and subsequent accusatory media coverage and Congressional attention compiled. Preempting pharmaceutical litigation would remove incentive for FDA and industry to improve product safety and would largely preempt discovery of concealment and misrepresentation of drug safety risks, which when identified have prompted FDA enforcement and new directions in drug safety research and therapeutics.[2]

Wyeth v Levine turns on the Supremacy Clause (Article VI, clause 2) of the United States Constitution preventing states from enacting laws conflicting with federal law and, absent explicit preemption language in the federal law governing FDA (the Federal Food, Drug, and Cosmetic Act (FDCA)), on purportedly implied Congressional intent. Bypassing many opportunities and substantial lobbying to do so the past three decades, Congress has not amended FDCA the way it codified the Medical Device Amendments of 1976, which expressly preempted tort litigation.

Much also depends on how the Supreme Court will view FDA and FDCA potencies. FDA, partnering with Wyeth, believes that its labeling approval provides optimal regulation of pharmaceutical risks and industry behavior and that lawsuits against the pharmaceutical industry impair FDA's enforcement of FDCA.[3] However, FDA's performance has proven itself to continually fall short of Congressional intent and public expectations.[4] Previously, FDA's position regarding preemption was just the opposite. In December 2000, FDA concluded that pharmaceutical labeling content did not preempt state law (e.g., tort litigation).[5] Moreover, FDA use to consider product liability lawsuits beneficial for drug safety and in 1997 held that drug approvals set only

Dr. Tiedt is Director, Med-Tox Group, Sarasota, FL.

minimal standards and states were free to provide additional protections.[6] FDA, a well meaning government agency with an especially wide mandate,[7] though mostly through voluntary mechanisms,[8] is the sole federal government agency authorized by Congress to enforce FDCA for federal government purposes, albeit subject to political pressures, government bureaucracy, executive branch priorities, virtually complete reliance on industry submissions, constraints against seeking internal corporate files and limited resources for independent research.

FDA's Putative Preemption Shield is Defective

Even after tens of thousands of pharmaceutical lawsuits there is no evidence supporting FDA's conversion to preemption. FDA's new position, if held to the standards of reliable evidence, would be preempted from testimony in the court room.[9] It is common knowledge that FDA has declining confidence in labeling and is constrained in what it can do.[10] Before the Senate Finance Committee in November 2004, David Graham, FDA's Associate Director of Science and Medicine in the Office of Drug Safety, testified that, "the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to dealing with serious drug safety issues."[11] Moreover, about two-thirds of FDA's drug reviewers lack confidence in FDA[12] and about one in five feel pressured toward drug approval.[13] The Government Accountability Office (GAO) found that "FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues."[14] The Institute of Medicine (IOM) found that "The approval decision does not represent a singular moment of clarity about risks and benefits associated with a drug …"[15] FDA's Science Board concluded that, "The agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities … FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak."[16]

In February and March, FDA Commissioner Andrew von Eschenbach reported that FDA is inadequate to regulate food and drugs and will fail in consumer protection.[17] FDA has yet to build a credible postmarketing surveillance system. The Food and Drug Administration Amendments Act of 2007 (FDAAA) enacted in response to FDA's poor performance increases funding for FDA's drug safety capabilities, though minimally, from $25 million for 2008 to $65 million in 2012 to regulate with about 100 staff, 3,000 prescription drugs and 11,000 drugs altogether having approximately $275 billion in annual revenues in the United States.[18] Complicating FDA's drug safety procedures is the method that FDA employs for new drug approval. Almost always, FDA relies on an advisory committee vote on whether the new drug's "benefits outweigh its risks" — a highly context-sensitive and sometimes unduly-swayed vote.[19] When a majority of committee members vote for approval FDA translates this vote to a regulatory term of art — "safe and effective." Confusing to many outside the regulatory bubble there is a mistaken belief that the approved new drug has been deemed safe by FDA when in fact, outside of "generally recognized as safe" food additives, FDA never deems a product to be safe. For the foreseeable future, FDA's drug safety system will continue to be less than minimally adequate.[20]

Powerful megatrends are burdening FDA's capabilities as well as revealing as precarious assumptions about FDA expertise, reliability and procedural rigor. Off-label drug use is now common, accounting for 21 percent of all prescriptions,[21] and 73 percent of off-label drug uses have little or no scientific support.[22] Further deregulating FDA's off-label use guidelines toward voluntary responsibilities,[23] "FDA is moving toward an even more minimal role in regulation."[24] FDA now believes that distributing large quantities of non-requested off-label use literature to physicians is not promotion and does not need FDA review because public health may be (theoretically) improved. Analogous to lessons learned about many new drug safety risks, "more and more frequently, it is not FDA action but litigation that raises important questions about off-label drug prescribing."[25] FDA lifted its approval requirement for direct-to-consumer (DTC) advertising in 1985, and its enforcement capacities have steadily weakened.[26] The number of letters FDA sent to marketers regarding advertising violations fell from 142 in 1997 to 21 in 2006 while DTC spending increased from $11.4 billion in 1996 to $29.9 billion in 2005.[27]

Pharmaceutical Research Impugned

Particularly disturbing, the integrity of pharmaceutical research has been impugned. Tort litigation has revealed that pharmaceutical marketers have manipulated safety data submissions to FDA and research reports published in the peer-reviewed literature.[28] For example, while internal reports revealed a significantly increased mortality risk for Vioxx, reports to FDA minimized this risk. Authors for published studies who had little role in the study allowed

themselves to be named as authors. The report for one published Vioxx study had actually been written by a business entity commissioned by Merck. Dr. Eric Topol reported that, "Neither of the two major forces in this five-and-a-half-year affair — neither Merck nor FDA — fulfilled its responsibilities to the public … Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity."[29] According to the chair of an FDA's advisory committee reviewing Avandia's cardiovascular risks, "The basic plot of the rosiglitazone story quickly became obvious to the advisory committee: a new "wonder drug," approved prematurely and for the wrong reasons by a weakened and underfunded government agency subjected to pressure from industry, had caused undue harm to patients."[30] Pharmaceutical research is sometimes skewed to create flawed expectations of safety and efficacy and shaky ground for informed therapeutic decisions, resulting in billions of dollars of waste in pharmaceutical expenditures and substantial preventable morbidity and mortality.[31] Additionally, corporate intimidation of the medical community likely has a chilling effect on its involvement with drug safety public policy. For example; John Buse, M.D., Ph.D., President of the American Diabetes Association and Director of Diabetes Care and the University of North Carolina School of Medicine, testified before the House Committee on Oversight and Government Reform June 6, 2007 that the Chairman of SmithKline Beecham Pharmaceutical Research and Development threatened Dr. Buse and the University of North Carolina with a lawsuit for the company's market capitalization loss of billions of dollars allegedly resulting from Dr. Buse's mention to a group of physicians in 1999 that Avandia may be associated with a risk of heart failure.[32]

Conclusion

Should the Supreme Court rule in *Wyeth v. Levine* that FDCA preempts product liability and failure-to-warn litigation against unsafe and inadequately labeled prescription drugs, long held patient rights and historically critical incentives for updated label warnings and drug safety research beyond the minimal data package needed for FDA approval will be removed. Some of the progress made in evidence-based medicine over the past few decades could retreat, thereby reducing physician education about and informed consent of patients to prescription pharmaceuticals. Reliance on a single government agency such as FDA burdened by political influences, inadequate resources and declining scientific capacities to be the sole means to regulate drug safety would produce a public health, medical research, physician education and informed consent conundrum. Since FDA partnered with the pharmaceutical industry in 2002 in legal arguments to preempt tort litigation, revelations of FDA inadequacies and pharmaceutical industry unethical conduct have only intensified; without this litigation, such revelations would have been preempted. Rather than the utopian approach sought by Wyeth and its partners in *Wyeth v Levine*, improvements in drug safety will be optimally achieved through pluralistic mechanisms, including drug safety litigation. Because Constitutional values will direct the Supreme Court's ruling, the Justices should consider that what we do with our Constitution is our ultimate expression of patriotism. The notion that a single federal agency's supremacy preempts litigation against marketers of inadequately labeled and wrongly approved dangerous drugs should be dismissed. ⚠

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