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BUYER BEWARE: *MUTUAL PHARMACEUTICAL CO. V. BARTLETT* CONTINUES TO ALTER THE TRUE COSTS AND RISKS OF GENERIC DRUGS

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Over the last few decades, the generic drug market has grown substantially. Today, generic drugs account for four of every five drugs sold. The affordability of generics has been a welcome change for drug purchasers throughout the value chain, but thinning protections for generic drug consumers are causing many reasons for concern. Recent Supreme Court decisions, such as Mutual Pharmaceuticals Co. v. Bartlett*, have eliminated certain legal remedies for generic drug consumers and lessened incentives for generic drug manufacturers to conduct ongoing safety research. Although federal law strives to ensure that generic drugs are the same as brand-name drugs,* Bartlett *provides many reasons to believe the distinctiveness of brand vs. generic extends far beyond a price point. Under pre-emption principles, generic consumers are now barred from seeking relief through design-defect or failure-to-warn claims, while brand-name consumers are still afforded these legal remedies. Although generic drugs remain affordable for end users to purchase, this Recent Development examines the true costs and safety risks now associated with generic drugs in light of* Bartlett.

I. INTRODUCTION

Every three days, the generic drug market saves the U.S. healthcare system more than $1 billion.[1] By 2014, several "blockbuster" drugs, the nation's largest selling pharmaceuticals, will lose patent

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[1] GEN. PHARM. ASS'N, SAVINGS ACHIEVED THROUGH THE USE OF GENERIC PHARMACEUTICALS 2000–2009, at 2 (2010), *available at* http://www.medicalhomeexchange.com/images/pages/Generic_Drug_savings_2000-09.pdf.

exclusivity and become exposed to generic drug competition.[2] Among those drugs losing patent protection is Lipitor, a cholesterol lowering medication[3] that now sells for roughly $5 a pill, despite costing only 10¢ to manufacture.[4] Similar to many other blockbuster drugs, such as Zocor, Norvasc, and Zoloft,[5] Lipitor has grossed more than $130 billion since entering the market.[6]

When presented with the option to purchase a brand-name drug or its generic alternative, the choice for many consumers is easy: save money and buy the generic. Since generic drugs first entered the market, the Food and Drug Administration ("FDA") has gone above and beyond to assure consumers that brand-name drugs and their generic counterparts not only contain the same "dosage form, safety, strength, route of administration, quality, performance characteristics and intended use," but have also "met the same rigid standards as the innovator drug."[7] The agency maintains that the only material difference between brand-name and generic drugs is the price.[8] For example, Percocet, a moderate to severe pain medication,[9] costs a consumer without drug coverage roughly $1,128 per month.[10] In contrast, its generic counterpart, oxycodone,

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[2] *Id.* at 4. "Blockbuster" drugs are the largest selling drugs on the market. *Id.* Blockbuster drugs that will lose patent protection in 2014 include Lipitor, Plavix, Zyprexa, Singulair, and Aricept. *Id.*

[3] LIPITOR, http://lipitor.com (last visited Oct. 19, 2013).

[4] *PBS Newshour: As Lipitor's Patent Expires, Is Era of 'Blockbuster Drugs' Over?* (PBS television broadcast Nov. 30, 2011), *available at* http://www.pbs.org/newshour/bb/health/july-dec11/lipitor_11-30.html

[5] GEN. PHARM. ASS'N, *supra* note 1, at 2.

[6] *See PBS Newshour*, *supra* note 4.

[7] *Understanding Generic Drugs*, FOOD & DRUG ADMIN., http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ (last updated June 28, 2013).

[8] *Facts About Generic Drugs*, FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last updated Sept. 19, 2013).

[9] *Percocet Outsert*, FOOD & DRUG ADMIN. (2013), http://www.fda.gov/ohrms/dockets/dailys/04/mar04/032604/04p-0150-cp00001-03-Attachment-02-vol1.pdf.

[10] *Brand-Name vs. Generic Drug Costs*, BLUE CROSS BLUE SHIELD MICHIGAN (2012), http://www.bcbsm.com/pdf/ps_generic.pdf.

costs a consumer only $52.50 per month—less than 5% of the brand-name drug.[11] Similarly, the cost of a diabetes medication like Glocotrol ranges from $42 to $84 per month, but its generic alternative, glipizide, costs only $4 to $8 per month.[12]

Because the average cost of a generic drug is 80% to 85% cheaper than its brand-name counterpart,[13] the generic drug market saves consumers $8 billion to $10 billion a year in pharmacy costs.[14] For this reason, the use of brand-name drugs dropped twenty percent in 2012, while generic drug purchases continued to rise dramatically.[15] For example, the fulfillment of generic prescriptions increased from just 57% of all drug purchases in 2007 to 75% in 2009.[16] Although generic drugs already constitute 80% of prescriptions filled today,[17] the generic market will

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[11] *Generic Drugs: The Same Drug for Less Money*, CONSUMER REPORTS (2012), *available at* http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/money-saving-guides/english/GenericDrugs-FINAL.pdf.

[12] *Id.* The higher prices of brand name drugs are necessary to enable innovators to recoup the high costs associated with the extensive, complex nature of the research and development process. *See* THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 2 (Patricia M. Danzon & Sean Nicholson eds., 2012) ("[T]he industry is heavily regulated in R&D, marketing, manufacturing, and, in many countries, pricing. New drugs must meet stringent standards of safety, efficacy, and manufacturing quality before receiving launch approval. Such regulation entails high costs as well as benefits, and the appropriate extent and structure of this regulation is debated in the academic and policy literatures."). Some studies have estimated the cost for developing a new drug is greater than $1 billion. *See, e.g.*, Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 470 (2007).

[13] *Facts About Generic Drugs*, *supra* note 8.

[14] *Generic Drugs: Questions and Answer*, FOOD & DRUG ADMIN., http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm (last updated Sept. 3, 2013); *Facts about Generic Drugs*, *supra* note 8.

[15] Alexi Friedman, *Study finds Americans are shifting from brand name to generic drugs*, NEW JERSEY ONLINE LLC (Sept. 25, 2013), http://www.nj.com/business/index.ssf/2013/09/study_finds_americans_spent_mo.html.

[16] *Expanding the Use of Generic Drugs,* OFFICE OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION 2 (2010), *available at* http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.pdf.

[17] *Facts About Generic Drugs*, *supra* note 8.

continue its expansion as many popular innovator drugs[18] are expected to lose their patent protection by 2015.[19]

Despite the affordability of generic drugs, the debate over whether generic drugs actually provide the same therapeutic benefits as their brand-name counterparts has persisted ever since generic drugs first entered the market following the implementation of the Drug Price Competition and Patent Term Restoration Act.[20] Although the Act established regulatory guidelines and an approval process for generic drugs, certain experts have argued that the benefits of generic and brand-name drugs are far from identical.[21] Some experts further assert that generic drugs are allowed to be more or less effective than brand-name drugs under current federal regulations,[22] but others maintain that generic drugs are equally safe and therapeutic.[23]

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[18] Innovator drugs are also known as "pioneer drugs" or "brand name drugs." Justina Molzon, *The Generic Drug Approval Process*, 5 J. PHARMACY & L. 275, 275 n.1 (1995).

[19] *Facts About Generic Drugs*, *supra* note 8.

[20] 21 U.S.C. § 355 (2013).

[21] Studies have revealed the acceptable bioequivalence variance between generic and brand-name drugs, under FDA standards, may be of concern for certain drugs. *See, e.g.*, Sheila Croze, Jeanne M. DeCara & Rodney H. Falk, *Generic Warfarin: A Cost-effective Alternative to Brand-name Drug or a Clinical Wild Card?*, 113 CHEST 261, 262 (1998) ("The potential variation in bioavailability among different brands of warfarin may cause significant problems because minor dose changes in susceptible patients, such as the elderly, can result in clinically significant and potentially life-threatening deviations in the INR.").

[22] Although the FDA requires testing to prove the equality of generic and brand-name drugs, debate has persisted over the quality of those standards and the sameness of generic and brand name drugs. *See* Charles Seife & Rob Garver, *Generic Drugs Are Actually Not the Same as Brand Name Drugs, Thanks to FDA Malfeasance*, ALTERNET (Apr. 24, 2013), http://www.alternet.org/drugs/generic-drugs-are-actually-not-same-name-brands-thanks-fda-malfeasance ("[T]he Food and Drug Administration determined that a major laboratory had committed such 'egregious' research violations that years' worth of its tests—many comparing generics to name-brand drugs—were potentially worthless."); s*ee also Drug expert explains how generics do and do not differ from brand-name drugs*, THE WASHINGTON POST (Oct. 8, 2012), http://articles.washingtonpost.com/2012-10-08/national/35502670_1_generic-drugs-biotech-drugs-brand-name-drugs ("For oral dosages—tablets and capsules—the generic

Despite the presence of such debate, the significantly lower price of generic drugs has made the purchase of generics attractive to many consumers. Few consumers realize, however, that the safety risks and financial costs associated with generic drug purchases may be changing dramatically due to recent Supreme Court rulings. In June 2013, the Supreme Court handed down its most recent decision regarding generic drug makers in *Mutual Pharmaceutical Co. v. Bartlett*.[24] In *Bartlett*, the Supreme Court held federal law preempts state law design-defect claims against generic drug manufacturers.[25] Two years prior, in *PLIVA, Inc. v. Mensing*,[26] the Court held federal law also pre-empts state law failure-to-warn claims against generic drug manufacturers.[27] These decisions have not only provided generic drug makers with immunity from state law tort claims that turn on the adequacy of drug warning labels, but have also compromised incentives for monitoring consumer safety risks by negating the legal remedies of consumers who wish to bring design-defect claims after experiencing dangerous reactions to a generic drug.[28] Simply put, the judiciary has given consumers many reasons to question their options at the pharmacy.

Accordingly, this Recent Development discusses the ways in which the *Bartlett* decision continues to alter the health risks and

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drug need not have the same inactive ingredients. In fact, generic manufacturers may not even know what the inactive ingredients are in the brand-name drugs."). *But see Generic Drugs: Questions and Answer*, *supra* note 14 ("A generic drug is the same as a brand-name drug in dosage, safety, strength, quality, the way it works, the way it is taken and the way it should be used.").

[23] *See, e.g.*, R. Lionberger, W. Jiang, S-M. Huang & G. Geba, *Confidence in Generic Drug Substitution*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 438, 440 (2013) ("Patients should have confidence based on more than 25 years of successful substitution that the generic drugs they are prescribed in the United States can be effectively substituted for the brand product or another generic product.").

[24] 133 S. Ct. 2466 (2013).

[25] *Id.* at 2480.

[26] 131 S. Ct. 2567 (2011).

[27] *Id.* at 2581–82.

[28] *See Bartlett*, 133 S. Ct. at 2468; *PLIVA*, 131 S. Ct. at 2582.

financial costs associated with generic drug purchases. This Recent Development further examines how *Bartlett* diminishes incentives for generic drug manufacturers to monitor long-term safety risks, particularly when the generic drug manufacturer becomes the sole drug application holder and the brand-name manufacturer no longer produces the drug at all. Part II provides a brief summary of federal law that has encouraged the growth of the generic pharmaceutical drug industry. Part III then considers pre-*Bartlett* discussions of failure-to-warn and design-defect claims against generic drug manufacturers. Part IV inspects the Supreme Court's holding, reasoning, and analysis in *Bartlett*. Part V reviews policy considerations relevant to generic drug consumers and generic drug makers under *Bartlett*. Finally, Part VI discusses the FDA's intention to propose a new regulation that may counteract *Bartlett* and redistribute liability to generic drug manufacturers.

II. THE RISE OF THE GENERIC DRUG: THE FOOD AND DRUG COSMETICS ACT AND THE HATCH-WAXMAN ACT

The Food, Drug and Cosmetics Act[29] ("FD&C Act") requires that the FDA approve all drugs, both generic and brand-name, before they are manufactured or delivered into interstate commerce.[30] Additionally, the FDA is responsible for ensuring the safety and efficacy of all drugs through its new drug application ("NDA") and abbreviated new drug application ("ANDA") approval processes.[31] Since 1938, the NDA has been "the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S."[32] The FDA's duties not only include ensuring the safety and effectiveness of a new drug, but also validating the appropriateness of labeling and package inserts and further confirming the

[29] 21 U.S.C. §§ 301–399 (2012).
[30] *Id.* § 355(a).
[31] *Id.* § 355(i).
[32] *New Drug Application (NDA)*, FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/ (last updated Feb. 21, 2013).

manufacturing process is conducive to the drug's "strength, quality, and purity."[33] Requirements for approval generally include a report demonstrating: (1) investigations of the safety and effectiveness of the drug; (2) components used in the drug; (3) composition of the drug; (4) methods, facilities and controls used to develop the drug; (5) research on pediatric use if applicable; (6) samples of the drug and its components; and (7) the proposed labeling of the drug.[34] After a drug maker submits its application, the FDA will either approve the drug, or disapprove the drug and provide the maker with an opportunity for a hearing.[35]

The FD&C Act requires generic drugs to have the same active ingredients, method of administration, and strength as the innovator drug.[36] Likewise, the statute also demands the generic drug be "bioequivalent to the listed drug."[37] The implementation of

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[33] 21 U.S.C. § 355(b)(1) (requiring applications for a new drug application include: "[1] full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; [2] a full list of the articles used as components of such drug; [3] a full statement of the composition of such drug; [4] a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; [5] such samples of such drug and of the articles used as components thereof as the Secretary may require; [and 6] specimens of the labeling proposed to be used for such drug").

[34] *Id.*

[35] *Id.* § 355(c)(1).

[36] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585. The FD&C Act was amended in 1984 to require generic drug applications prove the existence of the same active ingredients, method of administration, dosage, strength, and labeling. *See* 21 U.S.C. § 355(j)(2)(A)(i)–(v) (2012) (stating applicants seeking approval of generic drug applications must prove the use "proposed for the new drug have been previously approved for a drug listed[,] . . . the active ingredient of the new drug is the same as that of the listed drug[,] . . . the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred[,] . . . the new drug is bioequivalent to the listed drug[,] . . . [and] the labeling proposed for the new drug is the same as the labeling approved for the listed drug").

[37] 21 U.S.C. § 355(j)(2)(A)(i)–(v). A drug is considered to be "bioequivalent" if "the rate and extent of absorption of the drug do[es] not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar

the FD&C Act essentially provided drug makers with the ability to manufacture generic drugs following patent expiration.[38] The Act also permitted a shorter approval process if the generic drug had the necessary matching qualities of the innovator drug.[39] Generic drug manufacturers can now circumvent the lengthy, traditional NDA approval process by filing an ANDA.[40] To qualify for an ANDA, the new drug must bear the same "active ingredient(s), dosage form, strength, route of administration, and conditions of use" as the listed drug.[41] Accordingly, the median approval time for a generic drug is thirty-one months.[42] In contrast, the average time required for the discovery, development, and approval of a brand-name drug can span ten to fifteen years.[43]

After a generic or brand-name drug successfully completes the FDA application process, the agency allows no "changes [to the] qualitative or quantitative formulation of the drug product,

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experimental conditions in either a single dose or multiple doses." *Id.*§ 355(j)(8)(B)(i)–(ii). A drug is also considered bioequivalent if "the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient." *Id.* If the brand name and generic drug have different rates of absorption, the rate of absorption for the generic drug must be intentional, apparent in the labeling, and considered medically insignificant. *Id.* A "listed" drug is a new drug that has received approval and subsequently retained this approval for its safety and effectiveness. 21 C.F.R. § 314.3(b) (2013).

[38] *Id.*; *see also* Elizabeth Weiswasser & Scott Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 ANTITRUST L.J., 585, 586 (2003) ("Generic drug manufacturers were also provided a 'safe harbor' from claims of patent infringement by pioneers for activities reasonably related to obtaining and submitting data to the FDA.").

[39] 21 C.F.R. § 314.3(b) (2013).

[40] *Id.* § 314.92(a)(1) (2013).

[41] *Id.* § 314.92(a)(1).

[42] *Fact Sheet: New User Fees for Generic Drugs Will Enhance Americans' Access to Less Expensive Drugs and Generate Major Cost Savings*, FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm310992.htm (last updated Aug. 17, 2012).

[43] *Drug Discovery and Development*, PHRMA: INNOVATION.ORG (2007), *available at* http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf.

including active ingredients, or in the specifications provided in the approved application."[44] Changes to a warning label must be approved through a supplemental application process prior to distribution.[45] Additionally, the FDA will withdraw approval for a generic drug if it later discovers "the labeling for the drug product that is the subject of the [ANDA] is no longer consistent with that for the listed drug referred to in the [ANDA], except for differences approved in the [ANDA]."[46] The warning label is not limited to the packaging of the drug itself, but also includes other methods commonly used by manufacturers to convey drug safety information, such as "dear doctor" letters.[47] These letters must also be consistent with the approved drug labeling because if "generic drug manufacturers, but not the brand-name manufacturer, sent such letters, that would inaccurately imply a therapeutic difference between the brand and generic drugs and thus could be impermissibly 'misleading.'"[48] Any inconsistencies between letters to healthcare providers and approved labeling could result in violation of federal law.[49]

Since its enactment in 1938, the FD&C Act has been modified several times.[50] In 1984, for example, it was amended by the Drug Price Competition and Patent Term Restoration Act,[51] or commonly known as the Hatch-Waxman Act. The Hatch-

[44] 21 C.F.R. § 314.70(b)(2)(i).

[45] *Id.* § 314.70(b)(2)(v).

[46] *Id.* § 314.150(b)(10).

[47] *Id.* § 202.1(*l*)(2) (2013). "Dear doctor" letters are direct mailings frequently used to alert to healthcare providers about labeling changes and other updated safety information. *See* Kathleen Mazor, *Communicating safety information to physicians: an examination of dear doctor letters*, 14 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 869, 869–70 (2005). Although the purpose of these letters is to encourage healthcare professionals to modify their practices as new safety information becomes available, some studies have revealed these letters do not effectively result in change. *Id.*

[48] PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2576 (2011).

[49] *See* 21 CFR § 314.150(b)(3).

[50] *See Significant Amendments to the FD&C Act*, FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/default.htm (last updated Oct. 17, 2013).

[51] Pub. L. No. 98-417, 98 Stat. 1585.

Waxman Act requires the composition and labeling of a generic drug match that of the brand-name drug in order to attain approval from the FDA.[52] Since 1984, Congress has continued to modify the FD&C Act, broadening the FDA's power to regulate drug manufacturers as technology and public health has become more complex.[53] In 2007, for example, the FD&C Act was amended to require that manufacturers account for updated safety information that becomes available after a NDA has been approved.[54] This revision reinforced manufacturer responsibility by giving the FDA authority to require drug manufacturers to change their warning labels through the FDA's approval process.[55]

III. PRE-*BARTLETT* DISCUSSIONS OF DESIGN-DEFECT, FAILURE-TO-WARN CLAIMS AGAINST DRUG MANUFACTURERS

Although federal law strives to ensure that generic drugs are the same as brand-name drugs, *Bartlett* provides reasons to believe the risks and protections for generic and brand-name consumers are becoming increasingly dissimilar. Prior to *Bartlett*, failure-to-warn and design defect claims against drug manufacturers were fairly common. In *Wyeth v. Levine*,[56] for example, the Supreme Court upheld a $7.4 million judgment for Diana Levine, finding that brand-name drugs makers were not generally pre-empted from failure-to-warn claims because they were permitted to change their drug warning labels without FDA approval.[57] In April 2000,

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[52] 21 U.S.C. § 355 (2013).

[53] *See, e.g.*, Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296.

[54] *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823.

[55] *Id.*

[56] 555 U.S. 555 (2009). *Wyeth* was extremely favorable for consumers. *See* 2 Food & Drug Admin. § 26:79.50 (3d ed. 2013) ("[M]any defense pre-emption arguments in drug liability cases failed, where there is no evidence that the FDA would not have permitted the strengthening of the labels of drugs in a manner consistent with state law.").

[57] *Wyeth*, 555 U.S. at 591 (" '[C]hanges being effected' regulation allows drug manufacturers to change their labels without the FDA's preapproval if the changes 'add or strengthen a contraindication, warning, precaution, or adverse reaction,' or 'add or strengthen an instruction about dosage and administration

Levine went to a local clinic seeking relief after suffering from headaches and nausea.[58] Levine was given two medications for treatment, Phenergan for her nausea and Demerol for her headache.[59] The first medication, Phenergan, was the brand-name drug for promethazine hydrochloride.[60] This antihistamine nausea medication was injected in Levine's vein using the "IV-push" method, a type of administration that allowed the drug to be quickly injected directly into the vein.[61] As a corrosive drug, Phenergan can cause gangrene when it contacts an artery.[62] Consequently, Levine developed irreversible gangrene and her right forearm had to be amputated.[63]

Levine brought both negligence and strict liability claims against the drug's manufacturer, Wyeth,[64] alleging the warning label of the drug "was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration instead of the higher risk IV-push method."[65] Levine further asserted that the drug was not "reasonably safe for intravenous administration because the foreseeable risks of gangrene and loss of limb [were] great in relation to the drug's therapeutic benefits."[66] The FDA had approved Phenergan's warning label before it first entered the marketplace in 1955.[67] Wyeth subsequently submitted supplemental drug applications to change the drug's warning label in 1973, 1976, 1981, and 1988.[68] Although Wyeth made efforts to ensure the adequacy of

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that is intended to increase the safe use of the drug product,' in order to 'reflect newly acquired information,' including 'new analyses of previously submitted data,' ") (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A); *id.* § 314.70(c)(6)(iii)(C); 73 Fed Reg. 49603, 49609).

[58] *Id.* at 559.

[59] *Id.*

[60] *Id.*

[61] *Id.*

[62] *Id.*

[63] *Id.*

[64] Levine settled her claims against the local health center and clinician. *Id.*

[65] *Id.* at 559–60.

[66] *Id.* at 560.

[67] *Id.* at 561.

[68] *Id.*

Phenergan's warning label, the trial court found that its compliance was not enough because it had not sincerely attempted to change its label.[69] The jury agreed with Levine's arguments, finding not only that Phenergan was critically defective because of its instructions and warning label, but also that Wyeth was negligent.[70]

Wyeth argued that changing its warning label would have violated federal law and hindered Congress's objectives by "[substituting] a lay jury's decision about drug labeling for the expert judgment of the FDA."[71] After reviewing evidence containing twenty prior instances of amputations like Levine's, the trial court rejected Wyeth's pre-emption argument, finding that "regulations permit strengthened warnings without FDA approval on an interim basis."[72] Similarly, the Vermont Supreme Court reasoned Wyeth "could have warned against IV-push administration without prior FDA approval, and . . . federal labeling requirements create a floor, not a ceiling, for state regulation."[73]

Although *Wyeth* involved a brand-name drug maker, the Supreme Court was similarly forced to address pre-emption issues as it did recently in *Bartlett*.[74] The Court emphasized that

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[69] *Id.* Wyeth did submit a revised Phenergan label in 1988 following the FDA's suggestion to warn about the risk of artery exposure in 1987. *Id.* Although the FDA did not respond to Wyeth's 1988 submission, the trial judge in *Wyeth* instructed the jury that the FDA allows drug manufacturers to strengthen its warning label prior to approval, provided the manufacturer later submits the revised warning to the FDA for review. *Id.* at 561–62.

[70] *Id.* at 562.

[71] *Id.* at 564.

[72] *Id.* at 562.

[73] Levine v. Wyeth, 944 A.2d 179, 184 (Vt. 2006).

[74] *Wyeth*, 555 U.S. at 555. The Court has previously awarded compensation for plaintiffs in tort claims when pre-emption issues exist. *See* Silkwood v. Kerr-McGee Corp., 464 U.S. 238 (1984) (holding that the award of punitive damages under state law was not pre-empted by Atomic Energy Act of 1954 because Congress did not intend to prevent remedies for plaintiffs who suffered injuries from radiation); *see also* Bates v. Dow Agrosciences LLC, 544 U.S. 431 (2005) (holding that claims under state law were not pre-empted by Federal Insecticide, Fungicide, and Rodenticide Act when state law was fully consistent with federal requirements). Additionally, many critics have argued the importance of available remedies for plaintiffs who suffer injuries resulting from

Congress's 1962 amendments only allowed for state law invalidation if it presented a direct conflict with the FD&C Act.[75] The Court subsequently rejected Wyeth's argument that it was impossible to comply with both state and federal law because the FDA's "changes being effected" ("CBE") regulation permits certain preapproval labeling changes that add or strengthen a warning to improve drug safety.[76] The Court reasoned:

> Wyeth's cramped reading of the CBE regulation and its broad reading of the [FD&C Act]'s misbranding and unauthorized distribution provisions are premised on a more fundamental misunderstanding. Wyeth suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. Yet through many amendments to the [FD&C Act] and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.[77]

In holding that federal law did not pre-empt Levine's claim against Wyeth for Phenergan's inadequate warning, the Court reasoned it was "not impossible for Wyeth to comply with its state and federal law obligations and that Levine's common-law claims [did] not stand as an obstacle to the accomplishment of Congress' purposes in the [FD&C Act]."[78] The Court also made three other important findings: (1) the FD&C Act does not expressly provide the FDA with complete or absolute authority;[79] (2) the FDA failed to allow

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negligence, even when pre-emption issues exist. *See, e.g.*, Shane Levesque, *Pre-emption and the Public Health: How* Wyeth v. Levine *Stands to Change the Ways in Which We Implement Health Policy*, 3 ST. LOUIS U. J. HEALTH L. & POL'Y 307, 335 (2010) ("The Court's tendency to consider the availability of relief for those plaintiffs for whom compensation would be precluded entirely by pre-emption may therefore weigh against the FDA's assertion that its labeling requirements pre-empt state law failure-to-warn claims. After all, the [FD&C Act] does not include a federal remedy for those who are injured because of a drug manufacturer's negligence.").

[75] *Wyeth*, 555 U.S. at 567.

[76] *Id.* at 591.

[77] *Id.* at 570–71.

[78] *Id.* at 581.

[79] *Id.* at 576.

notice and comment in announcing its pre-emptive authority;[80] and (3) it is unlikely the FDA would be able to monitor the safety of consumers as well as states would.[81]

Although the Court highlighted the important role of states in monitoring consumer drug safety in *Wyeth*, the Court's reasoning was not so favorable for generic drug consumers two years later.[82] Despite the *Wyeth* Court's ruling that failure-to-warn claims are not pre-empted for brand-name drug makers, the Court determined that failure-to-warn claims against generic drug makers are pre-empted by the FD&C Act in *PLIVA v. Mensing*.[83] In separate claims that were later consolidated, petitioners Gladys Mensing and Julie Demahy alleged that the drug manufacturers of the generic metoclopramide drug failed to provide adequate warning labels.[84] In 2001 and 2002, each began taking the generic form of Reglan for several years before developing tardive dyskinesia.[85] Reglan, the brand-name for metoclopramide, is a drug designed to support the digestive system.[86] It was first distributed by generic

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[80] *Id.* at 559–60. *See* Administrative Procedure Act, 5 U.S.C. § 553 (2013) (requiring agencies to publish notice before adopting a rule and to provide the opportunity for the public to "participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation").

[81] *See Wyeth*, 555 U.S. at 578–79 ("The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the [FD&C Act]'s premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.").

[82] PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011).

[83] *Id.* at 2572.

[84] *Id.*

[85] *Id.* Tardive dyskinesia is a severe neurological disorder that can occur randomly, or as the result of antidopaminergic therapy. CHRISTOPHER U. CORRELL, ENCYCLOPEDIA OF AUTISM SPECTRUM DISORDERS 3067 (Fred R. Wolkmar ed., 2013). It is often irreversible in adults and is characterized by involuntary movement of the extremities, face, tongue, and lips. *Id.*

[86] *PLIVA*, 131 S. Ct. at 2572.

drug manufacturers five years after the FDA approved Reglan in 1980.[87] Following Reglan's distribution, studies revealed that a third of the patients using the drug developed tardive dyskinesia.[88] Since the drug first entered the market, several modifications had been suggested and implemented to modify the labeling of the brand-name drug to warn against excessive use and the risks of developing tardive dyskinesia.[89] It was not until 2009, several years after Mensing and Demahy started taking the drug, that the FDA began to require Reglan to include black box content to warn that "[t]reatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible."[90] Accordingly, Mensing and Demahy alleged that the warning labels of the generic Reglan were not adequate "despite mounting evidence that long term metoclopramide use carries a risk of tardive dyskinesia far greater than that indicated on the label."[91]

Mensing and Demahy alleged the manufacturer should have known that long-term use of Reglan could cause tardive dyskinesia and should have also known the generic label was not adequate.[92] They also argued that the manufacturers could have distributed dear doctor letters[93] or used the FDA's CBE process to modify their warning label without approval.[94] Unless the generic manufacturer alters its label to reflect a brand-name label change, however, the FDA stipulates the CBE process applies only to brand-name drug makers.[95] Any label change by the generic manufacturers outside of this scope would have violated federal law.[96] The Court also noted that dear doctor letters are considered a form of labeling by the FDA. Thus, even if the manufacturers

[87] *Id.* at 2569.
[88] *Id.* at 2572.
[89] *Id.*
[90] *Id.* at 2573.
[91] *Id.*
[92] *Id.* at 2574.
[93] *See supra* note 47 and accompanying text.
[94] *Id.* at 2575–76.
[95] *Id.*
[96] *Id.*

had attempted to warn healthcare professionals with these letters, such action would have violated federal law.[97]

Like the brand-name manufacturers in *Wyeth*, the generic manufacturers in *PLIVA* argued it was not possible for them to comply with state and federal law simultaneously.[98] In its reasoning, the *PLIVA* Court considered the laws of each state in which the petitioners resided, Minnesota and Louisiana. Under Minnesota law, drug manufacturers must give warnings when they have actual or constructive knowledge of dangers to users.[99] Louisiana law similarly imposed a duty on manufacturers to provide instructions for safe use of the drug.[100] Under each state law, the manufacturers were required to strengthen its warning label for metoclopramide.[101] The manufacturers argued that federal law prevented this change by requiring generic manufacturers to use the same safety labeling as the brand-name manufacturer of Reglan.[102] This argument was rejected by the Court of Appeals for the Fifth and Eighth Circuits, which held the state law tort claims were valid and not pre-empted by federal law.[103]

The Supreme Court ultimately reversed the Court of Appeals in *PLIVA*, holding that "federal law pre-empted state law's imposing the duty to change a drug's label upon generic drug manufacturers" and that strengthening the warning label of metoclopramide was impossible.[104] The Supreme Court reasoned that the FDA and generic drug labeling regulations only allow changes to warning labels when the brand-name changes its warning labels first.[105] Additionally, it asserted that lack of express pre-emption in federal law did not imply that state law was not pre-empted.[106] Despite the manufacturers' failure to ask the FDA for guidance on

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[97] *Id.* at 2576.
[98] *Id.* at 2573; *see also* Wyeth v. Levine, 555 U.S. 555, 567 (2009).
[99] *PLIVA*, 131 S. Ct. at 2573.
[100] *Id.*
[101] *Id.*
[102] *Id.* at 2577.
[103] Mensing v. Wyeth, Inc., 588 F.3d 603, 614 (8th Cir. 2009).
[104] *PLIVA*, 131 S. Ct. at 2573.
[105] *Id.* at 2577.
[106] *Id.* at 2579.

strengthening its warning labels, the Court determined this did not affect the "impossibility" analysis it employed.[107] The Court also reasoned it was not possible for the generic drug manufacturers to comply with a state law to make the drug labels safer and federal law that required generic drug manufacturers maintain the same label as the brand-name manufacturer.[108] Additionally, the Court added, "requesting FDA assistance would have satisfied the Manufacturers' federal duty [but] would not have satisfied their state tort-law duty to provide adequate labeling."[109] The Court further noted that although "[s]tate law demanded a safer label[,] it did not instruct the Manufacturers to communicate with the FDA about the possibility of a safer label."[110]

IV. *MUTUAL PHARMACEUTICAL, CO. V. BARTLETT* AND WARNING LABELS: LIMITING THE LEGAL REMEDIES OF GENERIC DRUG USERS

In 2013, the Supreme Court further narrowed consumer remedies against generic drug manufacturers in *Mutual Pharmaceutical, Co. v. Bartlett*.[111] In *Bartlett*, Karen Bartlett brought action against a generic drug manufacturer after she ingested sulindac, the generic form of Clinoril.[112] Although Bartlett was prescribed the brand-name drug, her pharmacy dispensed the generic drug manufactured by Mutual Pharmaceutical.[113] After taking the drug, Bartlett developed toxic necrolysis,[114] a condition that left her with severe lesions and burns covering nearly sixty percent of her body.[115] Bartlett also suffered from blindness and had to

[107] *Id.* at 2577.
[108] *Id.*
[109] *Id.* at 2578.
[110] *Id.*
[111] 133 S. Ct. 2466 (2013).
[112] *Id.* at 2471. Clinoril is a nonsteroidal anti-inflammtory drug ("NSAID") intended to relieve pain, swelling and tenderness. National Institute of Health, *Sulindac*, MEDLINEPLUS, http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681037.html (last updated Sept. 1, 2010).
[113] *Bartlett*, 133 S. Ct. at 2472.
[114] *Id.*
[115] *Id.*

undergo twelve eye surgeries.[116] Because Bartlett's reaction to the drug was so severe, she was put in a medically-induced coma.[117] The sulindac also caused disfiguration and several other disabilities.[118] The warning label on the generic and brand-name drug did not state that toxic necrolysis was a risk, but did caution against severe skin reactions and fatalities.[119] Subsequent to Bartlett's severe adverse reaction, the FDA suggested "changes to the labeling of all [nonsteroidal anti-inflammatory drugs], including sulindac, to more explicitly warn against toxic epidermal necrolysis."[120] Bartlett brought a failure-to-warn and design-defect claim because the warning label on the generic drug label did not list toxic necrolysis as a possible risk at the time she began using it for treatment.[121]

The U.S. District Court of New Hampshire dismissed the failure-to-warn claim for lack of causation,[122] but ruled in favor of Bartlett's design-defect claim, awarding her approximately $21 million in damages.[123] The First Circuit agreed with the lower court's finding that "neither the [FD&C Act] nor the FDA's regulations pre-empted respondent's design-defect claim."[124] It reasoned that Mutual Pharmaceutical could have chosen to comply with both state and federal regulations by not manufacturing the drug at all.[125]

The Supreme Court relied heavily on *PLIVA* to determine "[s]tate-law design-defect claims that turn on the adequacy of a

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[116] *Id.*
[117] *Id.*
[118] *Id.* at 2468.
[119] *Id.* at 2472.
[120] *Id.*
[121] *Id.* at 2468. Later in 2005, the FDA recommended a stronger warning label to include toxic necrolysis. *Id.*
[122] Bartlett v. Mut. Pharm. Co., 760 F. Supp. 2d 220, 229 (D.N.H. 2011). Although the District Court rejected Mutual Pharmaceutical's argument that its warning label was adequate as a matter of law, it found lack of causation because Bartlett's physician did not read the warning label before he prescribed the drug. *Id.*
[123] *Bartlett*, 133 S. Ct. at 2472.
[124] *Id.*
[125] *Id.*

drug's warnings are pre-empted by federal law."[126] Although Bartlett argued the manufacturer could comply with both the federal law and state law by not manufacturing the drug, the Court concluded that this proposed alternative did not change their conclusion that the state law was pre-empted.[127]

While New Hampshire imposes a duty on manufacturers to ensure their products are not "unreasonably dangerous,"[128] the Court reasoned that it was "impossible for Mutual to comply with both its state-law duty to strengthen the warnings on sulindac's label and its federal-law duty not to alter sulindac's label."[129] New Hampshire law requires a warning label that is " 'reasonable under the circumstances' to notify the doctor of the drug's safety risks."[130] Its adequacy is judged by its factual content, expression of facts, method of conveyance, and in light of the facts known at the time.[131] Therefore, in order for Mutual Pharmaceutical to comply with state law, it would have needed to either redesign the drug or change the warning label.[132] The Court noted that the redesigning of the label was not possible for two reasons: "First, the [FD&C Act] requires a generic drug to have the same active ingredients, route of administration, dosage form, strength, and *labeling* as the brand-name drug on which it is based . . . . Second, because of sulindac's simple composition, the drug is chemically incapable of being redesigned."[133]

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[126] *Id.* at 2470.

[127] *Id.* at 2478.

[128] *Id.* at 2474. In New Hampshire, a manufacturer has a "duty to design his product reasonably safely for the uses which he can foresee." Thibault v. Sears, Roebuck & Co., 395 A.2d 843, 847 (N.H. 1978). The Court rejected Mutual Pharmaceutical's argument that New Hampshire "imposes no substantive duties on manufacturers," but noted that the "unreasonably dangerous" standard is not meant to make manufacturers insurers of their products. *Bartlett*, 133 S. Ct. at 2474.

[129] *Bartlett*, 133 S. Ct. at 2473.

[130] Bartlett v. Mut. Pharm. Co., 731 F. Supp. 2d 135, 144 (D.N.H. 2010) (quoting Brochu v. Ortho Pharm. Corp., 642 F.2d 652 (1st Cir. 1981)).

[131] *Id.*

[132] *Bartlett*, 133 S. Ct. at 2474.

[133] *Id.* at 2475 (emphasis added).

Under state law, the manufacturer had a duty to change the warning label, but the Court subsequently held that Mutual Pharmaceutical was obligated to keep the label the same under federal law.[134] The Court rejected Bartlett's argument that Mutual Pharmaceutical could have complied with both state and federal law by no longer selling the drug at all.[135] In finding that this argument defeats the purpose of the impossibility defense, the Court noted "pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability."[136] The Court described Bartlett as a victim of unfortunate circumstances, including:

> [T]he FDA's decision to approve the sale of sulindac and the warnings that accompanied the drug at the time it was prescribed, the decision by respondent's physician to prescribe sulindac despite its known risks, and Congress's decision to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying either the drugs' compositions or their warnings.[137]

Following *Bartlett*, consumers who purchase brand-name drugs and experience severe adverse effects or other dangers can be compensated by sufficiently proving the existence of an inadequate warning label or other unreasonable risk. However, consumers who purchase generic drugs will not be compensated in otherwise factually identical situations.

V. POLICY CONSIDERATIONS: *BARTLETT* AND *PLIVA* LESSEN INCENTIVES FOR GENERIC DRUG MANUFACTURERS TO MONITOR HEALTH AND SAFETY RISKS

By expanding generic drug maker protection from liability, *PLIVA* and *Bartlett* seemingly uphold some of the practical reasons supporting the Hatch-Waxman Act and the FD&C Act by keeping

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[134] *Id.*
[135] *Id.* at 2477.
[136] *Id.*
[137] *Id.* at 2480.

the costs of generic drugs low.[138] However, other policy considerations, such as the diminishing incentives for generic drug manufacturers to monitor potential health and safety risks, are essential to evaluating the true effect of these rulings.[139] The ability for a consumer to bring a design-defect or failure-to-warn claim against a generic drug manufacturer promotes the mitigation of health risks and ensures that all drug manufacturers will attempt to invest in safety studies and provide adequate warnings upon becoming aware of dangerous risks.

The Hatch-Waxman Act was intended to benefit both consumers and stakeholders in the pharmaceutical industry. The Act was designed to "ensure that brand-name . . . drug manufacturers would have meaningful patent protection and a period of marketing exclusivity to enable them to recoup their investments in the development of valuable new drug."[140] Further, Congress hoped to "ensure that, once the statutory patent protection and marketing exclusivity for these new drugs has expired, consumers

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[138] *See, e.g.*, Aaron Kesselheim, Michael Green & Jerry Avorn, *Who Is Now Responsible for Discovering and Warning About Adverse Effects of Generic Drugs?*, 310 JAMA 1023, 1023 (2013). In discussing the developing differences between brand-name and generic drugs, Kesselheim et al. highlight safety concerns associated with diminishing incentives, noting:

> Manufacturers of brand-name and generic drugs now face different legal responsibilities for warning about the risks of what are the same drugs. Brand-name manufacturers must closely monitor the safety of their products after approval and update the adverse effects sections of their labels as necessary or else be subject to pay substantial damages based on liability to injured patients. By contrast, generic manufacturers do not face such liability. Thus, once a brand-name company's exclusivity ends and its market share declines, or it stops production altogether, active pharmacovigilance is likely to end, reducing the chance of discovering rare or delayed adverse effects later in a drug's market life that could vitally inform prescribing practice or change a product's risk-benefit assessment.

Id.

[139] *Id.*

[140] *Drug Price Competition and Patent Term Restoration Act of 1984 Before the S. Comm. on the Judiciary*, 113th Cong. (2003) (statement of Daniel Troy, Chief Counsel, Food and Drug Administration), *available at* http://www.fda.gov/newsevents/testimony/ucm115033.htm.

would benefit from the rapid availability of lower priced generic versions of innovator drugs."[141] The Hatch-Waxman Act provided generic drug makers with the ability to circumvent expensive clinical trials, thus saving costs and allowing for the production of cheaper drugs.[142] Similarly, the FD&C Act was enacted primarily to safeguard public health concerns and to ensure that new drugs being developed were effective. The statute provided the FDA with the authority to "demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections."[143]

In *Wyeth*, the Supreme Court declared that "[i]t is a central premise of the Federal Food, Drug, and Cosmetic Act and the FDA's regulations that the manufacturer bears responsibility for the content of its label at all times."[144] Although federal law prohibited the strengthening of the warning label and dear doctor letters in *PLIVA*, the Court noted that the manufacturer still had a duty to seek guidance from the FDA.[145] The FDA, in turn, would have worked with the brand-name manufacturer to change the warning label so that generic drug manufacturers could do so as well.[146] In *PLIVA*, the Court also stressed the FDA's suggestion that the manufacturer could have chosen an alternative solution:

> [The manufacturer] proposed—indeed, w[as] required to propose—stronger warning labels to the agency if they believed such warnings were needed. . . . If the FDA had agreed that a label change was

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[141] *Id.*

[142] 21 U.S.C. § 355(j)(2)(A) (2013). Studies have revealed varying costs of researching and developing a new clinical drug. Some estimates have ranged from as low as $92 million to as high as $883.6 million. *See* Steve Morgan et al., *The Cost of Drug Development: A Systematic Review*, 100 J. HEALTH POL'Y 4 (2010), *available at* http://moglen.law.columbia.edu/twiki/pub/LawNetSoc/BahradSokhansanjFirstPaper/100HealthPoly4_cost_of_drug_development_2010.pdf.

[143] *Regulatory Information: Legislation*, FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/Legislation/default.htm (last updated July 9, 2012).

[144] Wyeth v. Levine, 555 U.S. 555, 570–71 (2009).

[145] PLIVA, Inc. v. Mensing, 131 S. Ct. 2657, 2576 (2011).

[146] *Id.* at 2577.

> necessary, it would have worked with the brand-name manufacturer to create a new label for both the brand-name and generic drug.[147]

Such statements highlight an ongoing duty for both generic and brand-name manufacturers to protect the safety of its consumers. The FDA also highlighted this duty by requiring that labels "be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug."[148] Because the drug will otherwise be considered misbranded,[149] generic drug manufacturers that are aware of safety risks must notify the FDA to properly work toward an accurate label.[150]

Despite these admissions, *PLIVA* and *Bartlett* shield generic drug manufacturers from liability and generic drug users from a legal remedy. Since *PLIVA*, many claims against generic drug manufacturers have been dismissed.[151] Both Supreme Court decisions will likely eliminate incentives for generic drug manufacturers to research, evaluate, and update safety warning labels, leaving the burden to do so primarily on brand-name manufacturers.[152]

With the patents of several top selling blockbuster drugs set to expire in 2015, the generic drug market will continue to dominate

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[147] *Id.* at 2576.

[148] 21 C.F.R. § 201.57(c)(6) (2013).

[149] 21 U.S.C. § 352(f)(2). "Misbranded" drugs are those that lack warning labels guarding against "unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users." *Id.*

[150] 21 C.F.R. § 201.57(e).

[151] Katie Thomas, *Generic Drugs Proving Resistant to Damage Suits*, THE NEW YORK TIMES (Mar. 10, 2012), http://www.nytimes.com/2012/03/21/business/drug-lawsuits-hinge-on-the-detail-of-a-label.html?scp=1&sq=supreme%20court%20generic%20drug&st=cse&_r=0. Shortly after the *PLIVA* ruling in 2011, "[m]ore than 40 judges . . . dismissed cases against generic manufacturers . . . including some who dismissed dozens of cases consolidated under one judge." *Id.*

[152] *See* Marcia M. Boumil & Gregory D. Curfman, *On Access and Accountability—Two Supreme Court Rulings on Generic Drugs*, 369(8) NEW ENGL. J. MED. 696, 697 (2013).

the pharmaceutical industry.[153] Although the use of brand-name drugs is decreasing, only brand-name manufacturers currently bear the responsibility of investing in safety measures and reporting such risks during the FDA approval process.[154] One study revealed one-third of drugs are only available in generic form.[155] Once a brand-name patent has expired, only generic drug makers will be left to uncover safety risk, yet they currently have little incentive to do so.[156]

PLIVA and *Bartlett* are further troubling because many drugs are approved with data based solely on short-term safety studies that fail to adequately measure the long-term effects of the drug at the time of approval.[157] The importance of long-term studies can be observed in *PLIVA*, a case in which the drug did not reveal the risk of tardive dyskinesia until more than twenty years after the FDA first approved the brand-name form of the drug.[158] Some have pinpointed the drug approval process as the issue in monitoring the safety of generic drugs because "[b]y design, the FDA deters generic manufacturers' access to comprehensive data that are readily available to brand-name manufacturers."[159] Unlike brand-name manufacturers, generic drug makers do not have to invest in discovery, pre-clinical studies, and clinical studies. Following *PLIVA* and *Bartlett*, however, the responsibility of generic consumer safety could be shifted to generic drug makers under new federal regulations.

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[153] Stacey Lee, PLIVA v. Mensing*: Generic Consumer's Unfortunate Hand*, 12 YALE J. HEALTH POL'Y L. & ETHICS 209, 240 (2012).

[154] 21 U.S.C. § 355(b)(1) (2013).

[155] GEN. PHARM. ASS'N, *supra* note 1, at 4.

[156] Lee, *supra* note 153, at 241 ("This highlights a common practice in the pharmaceutical industry. A brand-name manufacturer monitors its product only for as long as it has a financial incentive and legal obligation to do so. Once a manufacturer loses its exclusivity, it also loses its revenue stream. As a result, it is not unusual for the brand maker to simply stop selling the drug when facing a dramatic reduction in profits. In these situations, there is no manufacturer with the legal responsibility or ability to uncover inadequate label warnings—or even warn consumers and healthcare providers.").

[157] Lee, *supra* note 153, at 241.

[158] PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2572 (2011).

[159] Lee, *supra* note 153, at 245.

VI. THE GOOD, THE BAD, AND WHAT'S NEXT: FDA REGULATIONS MAY TRANSFER LIABILITY TO GENERIC DRUG MANUFACTURERS

A major concern following *Bartlett* and *PLIVA* is whether laws will be enacted to motivate generic drug manufacturers to search for and identify safety risks even after a drug has been approved by the FDA. Currently, all drug manufacturers have a duty to notify the FDA of new safety risks in annual reports.[160] The report should notify the agency of any information "that might affect the safety, effectiveness, or labeling of the drug product" and future actions the drug maker intends to take in light of this knowledge.[161]

Although the FDA requires both generic and brand-name drug manufacturers to report safety risks, current policies allow only the reference listed drug ("RLD") holder, the brand-name drug manufacturer, to implement changes to the warning label.[162] When knowledge is obtained regarding new safety risks, the FDA mandates that "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug."[163] Brand-name drug manufacturers can make certain changes to warning labels after filing a supplemental application without immediate approval from the FDA. These changes include those intended to "add or strengthen a contraindication, warning, precaution, or adverse reaction [and] . . . add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product."[164] Such changes are appropriate for "newly acquired information" or new analyses of previously submitted data that reflects a "different type or greater severity or frequency than previously included in submissions to FDA."[165]

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[160] 21 C.F.R. §§ 314.81(b)(2)(i); 314.98(c) (2013).
[161] *Id.*
[162] *Id.*
[163] 21 C.F.R. § 201.57(e) (2013).
[164] 21 C.F.R. §§ 314.70(c)(6)(iii)(A)–(C) (2013).
[165] Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603-01, 49604 (Aug. 22, 2008) (to be codified at 21 C.F.R. pts. 314, 601, 814).

Although opinions regarding the court's ruling in *PLIVA* and *Bartlett* differ, both critics and supporters agree that decisions involving the safety of consumers should be left to the authority provided for in the FD&C Act, the FDA.[166] The FDA has previously recognized its regulations are not intended to pre-empt state law claims and instead serve as minimum standards.[167] The agency changed its policies in 2006, however, asserting its regulations did pre-empt state law.[168]

In February 2013, and prior to *Bartlett*, the FDA revealed a new policy following a change to the FD&C Act that would allow it to approve new generic drugs even when its brand-name counterparts are undergoing changes.[169] The new policy allows approval of generic drug applications despite situations in which the brand-name drug is in the process of revising its label.[170] The generic drug manufacturer must agree to subsequently change its

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[166] Industry advocates, such as the Generic Pharmaceutical Association, believe decisions concerning label safety should be in the hands of experts. *See Statement from Ralph G. Neas, President and CEO of the Pharmaceutical Association on the Mutual v. Bartlett Supreme Court Ruling*, GENERIC PHARM. ASS'N (June 24, 2013), http://www.gphaonline.org/gpha-media/press/statement-from-ralph-g-neas-president-and-ceo-of-the-generic-pharmaceutical-association-on-the-mutual-v-bartlett-supreme-court-ruling ("Today's Supreme Court ruling on the *Mutual v. Bartlett* case upholds a key principle: decisions about the safety and efficacy of prescription drugs should rest with scientific experts at the Food and Drug Administration (FDA). When it comes to decisions on safety and approval of prescription medicine, the FDA is best equipped to make judgments that affect patients. The experts at FDA alone have the scientific knowledge, regulatory experience, and complete data to make these decisions.").

[167] Howard L. Dorfman, Vivian M. Quinn & Elizabeth A. Brophy, *Presumption of Innocence: FDA's Authority to Regulate the Specifics of Prescription Drug Labeling and the Pre-emption Debate*, 61 FOOD & DRUG L.J. 585, 590 (2006).

[168] David A. Kessler & David V. Vladeck, *A Critical Examination of the FDA's Efforts to Pre-empt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 463–64 (2008).

[169] OFFICE OF GENERIC DRUGS, GENERIC DRUG LABELING REVISIONS COVERED UNDER SECTION 505(J) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM339381.pdf.

[170] *Id.*

labeling to correspond with the brand-name drug within two months of notification of the revised brand-name drug warning label.[171] To qualify for this exception, the generic drug must meet certain standards, and the FDA must find "that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug product."[172]

In July 2013, the FDA further progressed toward amending its rules on warning labels to provide additional protection for purchasers of generic drugs following *Bartlett*.[173] The agency revealed its intention to propose a new rule that would apply not only to new drug applications, but also to abbreviated new drug applications used by generic drug manufacturers for drug approval.[174] The FDA intends to propose a rule that would change its current regulations to "revise and clarify procedures for changes to the labeling of an approved drug to reflect certain types of newly acquired information in advance of FDA's review of such change."[175] The FDA asserts that the goal of the rule would be to "create parity between NDA holders and ANDA holders with respect to submission of CBE labeling supplements."[176] The current CBE process, first implemented in 1965, was created to communicate drug warnings to consumers and health professionals

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[171] *Id.*

[172] Alexander Gaffney, *FDA Now Able to Temporarily Approve Generic Drugs Using Different Label than RLD*, REGULATORY FOCUS (Feb. 14, 2013), http://www.raps.org/focus-online/news/news-article-view/article/2869/fda-now-able-to-temporarily-approve-generic-drugs-using-different-label-than-rld.aspx.

[173] OFFICE OF INFO. & REGULATORY AFFAIRS, FOOD & DRUG ADMIN., 0910-AG94, SUPPLEMENTAL APPLICATIONS PROPOSING LABELING CHANGES FOR APPROVED DRUGS AND BIOLOGICAL PRODUCTS (Sept. 2013), *available at* http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201304&RIN=0910-AG94.

[174] *Id.*

[175] *Id.* (implementing a process in which "information regarding a 'changes being effected' (CBE) labeling supplement submitted by an NDA or ANDA holder would be made publicly available during FDA's review of the labeling change. The proposed rule also would clarify requirements for the NDA holder for the reference listed drug and all ANDA holders to submit conforming labeling revisions after FDA has taken an action on the NDA and/or ANDA holder's CBE labeling supplement.").

[176] *Id.*

as early as possible.[177] The new amendment aims to synchronize the responsibilities of brand-name and generic drug manufacturers.[178] Essentially, generic drug manufacturers, like Mutual Pharmaceuticals, would be able to change a warning label after becoming knowledgeable of additional risks, regardless of whether or not its brand-name counterpart had done so.[179]

If implemented, the new amendment would help evenly distribute manufacturer responsibility. Currently, generic drug manufacturers have little say in the labeling changes.[180] Since the *PLIVA* ruling, consumer advocacy groups have encouraged the FDA to change its regulations to implement greater manufacturer liability.[181] One of these groups, Public Citizen, has argued such amendments should allow generic drug manufacturers to change its current label by also using the CBE and prior approval supplement processes.[182] Additionally, consumer advocacy groups favor modifying current procedure to prohibit the FDA from withdrawing generic new drug applications when the generic label is different from the brand-name label, suggesting the generic drug manufacturer should instead be allowed to invoke the CBE or prior

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[177] Supplemental New Drug Applications, 30 Fed. Reg. 993, 993–94 (Jan. 30, 1965) (to be codified at 21 C.F.R. pt. 130).

[178] *Id.*

[179] *See id.*

[180] *See* Lee, *supra* note 153, at 241. Lee emphasizes what little input generic drug manufacturers currently have in the drug labeling amendment process. *Id.* at 246 ("Once introduced into the market, the FDA cannot implement subsequent labeling revisions without first negotiating these changes with the drug brand manufacturer. Generic manufacturers are not included in these negotiations. Data and knowledge exchanged here are beyond the reach of the generic manufacturer. In fact, the FDA notifies the generic manufacturer of its proposed changes only if the brand-name manufacturer is no longer marketing the product. Similarly, generic manufacturers cannot access the results of phase IV clinical trials that brand-name manufacturers conduct at the FDA's request.").

[181] *See* Katie Thomas, *F.D.A. Rule Could Open Generic Drug Makers to Suits*, THE NEW YORK TIMES (July 3, 2013), http://www.nytimes.com/2013/07/04/business/fda-rule-could-open-generic-drug-makers-to-suits.html.

[182] Public Citizen, *Citizen Petition to Food and Drug Administration* (Aug. 29, 2011), *available at* https://www.citizen.org/documents/1965.pdf.

approval supplement procedure.[183] Although consumer advocates would like the FDA to protect against labeling changes that may not have any basis,[184] they have also encouraged the FDA to clarify a generic drug manufacturer's duty to immediately report any new safety concern to the FDA.

While this new rule would favor consumers, it could also increase the costs of generic drugs, thereby undermining one of the generic market's major purposes.[185] Estimates show that generic drugs have already saved the healthcare industry more than a trillion dollars since the passage of the Hatch-Waxman Act.[186] Unlike brand-name manufacturers, generic drug makers do not have to invest in clinical studies and, in contrast, do little advertising and promotion in comparison to their brand-name counterparts.[187] If generic drug makers were to be held independently responsible for the labeling of its drugs, they would have to fund and conduct their own safety studies rather than relying on pre-existing brand-name studies, as they currently do.[188] To the contrary, *PLIVA* and *Bartlett* impose no further incentives for manufacturers to invest in independent safety studies by shielding manufacturers from the potential harms experienced by consumers, therefore keeping the costs of generic drugs low.[189]

Although consumer advocates have encouraged the FDA to implement changes, industry advocates have expectedly

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[183] *See id.*

[184] *See id.* ("The amendment might also make exceptions to reflect situations in which the agency believes that particular ANDA holders lack an adequate basis to make labeling changes, such as, perhaps, during the first few months after the first ANDA holder enters the market or for an ANDA holder that sells very few prescriptions of a drug.").

[185] Boumil & Curfman, *supra* note 152, at 697.

[186] Aaron S. Kesselheim et al., *Who Is Now Responsible for Discovering and Warning About Adverse Effects of Generic Drugs?*, 310 JAMA 1023, 1023 (2013).

[187] Robert West, GENERIC DRUGS, *available at* http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM226568.pdf (last visited Nov. 2, 2013).

[188] Boumil & Curfman, *supra* note 152, at 697.

[189] Boumil & Curfman, *supra* note 152, at 696.

demonstrated favor for current regulations.[190] To the contrary, the potential for modification to federal law has received strong Congressional support.[191] Congress has noted that "sameness" is a critical factor in determining the best process for labeling drugs, but also believes "generics should have the ability to participate fully in the labeling process."[192] In *Bartlett*, the Supreme Court also provided commentary supporting the dispersal of responsibility.[193] By holding generic drug manufacturers to a new CBE regulation, generic drug makers could still be liable for inadequate warning labels, despite the *PLIVA* and *Bartlett* rulings. With little details on the new amendment and how courts might interpret new changes, only time will reveal an accurate depiction of its effects.

VII. CONCLUSION

Without the revamping of current FDA regulations, *Bartlett* places the burden of identifying and providing notice of dangerous risks solely on brand-name drug manufacturers.[194] With generic

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[190] Thomas, *supra* note 181. The Generic Pharmaceutical Association, which represents generic manufacturers and distributors, supported the principles upholding the *PLIVA* and *Bartlett* ruling. *See GPhA Pleased with Supreme Court Ruling in* Pliva v. Mensing, GENERIC PHARM. ASS'N (June 23, 2011), http://www.gphaonline.org/gpha-media/press/gpha-pleased-with-supreme-court-ruling-in-pliva-v-mensing ("GPhA believes the High Court has appropriately recognized that current law leaves generic manufacturers with no alternative but to make certain that its products have labeling that is identical to the labeling of the reference brand product."); *see also Statement from Ralph G. Neas*, *supra* note 166.

[191] *See* Letter from Sen. Tom Harkin, Sen. Patrick Leahy, & Sen. Al Franken, to Dr. Margaret Hamburg, Commissioner of Food and Drug Administration (May 9, 2012), *available at* http://www.justice.org/cps/rde/xbcr/justice/Pliva_Letter_to_FDA_5.19.12.pdf.

[192] *Id.*

[193] Mut. Pharm. v. Bartlett, 133 S. Ct. 2466, 2485 (2013) ("[T]he FDA, which is tasked with monitoring thousands of drugs on the market and considering new drug applications, faces significant resource constraints that limit its ability to protect the public from dangerous drugs.").

[194] *See* Lee, *supra* note 153, at 241. Lee argues the absence of generic drug liability can ultimately leave no party with the responsibility for identifying ongoing, long-term safety risks. *Id.* at 240 ("While a generic drug's branded

drug manufacturers already composing a strong majority of the pharmaceutical industry, more stringent federal regulations are needed to hold *all* manufacturers equally accountable for notifying consumers of long-term, dangerous risks. Barring consumers from failure-to-warn and design-defect claims that are based on inadequate warning labels may keep generic drug costs low, but this also increases the associated health and financial risks for consumers substantially.[195] Although the FDA maintains that generic and brand drugs are the same, the lack of incentives for generic drug makers to invest in ongoing safety research, compounded with the newly established lack of recourse for generic drug consumers, brings new uncertainty to this assertion. *PLIVA* and *Bartlett* have seemingly altered the risks of generic drugs. However, the true effect of these Supreme Court decisions will ultimately be determined by the future action or inaction of the FDA.

Until new federal regulations are put into place, the immediate financial savings of generic drugs that many buyers enjoy could turn out to be very costly for unfortunate consumers who experience adverse effects. Modifying the current CBE process to allow generic drug makers to change a drug warning label, without prior FDA approval, would hold them independently responsible for safeguarding the long-term health risks of their drugs. Whether the FDA decides to adopt a new rule could reinforce or curtail the implications of the rulings set forth in *PLIVA* and *Bartlett*.

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counterpart is still on the market, the regulatory framework requires brand-name manufacturers to uncover safety risks. Brand name manufacturers, however, often leave the market once generic versions are approved.").

[195] *See Bartlett*, 133 S. Ct. at 2468; PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2582 (2011).