NOS. 09-993 VIDE 09-1039, 09-1501

In the Supreme Court of the United States

PLIVA, INC., et al., 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH, LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS, INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

BRIEF OF THE AMERICAN MEDICAL ASSOCIATION, TEXAS MEDICAL ASSOCIATION, TEXAS MEDICAL LIABILITY TRUST, TEXAS ALLIANCE FOR PATIENT ACCESS, NORTH CAROLINA MEDICAL SOCIETY, CALIFORNIA MEDICAL ASSOCIATION, LOUISIANA MEDICAL MUTUAL INSURANCE COMPANY, AND LOUISIANA STATE MEDICAL SOCIETY AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE[1]

The American Medical Association ("AMA") is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in its House of Delegates, substantially all United States physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health.

The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition among the AMA and the medical societies of each state, plus the District of Columbia, whose purpose is to represent the viewpoint of organized medicine in the courts.

The Texas Medical Association ("TMA") is a medical professional membership association (an IRC section 501c6 Texas non-profit corporation) of over 45,000 physicians licensed by the State of Texas, medical residents and medical students. The interests that the Texas Medical Association seeks to protect through this lawsuit are germane to its organizational purpose. One mission of TMA—in fact, its primary mission—is to improve the health of all Texans by

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[1] Pursuant to Rule 37.6, Amici Curiae state that no counsel for a party authored this brief in whole or in part, and that no party or counsel for a party, other than Amici Curiae made a monetary contribution intended to fund this brief's preparation or submission. Each party has consented to the filing of this brief.

being an advocate for patients and the profession of medicine. By filing this brief, TMA is seeking to limit the adverse consequences for patients and physician defendants in medical professional liability litigation when the primary defendant is in fact the drug manufacturer.

The Texas Medical Liability Trust ("TMLT") is a not-for-profit health-care liability claim trust owned by its physician policyholders. TMLT was created in 1979, as a result of a legislatively-recognized health-care and medical malpractice crisis, to provide an affordable and stable source of professional liability insurance to Texas physicians. TMLT is an independent insurer writing professional liability policies for more than 14,000 Texas physicians and health-care providers. TMLT is extensively involved in underwriting and risk management matters for the health-care industry, and this requires TMLT to maintain knowledge and expertise of insurance industry standards as well as jurisprudential standards that affect liability insurance procurement and costs in Texas. TMLT is vitally interested in the consistency and predictability of Texas state, as well as federal courts' decision making in cases involving professional liability of physicians and health-care providers.

The Texas Alliance for Patient Access ("TAPA") is an association of over 250 health-care interests providing medical care to Texas residents. Its members include physicians, nurses, therapists, hospitals, trade associations, malpractice insurance carriers, managed care providers, and other individuals and entities that have an interest in assuring timely and affordable access to quality

medical and health care. TAPA seeks to improve access to health care by passing meaningful and sustainable medical liability reforms, requiring that TAPA maintain knowledge and expertise of jurisprudence standards affecting health care liability and liability insurance procurement and costs in the State of Texas.

The North Carolina Medical Society (the "Medical Society") is the largest physician organization in North Carolina. Originally founded in 1849, more than 150 years later, the Medical Society has approximately 11,000 members. The Medical Society unifies doctors across North Carolina in all specialties and work settings on issues related to, *inter alia*: the physician-patient relationship, health regulation, and patient safety. As the largest physician organization in North Carolina, the Medical Society devotes significant resources to advocating physician viewpoints in the public policy arena. Specifically, the Medical Society and its member physicians take an active role in issues addressed by private companies, institutions, and the state government and work to ensure that the views of the medical community are presented in an organized and effective fashion.

The California Medical Association ("CMA") is a nonprofit, incorporated professional association of more than 35,000 physicians who are engaged in the private practice of medicine, in all specialties and modes of practice, in the State of California. Its mission is to promote the science and art of medicine, the care and well-being of patients, the protection of the public health, and the betterment of the medical profession.

CMA and the thousands of physicians and patients it represents have their highest priority insuring that patients receive the best medical care possible. For that reason, CMA and its members diligently monitor and carefully consider the consequences to patients of important public policy issues such as preemption of pharmaceutical failure-to-warn claims. To protect patient safety, CMA files this brief in support of Respondents Gladys Mensing and Julie Demahy on its own behalf and on behalf of its members' patients who will be directly and adversely affected by preemption.

Louisiana Medical Mutual Insurance Company ("LAMMICO") is the largest medical professional liability insurer in Louisiana. LAMMICO was formed as a mutual company by physicians in 1981 to develop and deliver insurance products and services at the lowest rates consistent with sound operating principles. LAMMICO currently insures 6,000 physicians and other health-care providers, most of whom are located in Louisiana. LAMMICO is an advocate for the health-care community and patients. As such, LAMMICO has a substantial and legitimate interest that will be affected by this case.

The Louisiana State Medical Society ("LSMS") was founded in 1878 by a group of 80 physicians representing 14 parishes. Today, the society is a professional association of approximately 5,200 physicians who practice medicine in Louisiana and 1,350 medical student members. LSMS is a voluntary association of physicians providing leadership for the advancement of the health of Louisiana residents and serving as the premier advocate for patients and physicians. The members of the society practice in all fields of medicine.

SUMMARY OF THE ARGUMENT

The hallmark decision in *Wyeth v. Levine*[2] declared that brand name drug manufacturers bear ultimate responsibility for the content of their pharmaceutical product labels at all times and that Congress did not intend to preempt this duty in the Food, Drug and Cosmetic Act ("FDCA"). This Honorable Court is now presented with the opportunity to extend this policy to generic drug manufacturers as well. The arguments and considerations that compelled the result in *Levine* likewise urge a holding that generic drug makers have a duty to perform affirmative post-marketing safety surveillance and to act upon information gained in this process. The Medical Associations[3] respectfully propose that it should be the manifest public policy of this nation that all drug manufacturers – brand and generic – have a continuing duty to conduct themselves as vigilant, active, and responsible members of the health-care community in furtherance of the safety and well being of the American public.

The foremost priority of all physicians is the health of their patients. Prescription drugs serve as a critical ally in the treatment and cure of illness and disease. Even so, physicians must perform a risk-benefit analysis each time they prescribe a drug; this process requires knowledge of current and accurate drug safety information. Physicians have neither the manpower, nor the training or ability to conduct

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[2] 129 S. Ct. 1187 (2009).

[3] As used herein, "The Medical Associations" includes Amici Curiae, AMA, TMA, the Medical Society, CMA, and LSMS.

expansive post-marketing safety surveillance of drugs they utilize.

Physicians attempt to stay abreast of critical developments regarding the safety of drugs, with the drug maker serving as an essential source of product information. Physicians and other health-care providers rely upon the pharmaceutical industry to provide them with safe and effective medicines, subject to oversight of the Food and Drug Administration ("FDA"); this includes accurate and current information regarding the benefits and risks of pharmaceutical products.

It would disrupt the established patient care system to adopt a policy pursuant to which one member of the health-care community – generic drug manufacturers – was permitted to absolve themselves of their unique and vital role in ongoing drug safety. The policy of the medical community should be to enhance every reasonable mechanism that results in a better informed patient and physician population and, thereby, afford greater patient safety.

ARGUMENT

A. Comprehensive and Active System of Post-Marketing Safety Surveillance is of Vital Importance to Patient Health and Safety

The concept that drug safety is of paramount importance has long been held sacrosanct by the medical and scientific community. It is for this reason that The Medical Associations advocate a comprehensive and ongoing system by which drug

safety may be actively monitored.[4] This is not a passive endeavor; all participants in the manufacture and marketing of pharmaceutical products have a continuing duty to conduct themselves as vigilant, responsible members of this health-care team.

Levine implicitly recognizes a redundant and dynamic pharmacovigilance network is an important element of post-marketing drug safety. At the foundation of this network, however, is the declaration set forth in *Levine*: manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.[5]

History proves that the current drug approval system "virtually guarantees that the full risks and complete safety profile of [prescription] drugs will not be identified at the time of approval."[6] "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection."[7] Although it

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[4] *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, AM. MED. ASS'N (1994), http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9032.shtml (last visited Feb, 16, 2011); *AMA Policy H-125.984*, AM. MED. ASS'N (June 2007), http://www.ama-assn.org/ama/no-index/about-ama/17731.shtml.

[5] 129 S. Ct. at 1197-98.

[6] DeAngelis, C., *et al*., *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 (16) J. AM. MED. ASS'N, 1939-41 (2008).

[7] Porter, M, *The Lohr Decision: FDA Perspective and Position*, 52 FOOD DRUG L. J. 7, 11 (1997).

would be preferable to not be dependent on our justice system as a safety mechanism, experience proves that the elimination of a duty to reasonably conduct active safety surveillance will "result in the reduced safety of drugs … for the American people."[8] The medical community holds firm to the belief that all reasonable and prudent steps should be employed to assure the sustained viability and safety of prescription drugs.

The guiding principles of *Wyeth v. Levine*[9] inform the disposition of the issues here. There, the Court remarked that Congress has historically sought to ensure that the FDA "protect the public health" and "assure the safety, effectiveness, and reliability of drugs."[10] Since 1906, Congress has established a legislative framework intended to "bolster consumer protection against harmful products."[11] It is well recognized that the "FDA has limited resources to monitor the 11,000 drugs on the market," particularly "in the post-marketing phase as new risks emerge."[12] The evolution of the FDA's role and legislative mandate, along with an understanding about the convergence of medicine and law, supports the conclusion that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug

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[8] Curfman, G., *et al*., *Why Doctors Should Worry About Preemption,* 359(1) N. ENG. J. MED. 1, 1 (July 3, 2008).

[9] 129 S. Ct. 1187 (2009).

[10] *Id*. at 1197.

[11] *Id*. at 1199.

[12] *Id*. at 1202.

safety and effectiveness."[13] On the contrary, both the statutory framework and case law support the notion of an affirmative duty owed by drug manufacturers – regardless of their position in line – to maintain the accuracy and adequacy of labels for products they sell.[14]

The *Mensing* and *Demahy* appeals "are premised on a more fundamental misunderstanding"[15] regarding drug safety and responsibility. Regardless of their character as a brand or generic manufacturer, it should be inherently obvious that the manufacturer of a prescription drug "bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with insuring that its warnings remain adequate as long as the drug is on the market."[16] To hold otherwise would do violence to the spirit and eviscerate the purpose of the FDA regulatory scheme, and would amount to "an untenable interpretation of congressional intent."[17]

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[13] *Id.* at 1200.

[14] *See generally* Ramey, M., *Conte v. Wyeth: Caveat Innovator and the Case for Perpetual Liability in Drug Labeling*, 4 PITT. J. ENVTL. & PUB. HEALTH L. 73 (2010), http://pjephl.law.pitt.edu/files/Ramey.pdf.

[15] *Levine*, 129 S. Ct. at 1201.

[16] *Id.*

[17] *Id.*

B. Assuring Product Safety Mandates An Ongoing Duty to Monitor and Take Action

The Medical Associations advocate a national public policy declaring that all pharmaceutical manufacturers must actively and diligently participate in the surveillance of product quality; hence, there is an ongoing duty to monitor and to act.[18] The burden to exercise prudence in drug safety is one borne by drug manufacturers and supported by health-care professionals.[19] When safety concerns are discovered, the drug maker must act in a timely manner to warn customers, utilizing labeling revisions, communications to health-care providers, or alternative means consistent with the conduct of a responsible product manufacturer. The goal is to effectively communicate current product safety information in any means allowed by law using every resource at the disposal of the industry and the FDA.

Petitioners seek to shift the weight of this important responsibility for product safety to the other parties in the health-care delivery system. Petitioners

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[18] *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, *supra* note 4; *AMA Policy H-125.984*, *supra* note 4.

[19] The American Medical Association supports a strong FDA (*e.g.*, Health and Ethics Policy H-100.980) and enhanced physician access to drug adverse event data (*e.g.*, House of Delegates Directive D-100.982). AMA ethical policy recognizes that "[s]pontaneous reports of adverse events are irreplaceable as a source of valuable information about drugs and medical devices, particularly their rare or delayed effects, as well as their safety in vulnerable patient populations." *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, *supra* note 4; *see also AMA Policy H-125.984*, *supra* note 4.

first assert that this duty is shared between the FDA and the brand manufacturer.[20] This broad policy argument was rejected in *Levine*.

Second, generic drug defendants typically employ a litigation strategy that implicates the prescribing physician. The first prong of this defense is that the prescriber did not rely on the label for the specific generic drug at issue; this argument ignores the fact that the brand and generic labels are identical. Alternatively, the generic manufacturer contends that the physician was a "learned intermediary" to whom the duty to inform was solely owed.[21] Under either scenario, the generic drug maker seeks to escape any legal repercussions. Concern about the lack of a legal remedy for the injured patient would be "misplaced," because the patient could assert "state law claims against their physicians" who, it is commonly alleged, used the drug product in a manner inconsistent with the product labeling.[22] Amici Curiae conclude, therefore, that the position proposed by Petitioners is that the FDA, brand manufacturers, and prescribing physicians have an ongoing responsibility for product safety and warnings, while the actual, generic drug

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[20] Petitioner Pliva's Reply Brief at 1: Congress and the FDA placed "the burden of prescription drug labeling content on the branded drug manufacturer and the FDA…." *See also* Brief of Petitioner Actavis at 20.

[21] *See, e.g.*, *Pustejovsky v. PLIVA, Inc.*, 623 F.3d 271, 274 (5th Cir. 2010). The incongruity of these defense arguments is apparent; but, this strategy is pursued nonetheless.

[22] Brief of Petitioner Actavis, Inc. at 26, n. 14.

manufacturer has a limited obligation. This conclusion is neither equitable nor realistic.[23]

The scientific basis offered for excusing generic drug makers from a duty to affirmatively monitor and safeguard their products is that, "by the time a branded drug is eligible to generic versions, the safety profile of the drug has been identified; i.e., those adverse events that did not surface during the pre-approval clinical studies generally are identified."[24] Unfortunately, this assertion is not supported by historical fact.

The archives of medical- and product-liability litigation are replete with examples of drugs marketed for many years, yet their safety profiles remain elusive. The "fen-phen" litigation centered on the drug fenfluramine (Pondimin), introduced to the United States market in 1973. This drug, in combination with phentermine, became widely popular as a weight-loss therapy in the 1990s. In 1996[25] and 1997,[26] two

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[23] Even proponents of preemption for brand name drug manufacturers concede that the generic preemption argument is not commercially plausible ("we don't want our clients left holding the liability bag when they didn't sell the product and thus didn't make any profit from it"). *See Government Opposes Certiorari In Mensing Generic Preemption Case,* DRUG AND DEVICE L. (Nov. 4, 2010), http://druganddevicelaw.blogspot.com/search/label/Generic%20Drugs.

[24] Supplemental Brief of Petitioner Pliva at 13; *see also* Amicus Brief of Generic Pharmaceutical Association, at 17.

[25] Abenhaim, L., *et al*., *International Primary Pulmonary Hypertension Study (IPPHS), Appetite-Suppressant Drugs and the*

scientific articles brought to light significant pulmonary and cardiac adverse events that were not known or appreciated during the twenty-plus-year history of marketing of these drugs. Pondimin was withdrawn from the market in late 1997, leaving a legacy of a latent injury undiscovered by way of customary safety surveillance processes.

Propoxyphene is an opioid medication first approved by the FDA in 1957. This drug was sold in both brand and generic forms. In November 2010, based on newly-accumulated safety data, the FDA determined "the post-marketing safety signals for this drug dictated that the overall balance of risk and benefit can no longer be considered favorable." The agency thus recommended that propoxyphene products be removed from the United States market.[27]

Non-steroidal anti-inflammatory drugs ("NSAIDs") have been on the market since the 1970s. Examples include Motrin (ibuprofen) and Naprosyn (naproxen). The product labels for NSAIDs have been modified on an ongoing basis as the science pertaining to these drugs evolves. The most prominent changes include

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Risk of Primary Pulmonary Hypertension, 335(9) N. ENG. J. MED. 609 (Aug. 29, 1996).

[26] Connolly, H., *et al.*, *Valvular Heart Disease Associated With Fenfluramine-Phentermine,* 337(9) N. ENG. J. MED. 581, 588 (Aug. 28, 1997).

[27] *Propoxyphene-Containing Products,* U.S. FOOD AND DRUG ADMIN. (Dec. 6, 2010), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.html.

the addition of a black box warning and the implementation of a Medication Guide "highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use."[28] Labeling changes such as these are an important source of product safety information and result in different prescribing practices and patient perceptions. NSAID products are still on the United States market and are frequently prescribed, thereby rendering ongoing research and study a valid endeavor.

A timely example of the necessity of vigorous and continuous post-marketing safety surveillance is offered by the drug terbutaline sulfate. This drug was originally approved in the 1970s and was indicated for treatment of asthma. The drug has since evolved as a treatment for preterm labor in obstetrical patients. On February 17, 2011, the FDA announced that it was requiring a black box warning on this drug. "The decision to require a Boxed Warning and Contraindication is based on the FDA's review of post-market safety reports of heart problems and even death associated with terbutaline use for obstetric indications, as well as data from medical literature documenting the lack of safety and effectiveness of

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[28] *COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, U.S. FOOD AND DRUG ADMIN. (Apr. 7, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm. This link contains a listing of all non-steroidal anti-inflammatory drugs. NSAIDs are marketed as prescription and generic, as well as over-the-counter products.

terbutaline for preventing preterm labor, and animal data suggesting potential risks."[29] The safety announcement is particularly relevant to the discussion at hand because, as the FDA noted, "[t]here are multiple generic versions of terbutaline oral tablets and injectable formulations available. The brand name products were previously discontinued by the companies that made them."[30] Terbutaline, therefore, is a stark example of a drug that has no surveillance oversight by "the brand." Continuous, aggressive, and ongoing pharmacovigilance by the generic drug manufacturers is an absolute necessity to ensure patient safety. It is foreseeable that this scenario will be repeated many times as the pharmaceutical landscape evolves in the United States.

Metoclopramide is a final example of an old drug for which recent drug safety data prompted new label warnings. Reglan, the innovator drug, was approved by the FDA in 1980. The drug is now sold primarily in generic form. The product label historically included a warning about tardive dyskinesia; however, concerns about the adequacy of the label and the fact that the drug was routinely used for the long term resulted in the allegation that the label was misleading as to the risk level for developing this condition.[31] In 2009, the

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[29] *FDA News Release: FDA Warns Against Certain Uses Of Asthma Drug Terbutaline For Preterm Labor: Certain Uses Could Lead To Maternal Heart Problems And Death*, U.S. FOOD AND DRUG ADMIN. (Feb. 17, 2011), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm243840.htm.

[30] *Id.*

[31] *See, e.g.*, *McNeil v. Wyeth*, 462 F.3d 364, 373 (5th Cir. 2006).

FDA concluded that "new safety information"[32] required the implementation of a Risk Evaluation and Mitigation Strategy ("REMS") and labeling modifications, including the addition of a black box warning. Now, when a patient obtains a prescription for metoclopramide, it is required by law[33] that the patient be provided with the patient Medication Guide.[34] The use of a Medication Guide is a clear means of placing responsibility for communicating product safety information on the drug manufacturer. The policy of implementing REMs and the use of Medication Guides is persuasive evidence of congressional intent that the drug manufacturer has a continuing, active, and potentially direct responsibility to consumers to warn them of the risks of prescription drugs.[35]

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[32] "This information was not available when your ANDA was approved. We consider this information to be 'new safety information' as defined in FDAAA." U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf (last visited Feb. 25, 2011).

[33] "Under 21 C.F.R. 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Reglan (metoclopramide) Tablets/ODT/Injection." *Id*.

[34] *Medication Guide Reglan*, U.S. FOOD AND DRUG ADMIN. (June 2009), http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176362.pdf

[35] "FDA has determined that Reglan (metoclopramide) Tablets/ODT/Injection have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Reglan (metoclopramide) Tablets/ODT/Injection."

Many other examples have been reported of pharmaceuticals once thought to be reasonably safe and effective, but later recognized to present safety issues warranting their withdrawal or labeling modification.[36] Prerequisite to the proper functioning of this safety system is the willing and active participation by all members of the health-care community, including those who manufacturer and sell generic drugs.

"[W]ith regard to manufacturers of pharmaceuticals, most jurisdictions recognize a 'continuous duty' to remain apprised of new scientific and medical developments and to inform the medical profession of pertinent information related to treatment and side effects."[37] Hence, this duty is not passive, but requires ongoing diligence by the drug maker. This duty is fairly characterized as a "modest duty"[38] and one that flows from the recognition that a

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U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf (last visited 2/25/2011).

[36] *See, e.g.*, Wysowski, D., *Adverse Drug Event Surveillance and Drug Withdrawals in the United States 1969-2002: The Importance of Reporting Suspected Reactions*, 165 ARCH. INT'L MED. 1363-69 (2005); Gostin, L., *The Deregulatory Effects Of Preempting Tort Litigation: FDA Regulation Of Medical Devices*, 299(19) J. AM. MED. ASS'N 2313-16 (May 21, 2008).

[37] Ross, K., *Post-Sale Duty to Warn, A Report of the Products Liability Committee*, AM. BAR ASS'N, SECTION ON LITIGATION, at 13 (2004), http://www.productliabilityprevention.com/images/5-PostSaleDutytoWarnMonograph.pdf.

[38] Brief of the United States of America as Amicus Curiae, at 22.

pharmaceutical manufacturer "is held to the knowledge and skill of an expert; the manufacturer's status as expert means that at a minimum he must keep abreast of scientific knowledge, discoveries, and advances and is presumed to know what is imparted thereby."[39]

The inherent validity and necessity of a shared, affirmative duty of brand name and generic drug manufacturers to monitor drugs for safety is evidenced by the fact that the appellate courts addressing this issue have all held that such a duty is required by law and is consistent with congressional intent.[40] Similarly, commentators and policy makers do not distinguish between brand and generic manufacturers in finding a "continuing duty to keep abreast of scientific developments affecting the manufacturer's product and warn the medical community of any newly discovered risks."[41] The overriding importance of this

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[39] *Foster v. Am. Home Prods.*, 29 F.3d 165, 170 (4th Cir. 1994), citing *Owens-Illinois v. Zenobia,* 325 Md. 420, 601 A.2d 633, 639 (Md. 1992) (quoting *Borel v. Fibreboard Paper Prods. Corp.,* 493 F.2d 1076, 1098 (5th Cir.1973), *cert. denied,* 419 U.S. 869 (1974)).

[40] *Gaeta v. Perrigo Pharms. Co.*, No. 09-15001, 2011 WL 198420, at *1 (9th Cir. Jan. 24, 2011); *Demahy v. Actavis, Inc.*, 593 F.3d 428, 430 (5th Cir. 2010), *cert. granted*, 78 U.S.L.W. 3745 (U.S. Dec. 10, 2010) (No. 09-1501); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 607 (8th Cir. 2009), *cert. granted*, 78 U.S.L.W. 3522 (U.S. Dec. 10, 2010) (No. 09-993), *and cert. granted*, 78 U.S.L.W. 3523 (U.S. Dec. 10, 2010) (No. 09-1039).

[41] Ross, K. and Prince, D., *Post-Sale Duties*, 74 BROOK. L. REV., 963, 982 (2009), http://productliabilityprevention.com/images/BLS_PrinceandRoss_vol74.3,2009.pdf; *see also* Gastwirth, J., *The Need for Careful Evaluation of Epidemiological Evidence in*

watchful, dynamic approach to pharmacovigilance cannot be overstated.

Pharmacovigilance has evolved from a fragmented and unreliable data accumulation mechanism to become an important tool in formulating global health-care policy. The World Health Organization has often taken the initiative in advocating a coordinated global pharmacovigilance network. This venerable authority has declared:

> The principle [of product stewardship] requires pharmaceutical manufacturers to assume responsibility for the impact of their activities "from cradle to grave", including consideration of the key influences in regulatory, customer and community contexts. . . . Responsibility for their products extends to all manufacturers (including those who produce generic medicines) and suppliers of raw materials. More broadly,

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Product Liability Cases: a Reexamination of Wells v. Ortho and Key Pharmaceuticals, 2 LAW, PROBABILITY AND RISK 151-189 (2003), http://lpr.oxfordjournals.org/content/2/3/151.full.pdf; Reid. M., *Comment, Vermont Supreme Court Rules That Food and Drug Administration Regulations Do Not Preempt State Failure-to-Warn Claims*: *Levine v. Wyeth*, 4 J. HEALTH & BIOMEDICAL L. 413, 425 (2008); Zellmer, S., *Preemption by Stealth*, 45 HOUS. L. REV. 1659, 1694-95 (2009); Vladeck, D., *The FDA and Deference Lost: A Self-Inflicted Wound or the Product of a Wounded Agency? A Response to Professor O'Reilly*, 93 CORNELL L. REV. 981 (2008) ("Vladeck"), http://www.lawschool.cornell.edu/research/cornell-law-review/upload/Vladeck.pdf; Noah, L., *Platitudes About "Product Stewardship" in Torts: Continuing Drug Research and Education*, 15 MICH. TELECOMM. AND TECH. L. REV. 359 (2009), http://www.mttlr.org/volfifteen/noah.pdf; Ramey, *supra* note 14.

> the idea of stewardship is applicable to all industries.[42]

This policy declaration – in which all drug manufacturers are vested with responsibility for "product stewardship" – echoes the pharmacovigilance dictates of other developed countries. The Medical Associations' review of the available resources reveals that the developed nations of the world recognize that all drug makers – including those who manufacture generic drugs – share the burden of actively and responsibly monitoring the safety of marketed drugs.

The Canadian Generic Pharmaceutical Association voiced its posture on this issue in a statement to the House of Commons, explaining that "[a]ll pharmaceutical companies in Canada are required to monitor the use and effect of a given medication, and to detect, assess, understand and prevent any adverse reactions or any other medicine-related problems that arise."[43] This pharmacovigilance includes "ongoing monitoring and literature reviews on a global basis to identify any adverse drug reaction case reports."[44] As to a distinction between innovator and generic drugs:

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[42] *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*, WORLD HEALTH ORG. OFC. OF PUBLICATIONS, at 32 (2002), http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf.

[43] *Presentation to the House of Commons Standing Committee on Health: Study on Post-Market Surveillance*, CANADIAN GENERIC PHARM. ASS'N, 1 (Feb. 5, 2008), http://www.canadiangenerics.ca/en/news/docs/post-market_surveillance_English.pdf.

[44] *Id.* at 2.

"Post-marketing risk management activities should be identical for both brand-name and generic products. This is the current practice and it should continue."[45] Thus, in Canada, the "generic pharmaceutical industry remains committed to good pharmacovigilance practice, and to working collaboratively with both domestic and international health authorities and other stakeholders to minimize public risk and ensure the safe use of generic drugs."[46]

In Europe, both brand and generic drug manufacturers are subject to the "The Rules Governing Medicinal Products in the European Union, Volume 9A – Pharmacovigilance for Medicinal Products for Human Use."[47] The European Generic Medicines Association likewise validates the importance of ongoing and comprehensive drug safety surveillance, declaring "it is important to assess on a permanent basis that the risk-benefit of a given

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[45] *Id.* at 3.

[46] *Id.*

[47] "The pharmacovigilance obligations apply to all medicinal products authorized in the EU, including those authorized before 1 January 1995 and whatever procedure was used for their authorization. For example, the obligations are the same for products authorized under Articles 10(1), 10(4), 10a, 13 to 16 and 16a to 16i of Directive 2001/83/EC ('generic', 'similar biological medicinal product', 'well-established use', 'homeopathic' and 'herbal' products respectively) as for products authorized under Article 6 of the same Directive." *Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use*, at 15, EUROPEAN COMM'N (Sept. 2008), http://ec.europa.eu/health /files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf.

medicine remains positive during its entire life cycle. Therefore monitoring the use and effect of medicines is an essential part of the activities of a pharmaceutical company."[48] The same rules appear to generally apply on the Asian continent.[49]

The international health-care community, including its members who manufacturer and sell brand and generic pharmaceuticals, recognize the necessity of a comprehensive, sophisticated, and active system of pharmacovigilance for all marketed drugs.[50] The United States has historically been a leader in this endeavor. It would be a disservice to the public and

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[48] *EGA Fact Sheet on Generic Medicines, Pharmacovigilance and Generic Medicines: Ensuring On-going Patient Safety*, EUROPEAN GENERIC MEDICINES ASS'N, http://www.egagenerics.com/doc/ega_factsheet-09.pdf. (last visited Feb. 16, 2011).

[49] "Both innovator and generic companies operate in Asia. An observation is that the pharmacovigilance regulatory expectations in the region do not distinguish between generic and innovator companies. Therefore, generics companies need to sustain the same level of compliance to these regulatory obligations as much as their innovator counterparts." Sharma, V., *Pharmacovigilance: Playing by the Rules*, PHARMAASIA (June 1, 2009), http://www.pharmaasia.com/article-7805-pharmacovigilanceplaying bytherules-asia.html; *see also* Du, W., *et al.*, *Drug Safety Surveillance in China and Other Countries: A Review and Comparison*, 11 INT'L SOC. FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH S130–36 (2008), http://www.ispor.org/consortiums/asia/ViH/19-Guo.pdf.

[50] *See, e.g.*, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING, THE UPPSALA MONITORING CENTRE, http://www.who-umc.org (last visited Feb. 25, 2011); *see also* INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE, http://www.isoponline.org (last visited Feb. 25, 2011).

the health-care community to retreat from the progress made in this arena.

C. Principles of Federalism and Constitutional Recognition of States' Rights Warrant Respect for Local Health-Care Policy

In view of the foregoing arguments, it is difficult to fathom the basis for a policy declaration that excuses a critical member of the health-care community from active and responsible participation in the process of pharmacovigilance. We begin with the concepts espoused by *Levine*, dictating that one must first examine the "purpose of Congress" bearing in mind that "the historic police powers of States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."[51] Amici Curiae concur that federal preemption of local health-care laws and regulations is generally disfavored and unwarranted. Thus, what is the countervailing policy argument?

Petitioners go to great lengths to dissect and analyze the FDCA, its empowering regulations and provisions, and FDA pronouncements. The single goal of this exercise is to create the appearance of a conflict upon which they may base an argument for preemption of the affirmative and continuing responsibility for the safety of drugs they sell. The generic drug makers urge that Congress and the FDA both had "the vision" to "place the burden of

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[51] *Levine*, 129 S. Ct. at 1195 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)).

prescription drug labeling content on the branded drug manufacturer and the FDA…."[52] The industry minimizes its role in pharmacovigilance, proposing that it need only report adverse events they actually receive or reports they "happen to hear about."[53] This passive approach to drug safety would undermine the entire notion of responsible, valid surveillance. Finally, the industry seeks to excuse its members from active surveillance of a key source of adverse event data – the scientific literature - stating that "such a requirement would only increase costs to no meaningful end."[54] These arguments arise from a tangled interpretation of the applicable drug laws, which ultimately would disserve the patients and the medical community this industry was created to serve. Moreover, this construction obfuscates and undermines clear monitoring and reporting mandates.[55]

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[52] Petitioner Pliva's Reply Brief at 1; Brief of Petitioner Actavis at 20.

[53] Brief of Petitioner Pliva at 19.

[54] Amicus Brief of Generic Pharmaceutical Association at 19. Of note, Petitioner Actavis construes the FDA regulations to require that the medical literature be monitored. *See* Brief of Petitioner Actavis at 6: "A generic manufacturer is required to report adverse drug experiences that it 'obtain[s] or otherwise receive[s]' from any source, including scientific literature, and to submit new safety information in its annual report to FDA."

[55] Generic manufacturers must follow the same rules for record keeping and reporting of adverse drug experiences that name brand manufacturers must follow (21 C.F.R. § 314.98), which includes reports from the scientific literature (21 C.F.R. § 80(c) and (d)). This information requires communication with the FDA if it reveals "reasonable evidence of an association of a serious

Wyeth v. Levine[56] provides the guideposts for disposition of the current appeal. First, the one hundred year history of food and drug law in the United States manifests a clear congressional intent that such laws are designed to "protect the public health" and "assure the safety, effectiveness, and reliability of drugs" while taking care "to preserve state law."[57] The various amendments to the Food and Drug act all evidence a national policy to "bolster consumer protection against harmful products."[58]

Second, legislative action, as well as inaction, on the issue of express preemption statutes provides "powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness."[59] Thus, "the longstanding coexistence of state and federal law and the FDA's traditional recognition of state law remedies" buttress the conclusion that "state law offers an additional, and important, layer of consumer protection that complements FDA regulation."[60]

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hazard with a drug." (21 C.F.R. § 201.57(e), now re-designated as 21 C.F.R. § 201.80(e)).

[56] *Levine*, 129 S. Ct. 1187.

[57] *Id*. at 1195-96.

[58] *Id.* at 1199.

[59] *Id*. at 1200.

[60] *Id.* at 1202.

Finally, in view of the "demanding" nature of the defense of impossibility preemption,[61] it is difficult to envision that Congress nonchalantly, and without discussion, modified the comprehensive nature of the national system of pharmacovigilance by happenstance.[62] *Levine* also places the burden of proof on the proponent of this defense to establish that the FDA would have refused to approve a proposed labeling change or other proposal to convey improved safety information.[63] Absent in this case is the "clear and manifest purpose of Congress"[64] that the law demands to excuse an industry from its duty to serve as a vigilant, dynamic, and responsible member of the health-care community.

The appellate courts addressing the issue sought to respect congressional mandates while demanding a sensible construction and interpretation of the applicable laws and regulations. The challenge presented is that our system of pharmacovigilance arises from a morass of laws, regulations, and interpretations that provide less than optimal guidance to the courts, and that are subject to misinterpretation. The regulations and guidelines

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[61] *Id*. at 1199.

[62] "[T]he legislative history for the [Hatch-Waxman] act does not contain any signal that either brand name or generic manufacturers ever considered its liability implications." Ramey, *supra* note 14, at 91-92; *see also* Vladeck, *supra* note 41, at 986 n.29.

[63] *See id*. at 1198-99.

[64] *Levine*, 129 S. Ct. at 1195.

offer alternative methods of revising labels and disseminating product safety information. It should be demanded that generic drug makers select the most appropriate and timely vehicle by which important drug safety messages may be communicated to those who need and rely upon this information. Hence, the courts in *Mensing, Demahy*, and *Perrigo* clearly recognized the foundation for a duty to affirmatively monitor pharmaceuticals and take action to protect the public health, while conscientiously seeking to identify the mechanisms by which such action may be accomplished. The common thread in these opinions is that, "at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its product," it should then "*provide adequate supporting information to the FDA*, and the FDA will determine whether the labeling for the generic and listed drugs should be revised."[65]

In *Levine*, this Court rejected an "untenable interpretation of congressional intent"[66] even more far reaching than the one advocated by Petitioners. The Court now stands positioned, once and for all, to

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[65] *Mensing,* 588 F.3d at 613 (emphasis in original); *Demahy,* 593 F.3d at 434 (emphasis in original); *see also Perrigo,* 2011 WL 198420, at *6. The United States as amicus curiae likewise supports the notion of a duty to notify FDA "[i]f an ANDA applicant believes new safety information should be added to a product's labeling…." Brief for the United States as Amicus Curiae at 15-16. The Medical Associations suggest that an interpretation of the FDA rules and regulations that diminishes the role of generic manufacturers in the scheme of pharmacovigilance would justifiably be viewed as "inherently suspect." *Levine*, 129 S. Ct. at 1190.

[66] *Levine*, 129 S. Ct. at 1199.

declare that drug safety and patient well being are national priorities and that all members of the health-care system play an important role in this effort. Amici Curiae urge the Court to take this crucial step.

D. The Current Appeal Has Significant Ramifications for the Safety of Generic Drugs and Responsibility for Patient Safety

A final issue of importance to the health-care community is the ramifications of this appeal on drug-prescribing behavior. Physicians must consider many factors in making health-care decisions, with their first priority being patient safety. Even so, physicians are faced with mounting pressure to be conscious of costs. Doctors should be entitled to prescribe an "equivalent" generic drug with assurance that it is truly the same as the brand, not only on the date of its approval, but during its lifetime on the market.

The selection of the optimal drug to prescribe implicates an assessment of its benefit-risk profile. Doctors make prescribing decisions based on the most current product safety information, not uncertain or unreliable safety data. Nonetheless, medical science evolves, and the benefit-risk information for drugs must remain dynamic.

Physicians customarily include in their informed consent discussion relevant information about "the risks and benefits of a proposed treatment or procedure" as well as "the risks and benefits of [any]

alternative treatment or procedure."[67] If alternative drug therapies are available, such as a generic equivalent, the physician may find it relevant to broach this subject with the patient.

Divergent liability rules for brand name and generic drugs pose an ethical dilemma for physicians. The medical profession recognizes the benefit of generic drugs and supports the right of physicians to select generic equivalents.[68] If a physician specifies that a prescription be filled with a brand name drug,[69]

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[67] *Patient Physician Relationship Topics: Informed Consent*, AM. MED. ASS'N, http://www.ama-assn.org/ama/pub/physician-resources/legal-topics/patient-physician-relationship-topics/informed-consent.shtml (last visited Feb. 16, 2011); *Code of Medical Ethics: Opinion 8.08 – Informed Consent*, AM. MED. ASS'N (2006), http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion808.shtml (Physicians have an obligation to "sensitively and respectfully disclose all relevant medical information to patients.").

[68] *See, e.g.*, *AMA Policy H-125.984*, *supra* note 4. It is beyond the scope of this brief to address the impact of the cost of medications on patient compliance and health, but researchers have found compelling evidence of a direct correlation between the two. *See, e.g.*, Goldman, D., *et al.*, *Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health*, 298(1) J. AM. MED. ASS'N, 61-69 (2007). It would be unfortunate indeed if patients had to choose between their pocketbook and their well-being.

[69] After the FDA approves a generic, the question of whether it is generically substitutable is a matter of state law. The states differ on how they determine which products are "generically equivalent." Some states have a "positive formulary" which lists all of the products which may be generically substituted in that state. Others have a "negative formulary" which lists those drugs – generally narrow therapeutic index ("NTI") drugs – that may not

he or she has an assurance that the drug company is monitoring the safety of the drug. Conversely, if the generic drug industry's argument prevails, there will be no guarantee that the product safety information accompanying a generic drug is current or reliable.

The scope of the problem under consideration is startling. The generic industry advises that 10,072 of the 12,751 drugs listed in the FDA's Orange Book[70] have generic counterparts and that generic pharmaceutical products are used to fill nearly 2.6 billion prescriptions every year. Generic medicines account for 69% of all prescriptions dispensed in the United States, and the industry is expected to grow at an annual rate of more than 7.8%, a pace that is faster than the world pharmaceutical market.[71] At what

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be substituted. And, others default to the FDA's determination of whether the product is bioequivalent. Carpenter, L. *Generic Substitution and Biopharmaceuticals: Where Are All the Follow-On Biologies? And, How Much Money Will They Save?*, NAT'L L. REV. (Jan. 1, 2010), http://www.natlawreview.com/article/generic-substitution-and-biopharmaceuticals-where-are-all-follow-bi. Texas law, for example, allows for generic substitution unless the patient expressly requests a brand name drug. *See, e.g.*, *What is a generic drug?*, TEX. ST. BD. OF PHARM. (2002-2004), http://www.tsbp.state.tx.us/consumer/broch3.htm.

[70] *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD AND DRUG ADMIN. (Jan. 2011), http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[71] *Facts at a Glance*, GENERIC PHARM. ASS'N (U.S.), http://www.gphaonline.org/about-gpha/about-generics/facts (last visited Feb. 25, 2011). These statistics may be understated. A recent news article on the prevalence of the use of generic drugs reported that as much as seventy-five percent of daily prescriptions are filled with generic substitutes. Herper, M.,

point this issue becomes a matter of patient safety is uncertain but what is certain is that this concern inevitably will arise.[72]

The safety of generic drugs will remain a prominent topic among patients and prescribers. The usual course in the drug industry is that a brand-name drug maker will monitor its product for as long as it has a financial interest and a legal obligation to do so. "[O]nce a manufacturer loses its exclusivity, it also loses its revenue stream."[73] The legal duty to monitor continues, but it is not uncommon for the brand maker to simply stop selling the drug when profits can no longer be realized.[74] If the generic drug makers' preemption argument wins the day, there may be no

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America's Most Popular Drugs, FORBES (May 11, 2010), http://www.forbes.com/2010/05/11/narcotic-painkiller-vicodin-business-healthcare-popular-drugs_print.html. Overall, only 8 of the 50 most popular drugs are still branded, compared to 20 in 2003, according to IMS Health. *Id.* This includes the top selling drug in the nation, Vicodin (a combination of hydrocodone and acetaminophen), which has recently been the subject of an FDA investigation culminating in the recommendation that the drug's continued use be banned. *See, e.g.*, Harris, G., *Ban is Advised on Top 2 Pills for Pain Relief*, N. Y. TIMES (July 1, 2009), http://www.nytimes.com/2009/07/01/health/01fda.html.

[72] As the court noted in *Demahy,* it would be a "bizarre conclusion" to determine that Congress intended to provide greater protection for patients who use brand name drugs compared to those who are prescribed generic drugs. 593 F.3d at 449.

[73] Ramey, *supra* note 14, at 87.

[74] *Id*. at 98. This article notes that, in the case of Reglan, the brand manufacturer reportedly assigned its rights and liabilities associated with the drug to Schwarz Pharma, Inc. in 2002.

one responsible for drug safety oversight for many popular and widely-prescribed drugs. Common sense and fairness dictate that this obligation be accepted by the product manufacturer.

The most important issue in this discussion remains patient safety. Physicians and their patients are entitled to a reasonable assurance that the drugs they use are safe and effective, for as long as they are on the market.[75] Pharmacovigilance is a comprehensive, vibrant, and continuing responsibility in which many parties play a role.[76] It is now accepted that brand name drug companies have an ongoing duty to actively monitor drugs they sell and to notify the FDA and/or revise the product labeling if warranted. It should be the responsibility of all drug makers to conduct reasonable and affirmative safety surveillance and to take appropriate action when significant safety concerns arise.

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[75] Many drugs are sold both in brand name and generic form. With as much as seventy-five percent (75%) of the drugs prescribed by physicians being generic products, it is critical that the safety of these drugs be monitored, just like the monitoring required of brand name drugs. *See, e.g.*, Herper, *supra* note 71.

[76] The AMA supports the broad policy that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it, accept it, and act on it when prescribing a drug. *See, e.g.*, *AMA Policy H-125.984*, *supra* note 4.

CONCLUSION

The health-care system in the United States seeks to achieve a balance between competing factors, the most prominent of which is patient safety.[77] Even so, financial considerations cannot be ignored. The legislation authorizing the marketing of generic drugs was never meant to "pursue the objective of low-cost generic drugs without limitation."[78] "[T]he Hatch-Waxman Amendments were meant to provide an inexpensive and easy way for generic drugs to enter the market, they were not intended as a relief from the fundamental requirement of the FDCA that all marketed drugs remain safe."[79]

Health-care providers and their patients rightly expect that the drugs they use are reasonably safe and that their safety is being continually, aggressively monitored. The obligation for ongoing and affirmative safety surveillance lies with the party manufacturing the drug. The defense of "impossibility preemption" demands that the party seeking to avoid this obligation must affirmatively prove that the FDA would have refused to approve a proffered labeling change or other proposal to convey modified safety information to the public. Generic drug makers should

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[77] The Medical Associations respectfully present these arguments in view of the fact that this appeal "concerns a medical and scientific question of great importance: how best to save the lives of" all Americans. *See Bruesewitz v. Wyeth L.L.C.*, No. 09-152, 2011 WL 588789, at *13 (Feb. 22, 2011) (Breyer, J., concurring).

[78] Brief for the United States as Amicus Curiae, p. 20.

[79] *Perrigo*, 2011 WL 198420, at *11.

not be exempt from a duty to conduct continuous and affirmative pharmacovigilance of their products. If this surveillance reveals information relevant to the safety of their drugs, they should take action to assure that this information is communicated to prescribers and their patients. This responsibility may be fulfilled in any manner permitted by law but would include, at a minimum, furnishing adequate supporting information to the FDA, after which a determination may be made whether the product labeling should be modified. To do less would be an injustice to the public as well as the medical community.

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