

ARTICLES

PLIVA v. Mensing: Generic Consumers' Unfortunate Hand

Stacey B. Lee*

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* Assistant Professor, Johns Hopkins Carey Business School; J.D., University of Maryland School of Law. This piece was selected for the 2010 Health Law Scholars Workshop, sponsored by the Saint Louis University Center for Health Law Studies and the American Society of Law, Medicine & Ethics. Thank you to my reviewers: Professors Peter Jacobson, Judith Darr, Nicholas Terry, Efthimi Parasidis, and Robert Gatter.

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INTRODUCTION

The United States Supreme Court held in *PLIVA v. Mensing* that federal preemption immunizes generic drug manufacturers from liability for state law failure-to-warn claims.¹ As a result, consumers harmed by a mislabeled generic drug will be unable to bring actions against generic manufacturers under state law. The Court confessed that the resulting federal drug-labeling scheme dealt consumers an “unfortunate hand.”² By removing generic manufacturers’ duty to improve the adequacy of their products’ warning labels, the Supreme Court calls into question the safety of generic drugs.

This Article explores the unfortunate hand that *PLIVA* dealt generic drug consumers and proposes a framework to increase the odds that generic drug consumers are provided with safe, effective, and adequately labeled generic drugs. To fully understand how *PLIVA* recasts the generic manufacturers’ safety obligations to consumers, this Article begins with a discussion about the approval process for brand-name and generic drugs and the corresponding manufacturer responsibilities. In particular, this Article focuses on manufacturers’ post-approval responsibilities. Next, the discussion examines how *PLIVA* substantively alters generic manufacturers’ post-approval responsibilities and weakens the safety provisions in the drug-labeling framework. This Article then explores the implications this compromised framework could have on consumers, patients, physicians, pharmacists, and states. This Article offers a regulatory framework to remedy the deficiencies created by *PLIVA*. In doing so, the argument addresses anticipated criticisms and illustrates how the proposed framework fulfills the Hatch-Waxman Act’s goal of providing consumers with safe generic drugs.

Changes to the generic drug-labeling framework were instantiated after the Supreme Court determined the validity of the impossibility defense asserted by generic manufacturers to consumer state law failure-to-warn claims. Specifically, the *PLIVA* Court focused its preemptive lens on the regulatory requirements that govern generic manufacturers’ post-approval labeling responsibilities.³ This scrutiny assessed whether the federal regulations imposing a duty on generic manufacturers to maintain warning labels identical to their branded counterparts conflicted with, and therefore preempted, the state law duty to continuously change their warnings in order to produce increasingly safe labels.⁴ The Court concluded that the structure of the federal regulatory requirements rendered it impossible for generic manufacturers to comply with both.⁵

1. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577-78 (2011).

2. *Id.* at 2581.

3. *Id.* at 2575-77.

4. *Id.* at 2577.

5. *Id.*

By finding preemption grounded in “impossibility,” the Court settled much of the debate over the validity of generic manufacturers’ preemption defense. This debate touched on several important legal and moral issues: the appropriate level of judicial deference to agency pronouncements, the scope of State authority to protect citizens through the availability of product liability lawsuits,⁶ and the existence of factual predicates for drug manufacturers to claim preemption.⁷ In this respect, *PLIVA* resolved the question regarding the right of consumers to bring state-level failure-to-warn claims against generic drug manufacturers.

PLIVA exposes, but leaves unresolved, a more fundamental regulatory concern. A central premise of the federal drug regulatory framework is that “the manufacturer bears responsibility for the content of its label at all times.”⁸ Inherent in this responsibility is the federal requirement that generic manufacturers monitor the safety of their products.⁹ Nevertheless, generic manufacturers’ labeling requirements are bound by a regulatory scheme that is devoid of any formal requirements setting forth generic manufacturers’ duty to initiate a label change to warn consumers.¹⁰ The regulations also fail to articulate a label-changing process if a generic manufacturer wants to provide consumers with more accurate and timely product-labeling information.¹¹ Against this backdrop, *PLIVA* further erodes generic manufacturers’ nebulous labeling duties, by inoculating them against liability in situations in which they do not take steps to comply with state law requirements to strengthen their drugs’ safety labels.

While the need to address the inadequacies of the regulations governing generic manufacturers’ post-approval duties is exacerbated by the Court’s holding in *PLIVA*, fissures in the generic-labeling framework are longstanding. Prior to *PLIVA*, consumers faced divergent federal court interpretations regarding generic manufacturers’ obligation to comply with state law duty-to-warn requirements.¹² The split among the circuits intensified after the Supreme Court’s holding in *Wyeth v. Levine*. This decision seemingly sounded the death knell for brand-name manufacturers’ preemption defense to state law failure-to-warn claims when it rejected a similar preemption argument on behalf of brand-name manufacturers.¹³ Although the case did not directly reference generic

6. James M. Beck, *Federal Preemption in FDA-Regulated Product-Liability Litigation: Where We Are and Where We Might Be Headed*, 32 HAMLINE L. REV. 657, 684-87 (2009); Margaret Gilhooley, *Drug Preemption and the Need To Reform the FDA Consultation Process*, 34 AM. J.L. & MED. 535, 536 (2008).

7. Lesley A. Stout, *Making Changes: Generic Drug Labeling and the Case Against Federal Preemption*, 98 KY. L.J. 623, 636-44 (2010).

8. *PLIVA*, 131 S. Ct. at 2576 (quoting *Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009)).

9. *Id.* at 2586 (Sotomayor, J., dissenting).

10. *Id.* at 2582 (majority opinion).

11. *Id.*

12. See discussion *infra* Section II.A.

13. *Wyeth*, 555 U.S. 555.

manufacturers, a majority of circuits extended the Court's preemption exclusion to generic manufacturers.¹⁴

In *PLIVA*, the Supreme Court distinguished the error in such an application. The Court explained that "the federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully different than those that apply to generic drug manufacturers."¹⁵ As articulated by the FDA, the Supreme Court held that tools permitting brand-name manufacturers to change unilaterally their labels are not available to generic manufacturers.¹⁶ The practical effect of such a determination is twofold. First, generic manufacturers are prohibited statutorily from preventing consumer injury by independently strengthening inadequate warning labels on their products. Second, the ability of an injured consumer to bring a failure-to-warn claim against a drug manufacturer turns on "the happenstance" of whether the consumer's pharmacist dispensed the brand-name or generic version of the drug.¹⁷ The Court conceded that such a finding results in a federal drug scheme that deals generic consumers an "unfortunate hand."¹⁸ After this acknowledgement, however, the opinion ends.

This Article picks up where the Supreme Court's decision left off, by exploring the implications of *PLIVA* for individual consumers and drug safety in general. Specifically, the Court's opinion creates a schism in the complementary federal and state regulatory schemes. This may lead to situations in which no manufacturer has the legal responsibility or ability to make the necessary changes to improve warnings; such manufacturers also may not be able to warn consumers and healthcare providers. Moreover, *PLIVA* reinforces regulatory deficiencies that dramatically reduce the awareness of the FDA and drug manufacturers of adverse consumer reactions to generic and brand-name medications. Further, the Court's opinion may have the chilling effect of diminishing consumer confidence in the safety and effectiveness of generic drugs. In refusing to concede the finality of this decision, this Article proposes a regulatory framework that enables generic manufacturers to meet unilaterally their primary responsibility to provide safe and effective drugs to consumers by equipping them with the tools necessary to address labeling concerns.

Part I provides an overview of the drug approval process. Section A of this Part examines the regulatory framework that defines the pre- and post-approval processes for brand-name drugs. Section B provides similar background about the approval procedures for generic drugs. Part II offers a focused analysis of the regulatory framework that defines generic manufacturers' post-approval labeling

14. See *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225 (9th Cir. 2011); *Demahy v. Actavis, Inc.*, 593 F.3d 428 (5th Cir. 2010); *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009).

15. *PLIVA*, 131 S. Ct. at 2582.

16. *Id.* at 2575.

17. *Id.* at 2583.

18. *Id.* at 2581.

responsibilities, explores the duties of generic manufacturers in the wake of *PLIVA*, and examines the probable implications that truncated regulatory requirements will have on consumers, healthcare providers, and states. Section A of Part III highlights problems in the current regulatory framework by explaining how, at critical junctures of the generic drug's pre- and post-approval life cycle, manufacturers are denied data, consultation opportunities, and adequate access to compliance mechanisms. Finally, Section B articulates a practical framework in which generic manufacturers will have the necessary tools to fulfill their responsibility to provide consumers and the medical community with current and accurate labeling instructions for their products.

I. DRUG APPROVAL PROCESS

To appreciate the need for a more responsive legal and regulatory framework for generic drug manufacturers, it is necessary to explore the current drug approval process and how it incorporates generic drugs. In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act (FDCA).¹⁹ This Act granted the FDA exclusive authority to regulate the prescription drug industry.²⁰ Accordingly, it is the FDA's responsibility to ensure that drugs are safe, effective,²¹ and not mislabeled.²² To this end, the FDA is the principal governmental authority that establishes the regulations governing the manufacture, sale, and labeling of prescription drugs.²³

A. Brand-Name Drug Approval and Labeling Process

1. Pre-approval

Pursuant to the FDCA, all drug manufacturers must receive FDA approval before they introduce a new drug on the market.²⁴ For brand-name drugs, this requires the manufacturer to submit a new drug application (NDA) to the FDA. The NDA must contain information about the drug's safety and efficacy, which must be supported by data from clinical trials.²⁵ The manufacturer must also provide proposed labeling that reflects the appropriate drug use and warns about potential dangers and adverse reactions associated with the drug.²⁶

19. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301-399D (1938)).

20. 21 U.S.C. § 355(a) (2006).

21. *Id.*

22. *Id.* § 355(d).

23. *Id.* §§ 321(n), 331(a)-(b), (k), 352, 355, 393(b)(2)(B).

24. *Id.* § 355(a).

25. *Id.* § 355(a)-(b), (d).

26. *Id.* § 355(b)(1)(F). See also 21 C.F.R. § 201.80 (2009) for detailed specifications about a drug's labeling.

Under the FDCA, labeling comprises “all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”²⁷ Also, courts have interpreted labeling to include product advertising attendant to the product.²⁸ A drug label that contains false, misleading, or inadequate information will be rejected by the FDA on the basis that the drug is mislabeled.²⁹

To avoid rejection, brand-name manufacturers work closely with the FDA during the NDA approval process to determine the appropriate labeling for the drug.³⁰ Side effects, contraindications, and relevant hazards are extensively discussed between the manufacturer and the FDA in order to satisfy its requirement that the label includes warnings of known risks based on scientific evidence.³¹ During this process, the FDA takes careful steps to omit risks that are inadequately supported by the scientific research.³² Ultimately, the FDA determines what information is included in the labeling and the exact final version of the instructions.³³ Because drug labeling provides doctors and other medical professionals with information needed to make informed prescription decisions, the FDA’s review of new drugs and their labels typically takes years.³⁴ Under federal law, therefore, the evaluation of a drug’s safety and effectiveness is inextricably linked with the drug’s labeling.³⁵

2. Post-approval

Scrutiny of a drug’s labeling does not end with FDA approval of the NDA. Drug manufacturers have a continued responsibility to maintain accurate labeling information.³⁶ This ongoing responsibility is rooted in several factors. During the pre-approval phase, the drug is tested on relatively small cohorts—generally, between six hundred and three thousand research subjects—and only for a

27. 21 U.S.C. § 321(m).

28. *Kordel v. United States*, 335 U.S. 345, 350 (1948).

29. 21 U.S.C. § 352(a), (f).

30. Brief for Amicus Curiae The United States of America at 5, *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (No. 05-5500), 2006 WL 1724170 [hereinafter *Colacicco Amicus*] (noting that drug manufacturers and the FDA collaborate extensively when deciding about the content of proposed drug labeling).

31. See 21 C.F.R. §§ 201.56(a), 201.57(c).

32. See *Colacicco Amicus*, *supra* note 30, at 7-8.

33. See 21 C.F.R. §§ 201.56(a), 201.57(c).

34. Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 NATURE REVIEWS 417, 418 (2004) (estimating that research, development, testing, FDA review, and approval of a new drug take a minimum of three years).

35. See New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) (“Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.”).

36. 21 U.S.C. § 331(a)-(b), (k) (2006).

limited time period that is rarely in excess of two years.³⁷ As a result, pre-approval testing cannot readily detect adverse effects that occur infrequently, have long latency periods, or affect populations that are underrepresented.³⁸ Further, because underrepresented subgroups rarely provide sufficient data to permit refined analysis, the FDA's assessment of a drug's risks is performed on a population-wide, rather than on a subgroup-by-subgroup, basis.³⁹ In light of these limitations, the resulting FDA-approved labels cannot guarantee that a drug will not cause serious, unexpected adverse effects, even if properly used for the approved purposes.⁴⁰ To monitor the unanticipated adverse events, the FDA requires all manufacturers to submit adverse event reports to it.⁴¹

In the premarketing phase, the FDA is the exclusive authority for determining the adequacy and approval of the drug's label.⁴² The FDA's authority rests in part on its expertise in evaluating the studies provided by the manufacturer.⁴³ However, in the postmarket world, the burden rests squarely on the manufacturer to ensure that its labeling is adequate. In part, this shift in responsibility reflects the decreased data that the FDA receives regarding postmarket drug testing. For example, manufacturers are not required to provide the FDA with evaluations of the drug's performance in the market or assessments of the drug's safety profile after approval.⁴⁴ Even if such an ongoing obligation were to exist, the FDA might still lack sufficient manpower to make meaningful use of these data, in light of chronic resource constraints.⁴⁵

37. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts To Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 471 (2008).

38. INST. MED. NAT'L ACAD., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 37-38 (Alina Baciú et al. eds., 2006).

39. Most clinical studies can detect drug-related injuries that occur at a rate between 1 in 500 and 1 in 1000. "Yet, if the drug is used by 200,000 people . . . a serious adverse event appearing in as few as one in 10,000 people is very significant, since it would occur 20 times. These rare reactions can be identified only after a drug has been widely used." William B. Schultz, *How To Improve Drug Safety*, WASH. POST, Dec. 2, 2004, <http://washingtonpost.com/wp-dyn/articles/A26865-2004Dec1.html>.

40. Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta Analysis of Prospective Studies*, 279 JAMA 1200, 1202 (1998) (explaining that the FDA recognizes that even the most up-to-date, informative labels cannot avert adverse reactions); Kessler & Vladeck, *supra* note 37, at 471-72.

41. 21 C.F.R. § 314.80(b) (2011) (discussing postmarketing reporting obligations for NDA applicants); *id.* § 314.98 (discussing postmarketing reporting obligations for ANDA applicants).

42. 21 U.S.C. § 355(n) (2006). The day of approval is when the FDA is in the best position to comment on the drug's safety and efficacy. During the approval process, the FDA has had access to, and has invested considerable resources in, reviewing all available health and safety data pertaining to the drug.

43. *Id.* § 355(b)(1).

44. Kessler & Vladeck, *supra* note 37, at 492.

45. For example, the FDA's Office of Drug Safety—the unit responsible for monitoring adverse events that arise with the three thousand prescription, and approximately eight thousand over-the-counter, drugs that the FDA has approved—is staffed with one hundred professional employees. *FDA's Drug Approval Process: Up to the Challenge? Hearing Before the S. Comm. on*

As the maker and seller of the product, the primary responsibility to ensure that the drug is safe and effective is rightly placed on the manufacturer.⁴⁶ To this end, there are detailed procedures that regulate postmarket modifications to a drug's labeling.⁴⁷ For example, the brand-name manufacturer is required to conduct extensive postmarketing surveillance.⁴⁸ This includes review and analysis of reported adverse events and published medical and scientific literature.⁴⁹ The FDA requires brand-name manufacturers to disclose any relevant information discovered through this process—including information contained in the adverse reports regarding any version of their product.⁵⁰ In addition, the FDA commonly requires brand-name manufacturers to conduct follow-up phase IV clinical studies after selling their product.⁵¹ This analysis is conducted against the backdrop of the knowledge the manufacturer obtained during the clinical trials and other research conducted throughout the NDA approval process.⁵²

a. Mechanisms for Postmarket Modifications: Prior Approval Supplement

FDA regulations require brand-name manufacturers to provide additional warning labels “as soon as there is reasonable evidence of a causal association”⁵³ between the drug and the clinically significant hazard. The procedure for making these changes is set forth in 21 C.F.R. § 314.70⁵⁴ and includes the Prior Approval Supplement (PAS) and Changes Being Effected (CBE) mechanisms.⁵⁵ The PAS

Health, Educ., Labor and Pensions, 109th Cong. 11 tbl. (2005). In contrast, more than one thousand employees in the FDA's Office of New Drugs are involved in the review of a few dozen NDAs a year. *Ensuring Drug Safety: Where Do We Go From Here?: Hearing Before the S. Comm. on Health, Educ., Labor and Pensions*, 109th Cong. 42 (2005) (statement of Dr. Bruce S. Patsy).

46. Brent R. Gibson et al., *The U.S. Drug Safety System: Role of the Pharmaceutical Industry*, 17 PHARMACOEPIDEMIOL & DRUG SAFETY 110, 110-14 (2008).

47. Federal law requires brand-name manufacturers to file “postmarketing reports” with the FDA, notifying it of any serious and unexpected adverse incidents suffered by a user of the drug. *See* 21 C.F.R. § 314.80 (2009). In addition, manufacturers are required to submit annual reports detailing any other significant new information that might affect the safety, effectiveness, or labeling of the product. *Id.* § 314.81.

48. *Id.* § 314.80(b) (2011).

49. 21 U.S.C. § 355(k) (2006); 21 C.F.R. § 314.80.

50. 21 U.S.C. § 355(k); *see also* 21 C.F.R. § 314.80(b).

51. 21 C.F.R. § 314.510; FDA, CTR. FOR DRUG EVALUATION & RES. (CDER), CTR. FOR BIOLOGICS EVALUATION & RES., GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS - IMPLEMENTATION OF SECTION 505(O)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 3, nn.8-9 (2011), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf> [hereinafter *Clinical Trials Guidance*].

52. 21 C.F.R. § 314.510 (2011). During the period of market exclusivity, the brand-name manufacturer effectively has a monopoly not only on the market for the drug, but also on the accumulated data.

53. *Id.* § 201.57(c)(6)(i) (2006).

54. *Id.* § 314.70 (2011).

55. *Id.* § 314.70(b).

mechanism applies to “major changes” to an approved drug and requires manufacturers to submit a supplemental application to the FDA for approval prior to making significant changes to the approved product.⁵⁶ While PAS provisions enable certain labeling modifications, they expressly exclude labeling changes to “add or strengthen a contraindication, warning, precaution, or adverse reaction.”⁵⁷ Accordingly, manufacturers may not use the PAS mechanism to propose new warnings. Instead, the PAS strictly limits labeling changes to those that are necessitated by post-approval modifications, such as “qualitative or quantitative formulation of the drug product, including inactive ingredients”⁵⁸ that were listed on the original labeling.

b. Mechanisms for Postmarket Modifications: Changes Being Effected

The CBE mechanism also allows brand-name manufacturers to make postmarket modifications to their products’ labeling.⁵⁹ This provision gives brand-name manufacturers the ability to delete from any label “false, misleading, or unsupported indications”⁶⁰ about the drug’s use or effectiveness. Upon learning of a clinically significant hazard, a drug manufacturer can also unilaterally “add or strengthen a contraindication, warning, precaution, or adverse reaction,”⁶¹ without first obtaining FDA approval. This safety valve mechanism enables drug manufacturers to make post-approval label changes immediately to inadequately labeled products and inform doctors and patients about the new information.⁶² Through the CBE process, brand-name manufacturers may independently incorporate the latest safety information into their labels and quickly apprise the public of product changes.

c. Mechanisms for Postmarket Modifications: “Dear Doctor” Letters

A third way branded manufacturers can provide updated warnings about their products is through direct mailings to healthcare providers, commonly referred to as “Dear Doctor” letters.⁶³ These letters constitute a regulated

56. *Id.*

57. *Id.* § 314.70(c)(6)(iii)(A).

58. *Id.* § 314.70(b)(2)(i).

59. *Id.* § 314.70(c)(3).

60. *Id.* § 316.161(b)(1)(B) (2008).

61. *Id.* § 314.70(c)(6)(iii)(A).

62. The regulations, however, require the manufacturer to inform the FDA immediately of the change and to file a Supplemental New Drug Application at least thirty days prior to distributing the drug with the labeling changes.

63. 21 C.F.R. § 200.5 (2001); Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (codified at 21 C.F.R. pts. 201, 202); *see* FDA, CTR. FOR DRUG EVALUATION & RES., OFFICE OF NEW DRUGS, MANUAL OF POLICIES AND PROCEDURES (MAPP) 6020.10: NDAs: “DEAR HEALTH

“labeling” under the statute and case law.⁶⁴ Accordingly, they are subject to the same standards that govern all labeling, including the “misbranding” label provisions.

B. Generic Drug Approval and Labeling Process

1. Pre-approval

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act (the Hatch-Waxman Act), to aid generic drugs in coming to market as quickly as possible after the expiration of a brand-name patent.⁶⁵ This legislation created an abbreviated new drug application (ANDA) for generic drugs that eliminated the need for generic manufacturers to repeat the expensive and time-consuming clinical drug trials conducted by brand-name manufacturers.⁶⁶ The Hatch-Waxman Act permits ANDA applicants to rely on the FDA’s approval of the brand-name drug so long as the generic manufacturer establishes that the generic drug (1) is bioequivalent to its branded counterpart; (2) has the same route of administration, active ingredients, strength, and dosage form as the listed drug;⁶⁷ and (3) has the same labeling as that of the approved drug.⁶⁸ Because brand-name manufacturers hold their production processes as trade secrets, generic manufacturers demonstrate bioequivalence⁶⁹ through independent expertise. Accordingly, to formulate their drugs, generic manufacturers conduct both laboratory and clinical testing to ensure that their products are absorbed in the same manner as their branded counterparts.⁷⁰ They must also comply with the same elaborate chemical manufacturing controls as brand-name manufacturers. As a result, generic companies develop their own proprietary manufacturing processes.⁷¹ These clinical bioequivalence studies

CARE PROFESSIONAL” LETTERS 2 (2003), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082012.pdf> (establishing protocols for FDA review of such correspondence).

64. 21 U.S.C. § 321(m) (2006); see also *Kordel v. United States*, 335 U.S. 345, 350 (1948); 21 C.F.R. § 202.1(a)(1)(2) (2011).

65. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355) (1984).

66. 21 U.S.C. § 355(j).

67. *Id.* § 355(j)(2)(A)(ii).

68. 21 C.F.R. § 314.94(a)(8) (2008); see *Zeneca, Inc. v. Shalala*, 213 F.3d 161, 164 (4th Cir. 2000) (citing 21 U.S.C.A. § 355(j)(2)(A)(V)).

69. 21 C.F.R. § 320.1(e) (defining bioequivalence as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study”).

70. *Id.* §§ 210-11.

71. *Id.* §§ 314.50(d)(1), 314.94(a)(9).

require ANDA applicants to submit one or more bioequivalence studies in which human subjects are given the generic product, and drug concentrations in the blood are assessed statistically.⁷² The Hatch-Waxman Act, however, does not require applicants to submit clinical or nonclinical evidence to substantiate the safety and effectiveness of the active ingredients.

By requiring generic manufacturers only to prove bioequivalence and to maintain the same label as its branded counterpart, Congress intended a relatively inexpensive and streamlined approval process.⁷³ The resulting regulatory framework eliminated the need to conduct clinical trials because, as Congress noted, such trials would not only be “unnecessary and wasteful because the drug has already been determined to be safe and effective,”⁷⁴ but also would be “unethical because [trials] require[] that some sick patients take placebos and be denied treatment known to be effective.”⁷⁵

The 1992 regulations implementing the Hatch-Waxman Act’s ANDA requirements reiterated that labeling proposed for the generic must be “the same as”⁷⁶ the label of its branded counterpart.⁷⁷ This provision of the Hatch-Waxman Act illustrates the central premise of the ANDA process: that generic drugs are to be relied upon as the therapeutic equivalent of the listed drug.⁷⁸ The FDA places a high priority on ensuring consistency in labeling in order to minimize any cause for confusion among health care professionals and consumers and prevent a lack of confidence in the equivalency of generic versus brand-name products.⁷⁹

As part of the ANDA approval process, a generic manufacturer submits the following information: the proposed labeling for its product;⁸⁰ proof that the “conditions of use prescribed, recommended, or suggested”⁸¹ in the labeling of the generic drug have been previously approved for the brand-name drug; materials for a side-by-side comparison of the proposed labeling to the brand-name drug;⁸² and a statement affirming that the generic labeling is the same as

72. Barbara M. Davit et al., *Comparing Generic and Innovator Drugs: A Review of 12 years of Bioequivalence Data from the United States Food and Drug Administration*, 14 ANNALS PHARMACOTHERAPY 1583, 1584 (2009).

73. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355) (1984).

74. H.R. REP. NO. 98-857, pt. 1 (1984) (“The purpose of . . . the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs . . .”).

75. *Id.*

76. The FDA has defined “same as” to mean “identical.” 21 C.F.R. § 314.92(a)(1) (2008).

77. *Id.*

78. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,884 (July 10, 1989) (explaining that the purpose of 21 U.S.C. § 355(j) “is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts”).

79. *See* Division of Generic Drugs, FDA Policy and Procedure Guide 37 (1989); Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992).

80. 21 C.F.R. § 314.94(a)(8)(ii).

81. 21 U.S.C. § 355(j)(2)(A)(i).

82. 21 C.F.R. § 314.94(a)(8)(iv).

the labeling of the approved drug.⁸³ In contrast to the brand-name manufacturer's highly participatory role during the NDA approval process, the generic manufacturer's involvement in the ANDA process is restricted to establishing the extent of its identical nature to the branded counterpart. The scope of the FDA's labeling review of an ANDA is confined solely to whether the generic drug's labeling "is the same as the labeling approved for the [brand-name] drug."⁸⁴ In fact, the FDA rejects ANDAs that contain new warnings or safety precautions not present on the brand-name drug's label.⁸⁵

2. *Post-approval*

Once the ANDA is approved, the generic manufacturer's labeling responsibilities expand beyond merely demonstrating that its product's label is identical to that of the listed drug. As noted earlier, FDA labeling regulations reflect the reality that drug labels are subject to change.⁸⁶ In some cases, it is only after wide distribution and prolonged use that certain risks manifest.⁸⁷ Accordingly, after ANDA approval, FDA regulations charge generic manufacturers, as well as brand-name manufacturers, with the obligation to ensure that their products remain safe and effective as labeled.⁸⁸ All manufacturers must file annual reports that contain a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product"⁸⁹ and a "description of actions the applicant has taken or intends to take as a result of this new information."⁹⁰

All manufacturers have postmarket reporting duties. However, given the different regulatory frameworks that govern brand-name and generic manufacturers, their responsibilities are not the same. For example, the FDA does not require generic manufacturers to conduct post-approval clinical studies as a condition of ANDA approval,⁹¹ nor do FDA regulations require generic manufacturers to perform the same postmarketing surveillance, review, and data collection activities as brand-name manufacturers.⁹² Such manufacturers are required to review and analyze *all* reported adverse events.⁹³ This analysis is

83. *Id.* § 314.94(a)(8)(iii).

84. 21 U.S.C. § 355(j)(2)(A)(v).

85. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,884 (July 10, 1989).

86. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 603 (8th Cir. 2011).

87. *Id.*

88. 21 U.S.C. § 355(k).

89. 21 C.F.R. § 314.81(b)(2)(i).

90. *Id.*

91. *See* 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).").

92. 21 C.F.R. §§ 314.81(b)(2)(i), 314.98 (2009).

93. *Id.* § 314.80.

conducted based on the knowledge manufacturers obtain through the detailed clinical trials that they conduct, in order to obtain FDA approval of their branded drug. In contrast, generic manufacturers, who do not possess the underlying scientific data, are required only to forward to the FDA adverse event reports.⁹⁴ In addition, the duty to notify the FDA about a change in safety information for an approved drug differs depending on whether the manufacturer is an NDA or an ANDA holder. Under current regulations, generic manufacturers “should” notify the FDA about a change in safety information for an approved drug application.⁹⁵ Regulations governing brand-name manufacturers, however, state that they “must” notify the FDA about a change in safety information.⁹⁶

Similar to NDA holders, generic manufacturers are required to revise their product labels to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.⁹⁷ Failure to comply with these regulations could render the drug “misbranded” and in violation of the FDCA.⁹⁸ The regulatory mechanisms available for generic manufacturers to supplement and make other changes to an approved ANDA are contained in 21 C.F.R. § 314.97.⁹⁹ This section requires generic manufacturers to comply with 21 C.F.R. §§ 314.70¹⁰⁰ and 314.71,¹⁰¹ which address “major changes” and “moderate

94. *Id.* § 314.98(a) (requiring generic manufacturers to comply only with “the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences,” rather than the review, scientific literature, and postmarketing provisions of § 314.80). Generic drug manufacturers receive far fewer of the reports than their branded counterparts and the FDA. *See* FDA, CTR. FOR DRUG EVALUATION & RES., OFFICE OF GENERIC DRUGS., MANUAL OF POLICIES AND PROCEDURES (MAPP) 5240.8: HANDLING OF ADVERSE EXPERIENCE REPORTS AND OTHER GENERIC DRUG POSTMARKETING REPORTS 1 (2005), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079791.pdf> [hereinafter HANDLING OF ADVERSE EXPERIENCE REPORTS AND OTHER GENERIC DRUG POSTMARKETING REPORTS] (highlighting that the Office of Generic Drugs receives fewer adverse event reports, both because the reports frequently do not identify a generic manufacturer for the drug and the safety profile of a drug is well-known before the generic version is approved).

95. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992) (codified at 21 C.F.R. pts. 2, 5, 10, 310, 314, 320, 433).

96. 21 C.F.R. § 314.70(a) (2011).

97. *See id.* § 201.57(c)(6)(i) (2006) (NDA drugs after June 30, 2001); *id.* § 201.80(e) (NDA drugs before June 30, 2001).

98. A drug is considered misbranded when its labeling is false, misleading, or does not provide adequate instructions for use and adequate warnings. *See* 21 U.S.C.A. §§ 321(n), 331(a)-(b), (k), 352 (a), (f), (j), (n) (2006).

99. 21 C.F.R. § 314.97 (2012) (“The applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.”).

100. *Id.* § 314.70. This section allows the manufacturer to supplement its application and propose changes to the drug or its labeling through Prior Approval Supplement (PAS), *see id.* § 314.70(b), or through the CBE supplement, *see id.* § 314.70(c). The applicability of these provisions to generic manufacturers is discussed *infra* in Subsection I.B.2.

101. *Id.* § 314.71 (2008) (detailing the requirements for making changes to supplements). This regulation states that the procedures are identical to those required for drugs submitted under 21

changes.”

a. Mechanisms for Postmarket Modifications: Prior Approval Supplement

Major changes comprise a large portion of labeling modifications.¹⁰² The procedure for effectuating a major change requires submission of a supplemental application that must be approved by the FDA prior to modifying the label.¹⁰³ For generic manufacturers, however, this prior approval supplement only allows generic manufacturers to use the Prior Approval Supplement (PAS) to revise their product to mirror major changes that their branded counterparts implement.¹⁰⁴ The overarching uniformity requirements contained in the regulations prohibit a generic manufacturer from initiating independent labeling changes.¹⁰⁵

Even if a generic manufacturer could propose a label change through the PAS process, it is questionable if a generic manufacturer would be in a position to evaluate the available data to determine whether or which types of labeling changes are potentially needed. As noted previously, brand-name manufacturers’ reporting requirements necessitate collecting and analyzing all adverse event information associated with their drugs.¹⁰⁶ From that information and the background knowledge acquired through the clinical trials and NDA approval process, brand-name manufacturers have the ability to assess the reported adverse events and discern the need for, and wording of, a major labeling change.¹⁰⁷ The regulatory framework that governs generic manufacturers recognizes that they lack the research base of brand-name manufacturers. Consequently, generic manufacturers submit to the FDA only adverse event reports they receive directly.¹⁰⁸ Given this limitation, the quality of their reports

C.F.R. § 314.50 (2008).

102. *See generally* Revisions to 21 C.F.R. § 314.70: Supplement and Other Approved Changes to an Approved Application: PhRMA Perspective, FDA Public Meeting, PhRMA, 6-10 (Feb. 7, 2007), available at <http://www.fda.gov/OHRMS/DOCKETS/DOCKETS/06n0525/06n-0525-ts00009-LLucisano.pdf>.

103. 21 U.S.C. § 356a(c)(1); 21 C.F.R. § 314.70(b)(2)(v)(A).

104. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81,082 (proposed Dec. 22, 2000).

105. *See* 21 C.F.R. § 314.94(a)(8)(iii)-(iv); Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,960 (Apr. 28, 1992) (“After ANDA approval, FDA tracks the labeling status of the pioneer drug product and, if necessary, notifies ANDA holders when and how they must revise their labeling.”).

106. 21 U.S.C. § 355(k); 21 C.F.R. § 314.80.

107. 21 C.F.R. § 314.510 (discussing that post-approval requirements of the FDA typically include conducting additional clinical trials to support new drug indications or formulations, and satisfying safety and efficacy concerns that arise.); *see also* *Clinical Trials Guidance*, *supra* note 51, at 4.

108. 21 C.F.R. § 314.94.

and any resulting major change request could be compromised by the lack of data from clinical trials. FDA Deputy Commissioner Mark Novitch echoed this concern when he stated, “[I]f adverse reaction reports were received by firms unfamiliar with the clinical trials, and, because of the nature of their business, lacking ties with the research community, we are concerned about the adequacy of the reports we would receive.”¹⁰⁹

b. Mechanisms for Postmarket Modifications: Changes Being Effected

While major changes require prior FDA approval, moderate changes as specified in 21 C.F.R. § 314.71 do not. Moderate changes to an approved label include alterations to “add or strengthen a contraindication, warning, precaution or adverse reaction.”¹¹⁰ Such changes are brought to the FDA’s attention through the CBE process.¹¹¹ The flashpoint in the preemption debate that *PLIVA* settled was whether this process would be available to generic manufacturers. On one side of the debate were those who argued that when the FDA adopted the regulations implementing Hatch-Waxman, the FDA included a provision that required generic manufacturers to “comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.”¹¹² Read in isolation, these regulations appear to give generic manufacturers the ability to use the CBE process unilaterally to make changes to their approved labels.¹¹³ On the other side of the debate were those, including the FDA and the Eighth Circuit, who concluded that supplements and changes identified in 21 C.F.R. § 314.94 are subject to the substantive standards governing ANDA “applicants,” the person submitting an original ANDA, an amendment, or a supplement and any person who owns an approved ANDA.¹¹⁴ These pre-approval regulations specify that an ANDA application will not be approved unless the generic drug’s proposed

109. Reply Brief of Petitioners *PLIVA, Inc., et al.* on Petition for Writ of Certiorari at 7, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (No. 09-993).

110. 21 C.F.R. § 314.70(A).

111. *Id.*

112. 21 C.F.R. § 314.97; *see, e.g.*, *Stacel v. Teva Pharms., USA*, 620 F. Supp. 2d 899 (N.D. Ill. 2009); *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009); *Kellogg v. Wyeth*, 612 F. Supp. 2d 421 (D. Vt. 2008).

113. *See, e.g.*, *Stacel*, 620 F. Supp. 2d at 905 (“In other words, the regulations affecting generic drug applications state explicitly that the CBE provisions apply to generic drug manufacturers just as they do to name-brand manufacturers.”); *Bartlett v. Mutual Pharm. Co.*, 659 F. Supp. 2d 279, 296 (D.N.H. 2009) (“Just as nothing in the text of the Hatch-Waxman Amendments forbids a generic manufacturer from changing its label from the listed version’s post-approval, nothing in the text of the CBE regulation forbids a generic manufacturer from using the CBE process to do so.”).

114. *See* Brief for the United States as Amicus Curiae Supporting Respondents at 17-18, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 741927, at *17-18.

labeling is the “same as” that of the brand-name drug¹¹⁵ and that approval will be withdrawn unless the generic labeling *stays* the “same as” its branded counterpart.¹¹⁶ Accordingly, under this interpretation, generic manufacturers cannot use the CBE process to change unilaterally their products’ labeling from wording used by their branded counterparts. The centrality of the CBE process in defining the post-approval responsibilities of generic manufacturers necessitates a closer look at the FDA’s position.

The FDA has long stressed that generic drugs’ labels should be the same as their branded counterpart.¹¹⁷ In response to FDA-proposed regulations implementing the labeling requirements of the Hatch-Waxman Act, several comments addressed whether a generic manufacturer could include warnings or precautions in addition to those listed on the branded drug.¹¹⁸ The FDA summarily rejected each suggestion.¹¹⁹ One comment, specifically addressing the labeling requirements of 21 C.F.R. § 314.94(a)(8), proposed that labeling provisions be “revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information.”¹²⁰ In rejecting the suggested change, the FDA insisted that generic drugs labels “must be the same as the listed drug product’s labeling because the listed drug product is the basis for ANDA approval.”¹²¹

Another comment suggested that the “FDA accept ANDAs with warnings or precautions in addition to those on the reference listed drug’s label, provided that such information was not indicative of diminished safety or effectiveness of the generic drug product.”¹²² Again, the FDA rejected the proposed change and reiterated that Section 505(j)(3)(G) of Hatch-Waxman “requires the applicant’s

115. 21 C.F.R. § 314.94(a)(8)(iii); *see* 21 U.S.C. § 355(j)(4)(g) (2006); 21 C.F.R. § 314.150(b)(10) (providing that the FDA may withdraw approval of an ANDA for a generic drug if it finds that the labeling for such a drug is “no longer consistent with that for the listed drug”).

116. 21 U.S.C. § 355(j)(4)(g); 21 C.F.R. §§ 314.94(a)(8)(iii), 314.150(b)(10).

117. The FDA has reiterated this position several times in the 1992 Final Rule, 21 C.F.R. §§ 314.94(a), 314.94(a)(8), 314.127(a)(7), and public comments to the 1992 final rule, *see, e.g.*, 57 Fed. Reg. 17,961, cmt. 40 (“FDA disagrees with the comments [that] the labeling provisions should be revised to permit ANDA applicants to deviate from labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information . . . [and that] ANDA applicants should be allowed to delete some of the indications contained in the labeling for the reference listed drug . . . Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, the ANDA’s product labeling must be the same as the listed drug product’s labeling because the listed drug is the basis for ANDA approval.”).

118. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992) (codified at 21 C.F.R. § 314).

119. *Id.*

120. *Id.*

121. *Id.*

122. *Id.* at 17,953.

proposed labeling be the same as that of the reference listed drug”¹²³ and that “the exceptions in section 505(j)(2)(A)(v) and (j)(3)(G) of the [Hatch-Waxman Act] are limited.”¹²⁴ Similarly, the FDA disagreed with a suggestion that it accept petitions under Section 355(j)(2)(C) to submit an ANDA for a product whose labeling differs from its branded counterpart by being “more clear or offer[ing] better directions regarding how the drugs should be taken.”¹²⁵ The FDA admonished that “labeling differences, therefore, are not proper subjects for a suitability petition”¹²⁶ and “reminds applicants that the labeling for an ANDA product must be the same as the labeling for the listed drug product except for differences due to different manufacturers, exclusivity, etc.”¹²⁷

Shortly after the adoption of the Hatch-Waxman Act, the FDA issued a Policy and Procedure Guide. In the Guide, the FDA made it clear that, ultimately, it controls the labeling of generic drugs.¹²⁸ The Guide reiterates that generic manufacturers cannot unilaterally revise their product labels’ warnings, but instead must await FDA instructions before making any changes.¹²⁹ Part of the FDA’s rationale for this approach could be grounded in the recognition of the fragmented nature of the market for generic drugs. There are multiple generic competitors, each possessing only a portion of the accumulated safety data for a given drug. As a result, the FDA reasoned that generic drug manufacturers making unilateral changes could be both impractical and counterproductive¹³⁰:

[E]ach time there is a change in the innovator’s labeling, it could necessitate similar changes in the labeling of as many as 20 or 30 generic products. A change in any section of the package insert of the innovator’s product, particularly an important change, e.g., in WARNINGS, PRECAUTIONS, CONTRAINDICATIONS OR DOSAGE ADMINISTRATION, triggers action by the Labeling Review Branch to request submission from all generic manufacturers of that product. Prompt accomplishment of the revision process is important to assure that consistency is found in the labeling of all similar drug products.¹³¹

123. *Id.*

124. *Id.*

125. *Id.* at 17,957.

126. *Id.*

127. *Id.*

128. FDA, CTR. FOR DRUG EVALUATION & RES., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA: QUESTIONS AND ANSWERS (1999).

129. FDA, CTR. FOR DRUG EVALUATION & RES., DIVISION OF GENERIC DRUGS, CHANGES IN THE LABELING OF ANDAS SUBSEQUENT TO REVISION OF INNOVATOR LABELING, POLICY AND PROCEDURES GUIDE NO. 8-89 (1989) [hereinafter POLICY AND PROCEDURES GUIDE NO. 8-89].

130. In general, generic manufacturers only possess data required by 21 C.F.R. § 314.98 (ANDA post-approval requirements).

131. POLICY AND PROCEDURES GUIDE NO. 8-89, *supra* note 129, at 1.

By limiting the ability of brand-name manufacturers to implement changes unilaterally, and by requiring generic product's labeling to be the same as its listed drug, the FDA made clear the premium it places on uniformity (perhaps at the expense of safety).¹³²

In 2008, the FDA once again affirmed its position regarding the availability of the CBE process for generic manufacturers and stated, specifically, that CBE modifications are not available for generic drugs approved under an ANDA. To the contrary, the proposed rule indicated that generic manufacturers' ability to change a label unilaterally is confined to reflect "differences in expiration date . . . or omission of an indication or other aspect of labeling protected by patent."¹³³

To the extent that generic manufacturers may use the CBE mechanism to propose or effectuate certain labeling changes, the FDA consistently has held that such actions may be taken only to "conform" their product labeling to that of their branded counterpart.¹³⁴ In short, the FDA always has made clear that generic manufacturers may not use the CBE process to craft their own warning labels independently.¹³⁵

As discussed in the next Part, prior to *PLIVA*, the majority of courts interpreted the regulatory framework as providing a sufficient basis to reject generic manufacturers' preemption defense against state law failure-to-warn claims. Accordingly, generic manufacturers were forced to choose between compliance with FDA regulatory guidance or possible liability under state failure-to-warn laws. With that specter of liability now removed, Part II examines the FDA's position on generic manufacturers' labeling responsibilities as articulated in *PLIVA* and the Supreme Court's incorporation of that position into

132. See *supra* Subsection I.B.2; see also POLICY AND PROCEDURES GUIDE NO. 8-89, *supra* note 129, at 1.

133. 21 C.F.R. § 314.94(a)(8); see also Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,953, 17,961 n.1 (Apr. 28, 1992). The FDA issued its Final Rule on August 22, 2008. Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices - Final Rule, 73 Fed. Reg. 49,603 (Aug. 22, 2008).

134. FDA, CTR. FOR DRUG EVALUATION & RES. (CDER), GUIDANCE FOR INDUSTRY: REVISING ANDA LABELING FOLLOWING REVISION OF THE RLD LABELING 5 (2000), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072891.pdf> ("The sponsor of an ANDA is now responsible for ensuring that the labeling contained in its application is *the same as* the currently approved labeling of the [branded drug].").

135. Abbreviated New Drug Application Regulations, 57 Fed. Reg. at 17,955 ("[T]he agency wishes to remind ANDA applicants that . . . the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug."); see also *id.* at 17,961 ("After ANDA approval, FDA tracks the labeling status of the pioneer drug product and, if necessary, notifies ANDA holders when and how they must revise their labeling."); CTR. FOR DRUG EVALUATION & RES. (CDER), GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 24 (2004), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf> ("All labeling changes for ANDA drug products must be consistent with section 505(j) the Act.").

its holding. Next, this Part focuses on the implications of a framework that immunizes generic manufacturers from failure-to-warn claims and exposes consumers to potential harm from mislabeled medications.

II. THE FEDERAL PREEMPTION DEBATE'S EFFECT ON THE GENERIC-LABELING FRAMEWORK

The preemption debate serves as a lens with which to examine the inadequacies of the regulatory framework that prescribes generic manufacturers' labeling responsibilities. While *PLIVA* recently has thrust the issue into the limelight, consumers' tenuous ability to seek redress against generic manufacturers long has rested on courts' varied interpretations of the FDA regulations. Until *Wyeth v. Levine*, a majority of drug manufacturers had successfully avoided failure-to-warn liability by arguing that the federal regulatory framework preempted labeling changes prescribed by state law, because it was impossible for manufacturers to comply with both.¹³⁶ In addition, a number of courts had held that state law attempts to hold manufacturers liable for failing to strengthen warning labels on their products posed an impermissible obstacle to the effectiveness of federal regulations, and, thus, were preempted.¹³⁷ In 2009, the Supreme Court's decision in *Wyeth v. Levine* extinguished these defenses for brand-name manufacturers. Relying on the Supreme Court's analysis, several circuits extended the *Wyeth* rationale to generic manufacturers by holding that the existing regulatory labeling framework did, in fact, permit generic manufacturers to comply with state law failure-to-warn laws. Two years later in *PLIVA v. Mensing*, a consolidated appeal from the Fifth and Eighth Circuits, the Supreme Court ruled on the soundness of their interpretation.

A. Generic Manufacturers' Regulatory Framework Before *PLIVA v. Mensing*: *Wyeth v. Levine* and the Subsequent Circuit Split

The Supreme Court's decision in *Wyeth* called into question the viability of generic manufacturers' preemption defense and set the stage for *PLIVA*. The *Wyeth* decision, however, did not involve, or even reference, generic manufacturers, the Hatch-Waxman Act, ANDAs, or specific labeling

136. See, e.g., *Horne v. Novartis Pharm. Corp.*, 541 F. Supp. 2d 768 (W.D.N.C. 2008); see also *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006), *aff'd*, 521 F.3d 253 (3d Cir. 2008), *vacated*, 129 S. Ct. 1578 (2009).

137. *Mason v. Smithkline Beecham Corp.*, 546 F. Supp. 2d 618, 625 (C.D. Ill. 2008); *Dobbs v. Wyeth Pharm.*, 530 F. Supp. 2d 1275, 1279-82, 1288-89 (W.D. Okla. 2008); *In re Bextra*, No. M: 05-1699 CRB, 2006 WL 2374742, at *6-*9 (N.D. Cal. Aug. 16, 2006); *Conte v. Wyeth, Inc.*, No. CGC-04-437382, 2006 WL 2692469, at *4-*6 (Cal. Super. Sept. 14, 2006); *Gourdine v. Crews*, No. CAL 05-00480, 2006 WL 5277412 (Md. Cir. June 28, 2006), *aff'd*, 955 A.2d 766 (Md. 2008).

regulations.¹³⁸ Nevertheless, it is impossible to discuss the adequacy and contours of the labeling regulatory framework that governs generic manufacturers without starting with *Wyeth*.

In 2001, Diane Levine sued Wyeth for injuries she suffered after receiving a direct intravenous injection of Wyeth's nausea medication, Phenergan.¹³⁹ Using a procedure known as IV push, the drug was inadvertently injected into her artery instead of her vein, resulting in gangrene and the eventual amputation of her arm.¹⁴⁰ Levine filed failure-to-warn claims against Wyeth, the manufacturer of the product. She alleged that the FDA-approved label was inadequate because it failed to warn healthcare professionals of the risk that an improper IV push could cause injuries like those she suffered.¹⁴¹ Wyeth maintained that Levine's failure-to-warn claims were preempted by federal law because the FDA had approved Phenergan for direct IV injection and had approved the labeling that warned of its risks.¹⁴²

In March 2009, the Supreme Court held that Levine's failure-to-warn claims were not preempted against brand-name manufacturers.¹⁴³ The Court considered and rejected Wyeth's preemption arguments that (1) it would have been impossible for Wyeth to alter existing FDA-approved labeling to comply with the state law in question without violating federal law ("impossibility preemption"), and (2) Levine's state law failure-to-warn claims interfered with the congressional objectives by substituting a lay jury's decision of the adequacy of a drug's labeling for the expert judgment of the FDA ("obstacle preemption").¹⁴⁴

According to the *Wyeth* Court, the manufacturer, and not the FDA, bears responsibility for the content of its label at all times.¹⁴⁵ The Court underscored this point by noting that the FDA did not even possess the authority to require a drug manufacturer to alter its label until 2007.¹⁴⁶ Despite key differences in the regulatory frameworks that govern brand-name and generic drugs, courts increasingly relied on *Wyeth*'s reasoning to reinterpret the requirements of the regulatory framework governing generic manufacturers.

For example, in *Schrock v. Wyeth*,¹⁴⁷ an Oklahoma district court interpreted *Wyeth v. Levine* broadly, holding that "the United States Supreme Court has clearly concluded that Congress did not intend [to] preempt state-law failure-to-

138. *Wyeth v. Levine*, 555 U.S. 555 (2009).

139. *Id.* at 559.

140. *Id.*

141. *See id.*

142. *Id.*

143. *Id.* at 581. Justice Stevens wrote for the majority and was joined by Justices Kennedy, Souter, Ginsburg, and Breyer. Justice Thomas concurred in judgment, but wrote a separate opinion. Chief Justice Roberts and Justices Scalia and Alito dissented.

144. *Id.* at 569-71.

145. *Id.* at 570-71.

146. *Id.*

147. 601 F. Supp. 2d 1262 (W.D. Okla. 2009).

warn actions.”¹⁴⁸ In denying the generic manufacturer’s motion to dismiss, the court applied *Wyeth* without considering the regulatory differences between brand-name and generic manufacturers. The *Schrock* court quoted *Wyeth*’s analysis of congressional intent regarding a drug manufacturer’s responsibility to maintain adequate drug labeling, stating, “With respect to a change in drug labels based upon safety information which becomes available after a drug’s initial approval, Congress ‘adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels.’”¹⁴⁹ The court reiterated *Wyeth*’s analysis that unless a manufacturer makes a clear showing that the FDA would reject a label change, making such a change is not impossible.¹⁵⁰

In *Stacel v. Teva Pharmaceuticals, USA*, an Illinois district court cited *Wyeth* and its interpretation of the Code of Federal Regulations as the basis for denying the generic manufacturer’s preemption defense.¹⁵¹ Unlike *Schrock*, the *Stacel* court acknowledged the regulatory differences between brand-name and generic manufacturers. Nevertheless, after considering these differences and engaging in its own analysis of regulations applicable to generic manufacturers, the court concluded not only that the congressional objectives for generic drug labeling are the same as those for brand-name drug labeling, but also that the CBE process is available to both brand-name and generic manufacturers.¹⁵² The court further reasoned that “if the generic manufacturers can utilize the CBE, then the logic of *Wyeth* is directly applicable.”¹⁵³ In considering the *Wyeth* Court’s observation that Congress utilizes state tort actions to help regulate brand-name drugs, the court reasoned that Congress could not take a different position with respect to generic drugs.¹⁵⁴ The court noted that, while generic drugs must have the same labels as their branded counterparts during the application process, the Hatch-Waxman Act does not require the labels to remain the same after approval.¹⁵⁵ Accordingly, the court concluded that, because labeling is a manufacturer’s responsibility and the statute does not require identical labeling post-approval, state law consumer protection duties do not conflict with congressional objectives.¹⁵⁶

Finally, in *Gaeta v. Perrigo Pharmaceuticals Co.*, the Ninth Circuit relied in part on *Wyeth* to elevate generic manufacturers’ labeling responsibilities to that of their branded counterparts and, thus, to reject the generic manufacturer’s

148. *Id.* at 1264.

149. *Id.*

150. *Id.* (citing *Wyeth*, 555 U.S. at 564).

151. 620 F. Supp. 2d 899, 905-07 (N.D. Ill. 2009).

152. *Id.* at 905.

153. *Id.*

154. *See id.* at 907.

155. *Id.*

156. *Id.*

preemption argument.¹⁵⁷ The court justified its elevation of generic manufacturers' responsibilities by referencing the *Wyeth* conclusion that, "because manufacturers have 'superior access to information' about their drugs than does the FDA, especially in the post-marketing phase as new risks emerge, they 'bear primary responsibility for their drug labeling at all times.'"¹⁵⁸ As demonstrated by the legal analysis that formed *PLIVA* appeal, the Fifth and Eighth Circuits similarly relied on *Wyeth* to reject generic drug manufacturers' preemption defense.

B. *PLIVA v. Mensing Proceedings Below*

In 2001, Gladys Mensing's doctor prescribed her Reglan to treat her diabetic gastroparesis, a paralysis that prevents the emptying of the stomach.¹⁵⁹ A year later, Julie Demahy's doctor prescribed her Reglan to treat her gastroesophageal reflux disorder, a condition that prohibits contractions of the esophagus, stomach, and intestines.¹⁶⁰ Pursuant to their states' generic substitution laws, Mensing's and Demahy's pharmacists filled their prescriptions with generic versions of Reglan.¹⁶¹ Mensing and Demahy took the drug as prescribed for approximately four years.¹⁶² Subsequently, both women developed tardive dyskinesia, a severe neurological disorder.¹⁶³ In separate state court actions, Mensing and Demahy sued the generic manufacturers, Wyeth, Inc. and Actavis, Inc. respectively, over the medications.¹⁶⁴ Both state law complaints alleged that "despite mounting evidence that long term metoclopramide use carries a risk of tardive dyskinesia far greater than indicated on the label,"¹⁶⁵ the generic manufacturers took no steps to meet their state law obligations to modify their labels to warn of the risks.¹⁶⁶ In response, the generic manufacturers in both cases argued that the plaintiffs' state law tort claims were preempted by federal statutes and FDA regulations.

In *Mensing v. Wyeth*, the federal district court in Minnesota granted the generic drug manufacturer's motion to dismiss, holding that the Hatch-Waxman Act preempted state law failure-to-warn claims.¹⁶⁷ On appeal, the Eighth Circuit

157. *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225, 1127 (9th Cir. 2011).

158. *Id.* at 1230 (quoting *Wyeth v. Levine*, 555 U.S. 555, 578 (2009)).

159. Brief for Respondents Gladys Mensing and Julie Demahy at 4, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 686400, at *4.

160. *Id.*

161. *Id.* at *4-*5.

162. *Id.* at *5.

163. *PLIVA*, 131 S. Ct. at 2573.

164. *Id.*

165. *Id.* at 2573 (quoting *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 605 (8th Cir. 2009)).

166. *See, e.g., id.*

167. *Mensing*, 588 F.3d at 605.

reversed, citing the Supreme Court's decision in *Wyeth v. Levine*.¹⁶⁸ The Eighth Circuit acknowledged that "generic labels must be substantively identical to the name brand label even after they enter the market."¹⁶⁹ Nevertheless, the *Mensing* court rejected Wyeth's preemption defense by concluding that federal law would have at least allowed them to propose "a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved."¹⁷⁰

The Eighth Circuit supported its holding by stating that 21 C.F.R. § 201.57(e) requires a generic manufacturer to "take steps to warn its customers when it learns it may be marketing an unsafe drug."¹⁷¹ The court disagreed with the argument that generic manufacturers comply with the regulation simply by ensuring that their labels are identical to their branded counterpart.¹⁷² In the court's view, generic manufacturers are not "passively to accept the inadequacy of their drug's label as they market and profit from it."¹⁷³

Building on its interpretation that the regulations prohibit generic manufacturer passivity, the Eighth Circuit made short work of the generic manufacturer's impossibility defense.¹⁷⁴ Specifically, Wyeth argued that federal regulations requiring generic manufacturers to maintain warning labels identical to their branded counterparts prohibited these manufacturers from altering their labels to comply with stronger state law requirements through use of the CBE process.¹⁷⁵ In an interesting piece of legal draftsmanship, the court declined to address Wyeth's CBE argument directly. Instead, the court returned to its "steps could have been taken" refrain to render Wyeth's defense moot, stating, "In this case we need not decide whether generic manufacturers may unilaterally enhance a label warning through the CBE procedure because the generic defendants could have at least *proposed* a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved."¹⁷⁶ The court also noted that the manufacturer "'may seek to add safety information to a drug label' through the prior approval process or by requesting that the FDA send 'Dear Health Care Professional' letters."¹⁷⁷ The Eighth Circuit acknowledged that "Congress did not intend that generic manufacturers send out 'Dear Healthcare Provider' letters uncoordinated with other manufacturers of the drug."¹⁷⁸ Nevertheless, the court maintained that the generic manufacturer "could have suggested that the FDA send out [such] a warning letter to health care

168. *Id.* at 607-08 (discussing *Wyeth v. Levine*, 555 U.S. 555 (2009)).

169. *Id.* at 608.

170. *Id.*

171. *Id.*

172. *Id.*

173. *Id.* at 609.

174. *Id.* at 608.

175. *Id.*

176. *Id.*

177. *Id.* at 610.

178. *Id.*

professionals.”¹⁷⁹

In refusing to decide definitively on the applicability of the CBE process, the court appeared at least to entertain the notion that the regulatory framework does not provide a mechanism for generic manufacturers to change their labels unilaterally. Rather than concede impossibility, however, the Eighth Circuit offered a solution, namely, that generic manufacturers always have the option of not selling their product: “The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product.”¹⁸⁰

In *Demahy v. Actavis*, a federal district court in Louisiana similarly denied a motion to dismiss filed by the generic manufacturer.¹⁸¹ The Fifth Circuit affirmed, holding that Demahy’s state law claims were not preempted, based in large part on its reliance on *Wyeth*.¹⁸² Notwithstanding its broad reliance on *Wyeth*, the court offered several novel regulatory interpretations that are worth discussing.

In contrast to *Mensing*, where the Eighth Circuit chose not to address directly the applicability of the CBE process, in *Demahy*, the Fifth Circuit opted for a different approach. After a detailed review of FDA statements and regulations, the court determined that the statutory scheme was silent about the manufacturer’s obligations after the ANDA is granted.¹⁸³ From that silence, the court deduced that the FDA does not expressly prohibit generic manufacturers from using the CBE process.¹⁸⁴ As a result, the court stated, “[w]ithout explicit reference to the use of the CBE process by generic manufacturers, we decline to read in a bar to its use.”¹⁸⁵ The court applied this same “no specific prohibition” logic to its conclusion with respect to the availability of Dear Doctor letters.¹⁸⁶ The court conceded that, while these letters require pre-approval by the FDA, nothing in the regulations specifically prohibits generic manufacturers from at least proposing that the FDA send them out on their behalf.¹⁸⁷

When presented with arguments that inherent deficiencies in the regulatory framework made meeting both federal and state labeling requirements impossible, the court was unmoved. In particular, under the current regulatory scheme, if a generic manufacturer attempted to change its label, Actavis argued that the FDA could withdraw approval for the drug upon finding “a lack of

179. *Id.* at 611.

180. *Id.*

181. *Demahy v. Actavis, Inc.*, 593 F.3d 428, 430 (5th Cir. 2010).

182. *See also id.* at 430, 434-35, 446, 449 (“*Levine* is not the case before us.”).

183. *Id.* at 426, 436.

184. *Id.* at 442.

185. *Id.* at 444.

186. *Id.* at 444-45.

187. *Id.* at 445.

substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.”¹⁸⁸ Actavis further asserted that changing the label makes it no longer consistent with its branded counterpart and could also prompt the FDA to initiate withdrawal of approval proceedings.¹⁸⁹ Again relying on *Wyeth*, the Fifth Circuit responded it would be “difficult to accept” that the FDA would take punitive action against a manufacturer for strengthening a warning.¹⁹⁰ Instead, once additional risks to the drug emerge, federal law does not preclude the generic manufacturer from taking steps to change the label to provide adequate warnings.¹⁹¹ According to the court, the regulatory framework allows a generic manufacturer to comply with both FDA regulations *and* state law by updating its labeling, proposing to update its labeling, or warning healthcare providers directly.¹⁹²

The *Demahy* court also asserted that the regulatory framework requires all drug manufacturers to revise their products’ labeling as soon “as there is reasonable evidence of an association of a serious hazard with a drug.”¹⁹³ This assertion mischaracterizes the regulatory framework. As a threshold matter, 21 C.F.R. § 201.80(e) does not require generic manufacturers to revise their labels before their branded counterparts.¹⁹⁴ As *Wyeth* recognized, that regulation obligates the brand-name manufacturer “both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.”¹⁹⁵ The rationale for this requirement is the fact that brand-name companies conduct the original clinical studies, form postmarket studies, and are subject to extensive post-approval surveillance obligations.¹⁹⁶ As such, companies are able to place information they acquire in context, review it, analyze its significance, and craft the suitable labeling change based on “sufficient evidence” of the standards for which changes are met.¹⁹⁷ By contrast, generic manufacturers lack the comprehensive data possessed by brand-name manufacturers and lack the context to assess properly the limited post-approval information they received.¹⁹⁸ In recognition of this, the FDA interprets 21 C.F.R.

188. *Id.* at 438.

189. *Id.*

190. *Id.* at 439 (quoting *Wyeth v. Levine*, 555 U.S. 555, 570 (2009)).

191. *Id.*

192. *Id.* at 439, 444.

193. *Id.* at 437.

194. 21 C.F.R. § 201.80(e).

195. *Demahy*, 593 F.3d at 437 (quoting *Wyeth*, 555 U.S. at 571 and citing 21 C.F.R. §§ 201.80(e) and 314.80(b)).

196. 21 C.F.R. § 314.80(b) (discussing postmarketing reporting obligations for NDA applicants).

197. See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices – Final Rule, 73 Fed. Reg. 49,603, 49,603-605 (Aug. 22, 2008).

198. See, e.g., *id.* at 49,604 (“[T]he causal relationship between a product and an adverse

§ 201.80(e) as requiring generic manufacturers to conform their labeling to that of the brand-name manufacturer in a timely manner. Nevertheless, the Eighth Circuit's regulatory interpretation allowed it to hold that Demahy's state law failure-to-warn claims were not preempted. The generic manufacturers appealed. The Supreme Court granted their petitions for certiorari and consolidated the cases for review.¹⁹⁹ The issue on appeal was whether the duties imposed on generic manufacturers by federal regulations conflicted with, and therefore preempted, the state law duties that would have required a different label.²⁰⁰

C. PLIVA v. Mensing

Similar to their arguments in the proceedings below, Mensing and Demahy argued before the Supreme Court that the generic manufacturers could have, and should have, used the CBE process to modify their labels unilaterally to warn consumers of the true risks of the generic drug. They maintained that the CBE process is an effective way for generic manufacturers "to bring evidence of the need for a new warning to [the] FDA's attention and initiate consideration of whether the labels for both the [brand-name] and generic drugs should be changed."²⁰¹ Under their interpretation of the regulations, if the FDA ultimately were to approve the changes suggested by a generic manufacturer under the CBE process, the FDA then would require that the same change take place on the brand-name label.²⁰² Accordingly, plaintiffs reasoned that a temporary departure in the identical labeling between a generic and brand-name manufacturer "reflects [the] FDA's determination that such temporary differences are justified in the interest of drug safety."²⁰³ Plaintiffs further alleged that generic manufacturers also could have sent a Dear Doctor letter warning healthcare providers of the adverse risks associated with their product.²⁰⁴

The Solicitor General's amicus brief provided a different interpretation. In the FDA's view, federal regulations do not permit generic manufacturers to alter their labels unilaterally, because of the overriding statutory and regulatory requirements that generic drugs mirror the labels of their branded counterparts.²⁰⁵ Accordingly, the federal labeling scheme for generic manufacturers precludes

effect is often difficult to establish and may require large trials, often specifically designed to assess the risk."); *see also Wyeth*, 555 U.S. at 569 (noting that "risk information accumulates over time" and that subsequent developments might have meaning only in light of "reports previously submitted to FDA") (quoting 73 Fed. Reg. at 49,607).

199. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2573 (2011).

200. *Id.* at 2572.

201. Brief for Respondents Gladys Mensing and Julie Demahy, *supra* note 159, at *34.

202. *Id.*

203. *Id.* at *35.

204. *PLIVA*, 131 S. Ct. at 2576.

205. Brief for the United States as Amicus Curiae Supporting Respondents, *supra* note 114, at *15.

them from changing their labels, even under the CBE process.²⁰⁶ The Solicitor General explained further that use of a Dear Doctor letter is similarly unavailable to generic manufacturers.²⁰⁷ While the FDA conceded that no regulation precludes generic manufacturers from sending these letters, it maintained that such a letter “would only be appropriate in tandem with a corresponding change to the [brand-name] drug’s approved labeling.”²⁰⁸ Further, because a generic manufacturer cannot take advantage of the CBE process, the appearance of new risk information in a Dear Doctor letter would be contrary to FDA-approved labeling.²⁰⁹

The majority deferred to the FDA’s interpretations of the regulations regarding the CBE and Dear Doctor processes. In a consummate application of administrative deference, the Court concluded that the FDA’s views were “controlling unless plainly erroneous or inconsistent with the regulation[s].”²¹⁰ As a result, the Supreme Court chose not even to address the regulatory interpretations offered by either of the parties. Consequently, the Court adopted the FDA’s argument that generic manufacturers are prohibited from unilaterally changing their labeling under the CBE process, unilaterally issuing Dear Doctor letters or using the PAS process. Interestingly, however, this is where the Court’s blanket deference to the FDA’s regulatory interpretation ended.

The FDA maintained that, despite an inability to act unilaterally via the CBE process or through a Dear Doctor letter, generic manufacturers had various opportunities to inform the FDA about adverse reactions and risks caused by their products and seek permission to revise their label.²¹¹ After notification from the generic manufacturer of possible adverse health risks caused by the approved drug, the Solicitor General asserted that the FDA could evaluate the risks, and, if necessary, request that the brand-name manufacturer change its label or withdraw the drug’s approval.²¹² As support, the FDA referenced the final rule implementing the ANDA process, which directs a generic manufacturer to contact the FDA if it believes new safety information should be added to its labeling.²¹³ The FDA also noted that ANDA holders could contact the Office of Generic Drugs (OGD) with concerns regarding their products. According to the FDA, the OGD gives high priority to “ANDAs with possible serious safety

206. *Id.*

207. *Id.* at *18-*19 (citing 21 C.F.R. § 201.100(d)(1)).

208. *Id.* at *18.

209. *Id.* at *19 (citing 21 C.F.R. § 201.100(d)(1)).

210. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2575 (2011) (quoting *Auer v. Robbins*, 519 U.S. 452, 461 (1997)).

211. Brief for the United States as Amicus Curiae Supporting Respondents, *supra* note 114, at *20-*35.

212. *Id.* at *21-*22 (citing 21 U.S.C. § 355(e); 21 C.F.R. §§ 314.70, 314.150(a)(2)).

213. Brief for the United States as Amicus Curiae Supporting Respondents, *supra* note 114, at *20 (citing Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992)).

concerns.”²¹⁴ From this process, the FDA reasoned that generic manufacturers were not powerless to set in motion a process that could lead to safety-enhancing label changes or product removal, both of which could be consistent with state law duties. The FDA maintained that, before a generic manufacturer could claim the affirmative defense of preemption, it must show that (1) the manufacturer proposed to the FDA a label change that could have prevented plaintiffs’ injuries, and, (2) the FDA would have denied any request for that label change.²¹⁵ According to the Solicitor General, only after the manufacturers had asked the FDA for a stronger warning when learning about the link between their product and tardive dyskinesia, and the FDA had rejected a label change, could the manufacturers claim that compliance with the state law duty to warn was truly impossible.

The Supreme Court rejected this regulatory interpretation. In the Court’s view, preemption was proper because there were no steps that the generic manufacturers could have taken independently to comply with both state and federal requirements. In doing so, the Court shed light on why the FDA’s no-preemption position and the “steps could have taken” approach affirmed by the Fifth and Eighth Circuits were unpersuasive. The majority pointed out that the state law’s duty is satisfied only by securing a safer label, not by communicating with the FDA about the possibility of a safer label.²¹⁶ The Court reasoned that had the generic manufacturers alerted the FDA to the increased risk, rather than satisfied their state tort law duties, they would have done no more than “started a Mouse Trap game that eventually [could have led] to a better label on generic metoclopramide.”²¹⁷ In the Court’s view, the Mouse Trap game is not enough to avoid preemption. Rather, the test to overcome preemption is “whether the private party could independently do under federal law what state law requires of it.”²¹⁸ Because “asking the FDA for help” in changing the label, and not changing label on their own, was the only action generic manufacturers could independently take, the Court concluded that plaintiffs’ failure-to-warn claims were preempted.²¹⁹

D. Implications for Consumers, Healthcare Providers, and States

To understand the far-reaching effects that *PLIVA* could have on patient health and safety requires an examination of the dominant role that generic drugs play in today’s healthcare industry. Since passage of the Hatch-Waxman Act, the

214. *Id.* at *21 (quoting CENTER FOR DRUG EVALUATION AND RES., MANUAL OF POLICIES AND PROCEDURES 5200.6, at 3 (May 9, 2001)).

215. *PLIVA*, 131 S. Ct. at 2578.

216. *Id.*

217. *Id.*

218. *Id.*

219. *Id.* at 2580.

impact of generic competition on overall drug prices has been dramatic. Approximately seventy-five percent of all drugs prescribed in 2009 were generic.²²⁰ As a result of concerted efforts by Congress, states, insurers, generic drug companies, physicians, and pharmacists, generic drugs fill nearly 2.6 billion prescriptions a year.²²¹ The Congressional Budget Office reported that generic drug use in 2007 saved senior citizens and the federal government thirty-three billion dollars just on Medicare Part D prescriptions alone.²²² Another recent study reported that dispensing generic versions of brand-name drugs saved the American healthcare system more than \$824 billion over approximately the past decade (2000-2009) and \$139.6 billion in 2009 alone.²²³ Today, the average generic drug costs barely a quarter of its branded counterpart.²²⁴ A 2009 IMS National Prescription Audit illustrated this saving by comparing the typical insurance or government formulary charges: \$6 for generic medications; \$29 for preferred brand-name drugs; and \$40 or more for non-preferred brand-name drugs.²²⁵ The natural effect of the affordability of generic drug alternatives is a dramatic increase in their use.

Adding to the pervasive use of generics are state substitution laws. These laws permit or require pharmacists who receive prescriptions for brand-name drugs to fill them with the drugs' generic equivalent.²²⁶ In addition, even in those states where pharmacists are only permitted (not required) to substitute generics for brand-name drugs, consumers tend to opt for generics because insurance companies often charge higher co-pays for a brand-name drug when a generic is available.²²⁷ State policies favoring generic substitution also receive extra force in the context of publicly funded programs such as Medicare, Medicaid, and the

220. *Id.* at 2884 (Sotomayor, J., dissenting).

221. *Facts at a Glance*, GENERIC PHARM. ASS'N (Mar. 10, 2012), <http://www.gphaonline.org/about-gpha/about-generics/facts> (noting that, overall, only eight out of the fifty most popular drugs are still brand names, compared to twenty in 2003).

222. CONGR. BUDGET OFFICE, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING vii (2010), available at <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/118xx/doc11838/09-15-prescriptiondrugs.pdf> [hereinafter CBO 2010].

223. *Press Release, Generic Medicines Saved U.S. Health Care System \$139.6 Billion in 2009; \$824 Billion Saved Over the Last Decade*, GENERIC PHARM. ASS'N, July 26, 2010, <http://www.gphaonline.org/media/press-releases/2010/generic-medicines-saved-us-health-care-system-1396-billion-2009-824-billio>.

224. CBO 2010, *supra* note 222, at 8-9.

225. Murray Aitken et al., *Prescription Spending Trends in the United States: Looking Beyond the Turning Point*, 28 HEALTH AFFAIRS w151, w151-60 (2009).

226. William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 HEALTH AFFAIRS 1383, 1386 (2010).

227. Experts Brief, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 794111, at *19-*20 (citing Geoffrey F. Joyce et al., *Employer Drug Benefit Plans and Spending on Prescription Drugs*, 288 JAMA 1733 (2002)); Haiden A. Huskamp et al., *The Effective Incentive-based Formularies on Prescription-Drug Utilization and Spending*, 349 NEW ENG. J. MED. 2224, 2225 (2003).

State Children's Health Insurance Program.²²⁸ Many states require the prescriptions for patients, whose drug expenses are covered by those programs, to be filled with generic drugs.

In addition to state substitution laws, pharmacies have incentives to substitute generic drugs when possible. The federal reimbursement rules in industry pricing structures typically mean that pharmacies can earn a higher markup on the generic option than the branded one.²²⁹ Insurers in the private market may offer direct incentives to pharmacies to substitute cheaper generic drugs for the more expensive branded ones.²³⁰

These features combine to help generic manufacturers earn above-average profit margins. In 2007, profit margins for the top fifty industries in the United States averaged 7.4%.²³¹ Several of the top generic manufacturers saw profits of 12% to 25%—some of which even top the pharmaceutical industry's 15.8% profit margin—without incurring the risk undertaken by brand-name manufacturers in researching potential new drugs that may never come to market.²³² The above facts indicate that, as regulatory and institutional factors have enabled them to obtain an increasing share of the prescription market, generic manufacturers have enjoyed considerable growth in revenue and profits.

Going forward, a number of factors will further increase the growth of generic drugs. The implementation of various provisions of the Affordable Care Act (ACA) will increase Americans' access to care and prescriptions. Specifically, the ACA provides significant expansion of coverage to the uninsured through a Medicaid expansion, an individual requirement to obtain health insurance, and subsidies to help low- and middle-income individuals buy coverage through newly established Health Benefit Exchanges.²³³ Under the terms of this Act, prescription drugs are one of the "essential health benefits" that

228. See, e.g., IND. CODE § 1396b(z)(2)(E); Office of Inspector General, Department of Health and Human Services, *Generic Drug Utilization and State Medicaid Programs*, Jul. 2006, at i, available at <http://oig.hhs.gov/oei/reports/oei-05-05-00360.pdf> ("The Centers for Medicare & Medicaid Services (CMS) has encouraged generic drug substitution (i.e., substituting a generic drug for its brand name equivalent) as a safe and effective way for states to increase drug utilization and reduce costs.").

229. See S.P. Congressional Budget Office, *Medicaid's Reimbursements to Pharmacies for Prescription Drugs*, at 4 (2004).

230. Helene L. Lipton et al., *Pharmacy Benefit Management Companies: Dimensions of Performance*, 20 ANN. REV. PUB. HEALTH 361, 370-96 (1999).

231. *Top Industries: Most Profitable*, CNNMONEY, <http://money.cnn.com/magazines/fortune/fortune500/2008/performers/industries/profits> (last visited July 31, 2012).

232. See PLIVA, ANNUAL REPORT 2007, at 4 (2008); see TEVA PHARMACEUTICAL INDUSTRIES LIMITED, 2009 ANNUAL REPORT; Ben Hirschler & Quentin Webb, *Actavis Sees Record Year, No Rush to Sell*, Sept. 30, 2010; Wockhardt Unlimited, Annual Report 2009-10, at 73 (2010).

233. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 1501(b), 10106(b), 124 Stat. 119, 244-49, 909-10 (2010), as amended by the Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, §§ 1002, 1004, 124 Stat. 1029, 1032-34 (2010) (to be codified at 26 U.S.C. § 5000A).

must be included in health plans.²³⁴

Between now and 2014, the patents of seven of the world's twenty best-selling drugs will expire.²³⁵ The loss of patent protection for these blockbuster drugs will invite competition from generic manufacturers. The ability of generic drug manufacturers to capture significant portions of the market share after a brand-name drug loses its patent is increasing. For example, between 1991 and 1993, generic drugs represented 44% of a market after one year.²³⁶ By 2008, generic drugs controlled as much as 86% to 97% of a market within the first month of entry.²³⁷

It is against this backdrop that the Supreme Court held that generic manufacturers are prohibited from unilaterally taking any steps to ensure the safety and accuracy of their products' warning labels.²³⁸ The following are barred: altering warning labels through the CBE process to reflect the most up-to-date warnings; issuing additional warnings to healthcare providers through Dear Doctor letters; and publicly disseminating any additional warnings on their own.²³⁹ Further, the Court held that consumer state law failure-to-warn claims based on these inadequately labeled products are preempted as a matter of law.²⁴⁰

Of the possible harms that can result from *PLIVA*, the most serious is the extent to which it jeopardizes the health of the growing number of consumers taking generic drugs. As noted previously, once a brand-name manufacturer loses patent protection, generics quickly capture large portions of the market.²⁴¹ While a generic drug's branded 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. According to IMS Health, a leading aggregator of prescription and pharmaceutical sales, out of 4,318 unique drug molecules with active sales, nearly one-third are available exclusively in generic form.²⁴² In other words, the only version of the prescribed drug is one that is subject to ANDA regulations.

234. *Id.*

235. MEDCO, *Estimated Dates of Possible First Time Generic/Rx-to-OTC Market Entry* (Jan. 2012), http://www.medcohealth.com/art/corporate/anticipatedfirsttime_generics.pdf.

236. CONG. BUDGET OFFICE, *HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY*, at 28 (Jul. 1998), *available at* <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/6xx/doc655/pharm.pdf>.

237. *Protecting Consumer Access to Generic Drugs Act of 2009: Hearing on H.R. 1706 Before the H. Subcomm. on Commerce, Trade and Consumer Protection, of the Comm. on Energy and Commerce*, 111th Cong. 8 (2009) (statement of Diane E. Bieri, Exec. VP and Gen. Counsel, Pharm. Res. & Mfrs. of Am.).

238. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011).

239. *Id.* at 2575-76.

240. *Id.* at 2577-78.

241. *Id.* at 2584 (Sotomayor, J., dissenting).

242. GENERIC PHARM. ASS'N, *SAVINGS ACHIEVED THROUGH THE USE OF GENERIC PHARMACEUTICALS 2000-2009*, 7 (2010) *available at* http://www.prescriptionaccess.com/2010_Report_Generic_Savings_GPhA.pdf.

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.²⁴³ As a result, it is not unusual for the brand maker to simply stop selling the drug when facing a dramatic reduction in profits.²⁴⁴ 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.

Compounding this safety concern is the fact that many long-term risks do not emerge until after a drug is sold as a generic. Often brand-name drugs are approved after short-term safety studies and the long-term effects of a drug are not known for years. Continual monitoring of possible side effects is critical to ensure safety, even in drugs that have lost their patent protections. For example, Metoclopramide, first marketed as Reglan, was approved by the FDA in 1980.²⁴⁵ The drug was available in generic form by the mid-1980s.²⁴⁶ New risk information about the safety of the drug emerged in 2004 and again in 2009.²⁴⁷ Both times, the information resulted in significant label changes. As *PLIVA* makes clear, under the regulatory system, the FDA and brand-name manufacturers are solely responsible for developing drugs, crafting labeling changes, and communicating labeling revisions to healthcare providers and consumers.²⁴⁸ While the Court acknowledges that generic manufacturers have a duty to monitor the ongoing safety of their products and ensure the adequacy of their product labels, these duties are in large part passive.²⁴⁹ The Court sidesteps the issue of holding that generic manufactures have an affirmative duty to take steps to revise by alerting the FDA and providing information about product risks.²⁵⁰ Further, patients have no recourse against generic manufacturers who fail to take these steps.²⁵¹

This absence of generic manufacturer oversight may reasonably diminish consumer confidence in the safety and effectiveness of generic drugs. Since the passage of the Hatch-Waxman Act and the resultant proliferation of generic

243. Cf. Martin A. Ramey, Conte v. Wyeth: *Caveat Innovator and the Case for Perpetual Liability in Drug Labeling*, 4 PITT. J. ENVTL. PUB. HEALTH L. 73, 87 (2010) (noting that generics quickly capture the majority of market share for drug).

244. Brief for Marc T. Law et al. as Amici Curiae in Support of Respondents at 18, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 794111.

245. *Id.* at 15.

246. *Id.*

247. Brief of the American Medical Association et al. as Amici Curiae in Support of Respondents at 15-16, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 794118 [hereinafter *AMA Brief*].

248. *PLIVA*, 131 S. Ct. at 2574.

249. *Id.* at 2584-85.

250. *Id.*

251. *Id.* at 2581.

drugs, Congress and the FDA have gone to great lengths to assure consumers that generic drugs are “just as safe and effective” as brand-name drugs.²⁵² For many, these assurances imply that brand-name and generic manufacturers are bound by the same requirements to actively monitor and ensure the safety of their products that are prescribed to consumers. Echoing an expectation reinforced through products liability case law, many also might presume that, if there is a defect in a product, then both generic and brand-name manufacturers have a responsibility to correct the problem, or, at a minimum, to alert the public. Given these assumptions, consumers may rightly balk at the divergent responsibilities and liability rules to which they can hold manufacturers of seemingly identical products.

In addressing this strange statutory result, the dissent in *PLIVA* contends that, as a result of the Court’s holding, a drug consumer’s right to seek redress for inadequate warnings turns solely on the “happenstance” of whether her pharmacist fills her prescription with the brand-name or a generic.²⁵³ The incongruity of the current framework is made more absurd by the fact that “brand name manufacturers may elect to manufacture and distribute a generic version of their own brand name drug—as Wyeth has done with Reglan—once the brand name drug loses patent protection.”²⁵⁴ In such a situation, injured consumers using the same drug, manufactured by the same company, would be treated differently under the law based solely on fortuity.

In defining the manufacturer’s duties in *PLIVA*, the Court established a hierarchical distinction between brand-name and generic drugs. By mandating substantially stricter safety monitoring requirements for brand-name drugs than generic drugs, the Court undercut the congressional goal of promoting generics as brand-name equivalents. *PLIVA* further deepened this divide by creating a system where consumers of brand-name drugs can sue manufacturers for inadequate warnings, but consumers of generic drugs cannot. This divergent treatment results in two separate, but equally significant, categories of harm. First, it robs individual plaintiffs of their right to be compensated for harm incurred. Second, it eliminates legal incentives for generic drug manufacturers to strive for safety, because they no longer have to worry about state failure-to-warn claims.

Foreclosing consumer state failure-to-warn claims creates a schism in the complementary federal and state regulatory schemes. The contributions of tort law to product safety are well recognized. As the Supreme Court noted in *Wyeth*, “[s]tate tort suits uncover unknown drug hazards and provide incentives for drug

252. *Facts About Generic Drugs*, FDA (Jul. 1, 2012, 11:31 PM), <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm>.

253. *PLIVA*, 131 S. Ct. at 2592 (Sotomayor, J., dissenting).

254. *Kellogg v. Wyeth*, 612 F. Supp. 2d 437, 441 (D. Vt. 2009).

manufacturers to disclose safety risks promptly.”²⁵⁵ In this regard, courts have relied on state law as an important “layer of consumer protection that complements FDA regulation.”²⁵⁶ *PLIVA* eviscerates that traditional state law incentive for generic manufacturers in terms of monitoring and disclosing safety risks. Failure to hold generic manufacturers accountable for nondisclosure of known risks associated with their products also could create a schism between branded and generic drugs that likely would be exploited in marketing campaigns, and, ultimately, result in a turning away from generics by physicians and consumers.

Generic manufacturers need to be incentivized beyond the federal regulatory system to report known safety risks of their products. State tort suits aid in protecting consumers when harmful consequences become evident in drugs already approved by the FDA.²⁵⁷ When such information becomes apparent, manufacturers may not take appropriate action. The practical reality is that manufacturers often continue to sell their products for many years, while denying serious safety risks or downplaying emerging safety concerns.²⁵⁸ The potential damage awards from state failure-to-warn litigation provides drug manufacturers with incentives to quickly provide full and clear information to physicians and the FDA that otherwise may not come to light. Without such a mechanism, generic manufacturers may be motivated to act merely in their immediate financial interest, and, subsequently, become less forthcoming in providing safety-related data.

Litigation brought by individual patients helps to uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in a regulatory system.²⁵⁹ *PLIVA* has the potential to dramatically reduce the awareness of both the FDA and manufacturers of adverse consumer reactions to generic and brand-name medications. In some cases, it is only when consumers file failure-to-warn lawsuits that the harmful effects of drugs are revealed. In fact, the Supreme Court noted that a benefit of the state law regulatory scheme was that it “motivates injured persons to come forward with

255. *Wyeth v. Levine*, 555 U.S. 555, 579 (2009).

256. *Id.* For example, the Medicaid program provides medical assistance to persons who cannot afford to pay their own medical costs and is funded in significant part by the states. Under the program’s third party liability provisions, states can recoup Medicaid payments from the medical costs portions of tort judgments and settlements. *Arkansas Dept. of Health & Human Servs. v. Ahlborn*, 547 U.S. 268 (2006).

257. *Wyeth*, 555 U.S. at 579.

258. Bruce M. Psaty & Richard A. Konmal, *Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation*, 299 JAMA 1813, 1813-17 (2008); Bruce M. Psaty et al., *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, 292 JAMA 2622, 2626-30 (2004).

259. See Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 308-11 (2007).

information.”²⁶⁰ By preempting future state law failure-to-warn claims, the Supreme Court virtually eliminated this valuable conduit of information.

The current regulatory framework also could have far reaching implications for states. The *PLIVA* Court’s holding has, in effect, made the states financially responsible for injuries caused by the negligence of a class of for-profit corporations. By immunizing manufacturers from costs that their negligence imposes on the healthcare system, injuries to consumers will go uncompensated by the wrongdoer.²⁶¹ Many of the costs of providing medical care, rehabilitation, and family support services will now be borne by state-funded programs.²⁶² In addition, states no longer can recoup Medicaid payments from the medical costs portion of tort judgments and settlements through Medicaid’s third party liability provisions.²⁶³ This may lead some state legislatures to rethink their support for generic drugs through state substitution laws. Moreover, providing immunity for generic manufacturers seems at odds with a state’s roles as both principal protector of its citizens’ health, safety, and welfare²⁶⁴ and regulator of its health professionals.²⁶⁵

Finally, the Court’s opinion could also adversely affect physician drug-prescribing behavior. As noted by the American Medical Association (AMA), physicians consider many factors in making healthcare decisions.²⁶⁶ Without question, their first priority is patient safety. Nevertheless, in the current healthcare environment, physicians are also under continual pressure to control costs. As such, physicians should be able to prescribe an “equivalent” generic drug with assurance that it is truly the same as the brand-name drug, not only on the date of its approval, but during its lifetime on the market.²⁶⁷ In fact, the AMA recognizes the benefits of generic drugs and supports the right of physicians to prescribe generic equivalents.²⁶⁸ To determine the optimal drug to prescribe, frequently physicians rely on a benefit-risk profile.²⁶⁹ These profiles encompass the most current product safety information from brand-name manufacturers under comprehensive regulatory requirements, not uncertain or unreliable safety data. Divergent labeling responsibilities and liability rules for brand-name and generic manufacturers, however, may now influence that assessment.²⁷⁰ When a

260. *Wyeth*, 555 U.S. at 579.

261. Brief for Nat’l Conf. of State Legislatures as Amici Curiae in Support of Respondents at 18, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 794119.

262. *Id.*

263. *Arkansas Dep’t of Health & Hum. Servs. v. Ahlborn*, 547 U.S. 268, 280-92 (2006).

264. *H.P. Hood & Sons, Inc. v. Du Mond*, 336 U.S. 525, 532 (1949).

265. *Barsky v. Bd. of Regents*, 347 U.S. 442, 470 (1954).

266. *See AMA Brief*, *supra* note 247, at 28.

267. *Id.*

268. *See id.* at 29.

269. *Id.* at 5, 21.

270. *Id.* at 29.

physician specifies a prescription to be filled with the brand-name drug, he or she has an assurance that the drug company is monitoring the safety of that drug. In contrast, if the generic drug is prescribed, there can be no guarantee that the product safety information accompanying the generic drug is current or reliable. As noted by Justice Sotomayor, this poses an ethical dilemma for prescribing physicians and may cause them to question the substitution of a generic for a brand-name drug.²⁷¹

III. THE NEED FOR A NEW FRAMEWORK

A. Inadequacies of the Current Framework

1. Generic Manufacturers' Lack of Data

To market a brand-name drug, the current regulatory framework requires manufacturers to conduct the original clinical studies, perform postmarketing studies, and adhere to extensive post-approval surveillance requirements.²⁷² Complying with these duties affords the brand-name manufacturer access to (1) virtually all clinical data on the branded and the generic versions of the drug, (2) all world literature regarding the product, and (3) years of adverse reports from all sources since the drug's approval.²⁷³

By design, the FDA deters generic manufacturers' access to comprehensive data that are readily available to brand-name manufacturers.²⁷⁴ This exclusion begins during the initial ANDA submission to the FDA and persists throughout the post-surveillance requirements.²⁷⁵ In establishing bioequivalence as part of the ANDA process, generic manufacturers cannot access directly any information contained in the brand-name manufacturers' NDA, including clinical data. Rather, generic manufacturers are forced to rely on publicly available literature and the FDA's prior findings of safety and effectiveness of an approved medication.²⁷⁶

271. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2593 (2011).

272. See *supra* Part I for a discussion of the brand-name drug approval process.

273. *Id.*

274. See pre- and post-approval processes discussed *supra* Section I.B.

275. Jane A. Fisher, *Disclosure of Safety and Effectiveness Data Under the Drug Price Competition and Patent Term Restoration Act*, 41 FOOD, DRUG COSM. L.J. 268, 270 (1986) (setting down the historical basis of FDA's interpretation and implementation of the trade secrets doctrine to data).

276. Some innovator manufacturers have filed citizen petitions against the use of the FDA's prior findings. These findings often are based on data from studies submitted as part of an approved NDA. While published literature is available in the public domain, data from NDA submissions remain proprietary. Although the statutory language clearly allows for full NDA applications that rely on data to which the applicant does not have right of reference, language does not clearly specify whether this information can extend beyond published literature. Some pharmaceutical manufacturers have argued that the intent of Section 505(b)(2) was to allow referencing only of

Before a manufacturer submits an NDA for FDA approval, the FDA's Center for Drug Evaluation and Research offers a consulting program to foster early communications between the manufacturer and the FDA. Through this program, brand-name manufacturers receive guidance on the data necessary for submission as well as the regulatory requirements for demonstrating safety and efficacy.²⁷⁷ During the NDA review, the brand-name manufacturer and FDA work together on the drug's warnings and package insert. By the time the drug is ready for marketing, its labeling reflects both the joint efforts of the FDA's years of experience reviewing drugs and drafting warnings and the brand-name manufacturers' firsthand knowledge of the clinical trial results.²⁷⁸

Once introduced into the market, the FDA cannot implement subsequent labeling revisions without first negotiating these changes with the drug brand manufacturer.²⁷⁹ 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.²⁸⁰ Similarly, generic manufacturers cannot access the results of phase IV clinical trials that brand-name manufacturers conduct at the FDA's request.²⁸¹ Perhaps it is in light of this systematized restriction from data that the FDA limited the responsibility of generic manufacturers to ensuring that their products were the same as those of the branded counterparts. This rationale for the FDA's approach gains even more traction when one examines the quality of the information that the generic manufacturer receives.

As noted previously, the FDA keeps current on postmarket surveillance by requiring both generic and brand-name manufacturers to submit adverse events. The generic manufacturer's responsibility is limited to submitting only those adverse events that it receives directly.²⁸² While, theoretically, this would appear to give generic manufacturers a knowledge base to suggest labeling changes, in reality, it does not. As observed by the FDA, generic manufacturers rarely receive adverse reports, since most are submitted to the brand-name manufacturer or the FDA directly.²⁸³ In fact, adverse reports often fail to specify

portions of an NDA application available in the published literature, not proprietary portions of data. The FDA has upheld its position that Section 505(b)(2) permits reliance on previous FDA findings of safety and efficacy.

277. See *Colacicco Amicus*, *supra* note 30, at 4-5.

278. *Id.*

279. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX § 901(a), 121 Stat. 823 (2007) (codified as amended in sections of 21 U.S.C.).

280. 21 U.S.C. §§ 355(o), 255-1(g), 333(f).

281. *Id.*

282. 21 C.F.R. § 314.98.

283. HANDLING OF ADVERSE EXPERIENCE REPORTS AND OTHER GENERIC DRUG POSTMARKETING REPORTS, *supra* note 94 ("Generally, OGD [FDA's Office of Generic Drugs] receives few [adverse event reports] or similar reports since the reports may not specify a generic

generic manufacturers of the products entirely.²⁸⁴ While brand-name manufacturers are required to submit all adverse reports to the FDA, they are not required to share such information with the generic manufacturers of their product.²⁸⁵ It is ultimately up to the FDA to determine what and how information will be displayed to the public.²⁸⁶

To this end, the FDA requests that manufacturers not submit adverse reports unless there is (1) an identifiable patient and reporter, (2) a suspect drug, and (3) an adverse event or fatal outcome.²⁸⁷ The FDA is of the opinion that “reports without such information make interpretation of their significance difficult, at best, and impossible, in most instances.”²⁸⁸ It even has gone so far as to encourage “manufacturers to submit requests to the Agency . . . to waive the requirement to submit [forms] to the FDA for each adverse experience that is determined to be both nonserious and labeled.”²⁸⁹ Given these constraints and the current data vacuum in which generic manufacturers operate, it is hard to premise wholesale labeling revisions based on one or two adverse reports, generated years after approval.²⁹⁰

Another complication of the regulatory scheme is that once brand-name manufacturers remove their products from the market in favor of generics, there is typically no listing for either the brand-name drug or its generic equivalents in the Physician’s Desk Reference on prescription drugs. Without such listings and with the generic manufacturers’ inability to communicate independently with the physicians, it seems almost impossible for physicians to communicate up-to-date information regarding adverse affects to the manufacturer.

In 2007, Congress passed the Food and Drug Administration Amendments Act, which strengthened the FDA’s authority to compel labeling changes and identify postmarket risks.²⁹¹ Specifically, 21 U.S.C. § 355(j)(2)(A) authorizes the

manufacturer for the drug product.”).

284. *Id.*

285. 21 C.F.R. § 314.80(b).

286. See FDA, Adverse Drug Reaction Reporting Regulations Working Group, Center for Drug Evaluation & Research, *Guidance for Industry, Post-marketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report 1-2* (1997), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf>.

287. *Id.*

288. *Id.* at 3.

289. *Id.* at 4.

290. Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices - Final Rule, 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (“[T]he causal relationship between a product and an adverse effect is often difficult to establish and may require large trials, often specifically designed to assess the risk.”); *id.* at 49,607 (noting that risk information accumulates and reasoning that subsequent developments may only be relevant in light of “reports previously submitted to FDA”).

291. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (codified as amended in sections of 21 U.S.C.).

FDA to require manufacturers to make certain labeling changes. Yet, as illustrated by the FDA in the *PLIVA* facts, some generic manufacturers are excluded from receiving FDA warning revisions.²⁹² Specifically, the FDA did not send letters to all metoclopramide manufacturers. Only brand-name and generic manufacturers, with product labels identical to that of the brand-name product that was on the market, were contacted.²⁹³

The data vacuum that the framework creates has taken on added significance for consumers in the post-*PLIVA* world. The FDA maintains, and the Supreme Court assumes, without deciding, that federal law requires generic manufacturers to propose stronger labels.²⁹⁴ The regulatory framework, however, does little to facilitate carrying out such a duty. As discussed in more detail in the following Section, generic manufacturers' access to meaningful data, upon which they could make such recommendations, is severely curtailed. For example, in the *PLIVA* facts, the only information available to the generic manufacturer that might have motivated the manufacturers to approach the FDA for a recommended change was restricted to a handful of adverse reports and publicly available information. In contrast, the FDA and the brand-name manufacturer could rely on the original clinical data, all the world literature regarding the drug, and twenty-nine years of data from adverse reports submitted by all brand-name and generic manufacturers of the drug since it was approved. The harm in such a framework is twofold. First, it essentially requires a generic manufacturer to carry out its duty to monitor the safety of its drugs with one hand tied behind its back. Second, thanks to *PLIVA*, it requires consumers to rely on a regulatory framework that immunizes generic manufacturers against state law claims that would flow from their failure to carry out their duty to continually monitor their products' safety and propose stronger labels to the FDA. To support a warning label revision, a generic manufacturer needs to demonstrate a change in the product's risk-benefit analysis. This type of substantiation necessitates that a generic manufacturer either produce or have access to clinical trial data. The time and expense necessary to generate such data effectively deprive the Hatch-Waxman Act's overriding purpose of providing American consumers and state and federal governments with low-cost generic drugs. Consequently, regulatory changes are needed to ensure that other options are available.²⁹⁵

292. 21 U.S.C. § 355(j)(2)(A) (2006).

293. Brief of Petitioners Actavis Inc. and Actavis Elizabeth LLC, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 288895, at *10.

294. *PLIVA*, 131 S. Ct. at 2576.

295. *Drug Legislation: Hearings on H.R. 1554 and H.R. 3605 Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce*, 98th Cong. (1983) [hereinafter *Hearings on H.R. 1554 and H.R. 3605*].

2. *Lack of Appropriate Mechanisms for Generic Manufacturers To Change a Drug's Label*

In *PLIVA*, the Supreme Court departed from its deference to all of the FDA's ultimate conclusions over the issue of impossibility. As previously noted, the FDA claimed that generic manufacturers had several mechanisms available to them to advise the FDA about products' risks and adverse events. In describing how generic manufacturers should meet their duty to provide adequate warnings, the FDA referenced the preamble to the final rule implementing the ANDA application process²⁹⁶:

If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.²⁹⁷

In the twenty-three years since implementing the ANDA process, the FDA has failed to promulgate any regulations to govern this procedure.²⁹⁸ Should a generic manufacturer want to raise a safety issue, it is forced to flounder about in an ill-defined process of contacting various members within the FDA's OGD. The FDA provides no timeline for review, contact names for follow-up, specifications of what a concerned manufacturer should submit, or description regarding what happens after the proposed change is submitted. The only vague reference about which type of investigation the FDA conducts after receipt is that "some labeling reviews" will require the OGD to consult with various FDA components before any change can be made.²⁹⁹ To date, the FDA has not identified which labeling reviews trigger this type of consultation, nor has it identified the other components within the FDA that participate in examining these requests. The FDA justifies this haphazard approach by stating that such instances arise infrequently.³⁰⁰ The Supreme Court found this "solution" insufficient for preemption purposes. This Article draws an additional conclusion from the absence of procedures to improve drug labeling.

The need for regulatory reform to ensure that generic drugs are properly

296. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992).

297. *Id.*

298. Brief for the United States as Amicus Curiae Supporting Respondents, *supra* note 114, at 16.

299. *Id.* at 21.

300. *Id.*

labeled is evidenced by the inadequate FDA procedures that remain when a brand-name manufacturer withdraws its product from the market. While the FDA designates one of the remaining generic companies to serve as the new reference drug, the generic manufacturer is still prohibited from using the CBE process to change the label. Arguably, ensuring consumer confidence and avoiding confusion requires brand-name and generic drug warning labels to be identical when both drugs remain on the market. Perhaps it even justifies limiting a generic manufacturer's postmarketing labeling duty to that of merely mirroring its branded counterpart. This argument, however, ceases to be sound once the brand-name drug exits that market. Nevertheless, the FDA, not the generic manufacturer, is responsible for updating the product warnings. If the FDA determines that labeling for the product should be revised to meet current standards, it will advise the generic manufacturers to submit such labeling.³⁰¹ This seems to defy logic. As Congress has noted, "Clearly, the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA, and no matter what we do, they will always have vastly greater resources to monitor the safety of their products than the FDA does."³⁰² Given this reality, the duty and ability to provide adequate warning labels should reside with the generic manufacturer.

3. The FDA's Constraints Prevent Adequate Postmarket Monitoring of Generic Drugs To Ensure Consumer Safety

By immunizing generic manufacturers and essentially removing the crucial role the tort system has played in uncovering critical safety information, the courts have placed total reliance on brand-name manufacturers and the FDA to protect the public against pharmaceutical risks. At present, the FDA regulates products constituting twenty-five percent of the U.S. GDP.³⁰³ The FDA approves several hundred new and generic drugs each year, and it analyzes hundreds more.³⁰⁴ Over the past six years, the number of ANDAs submitted to the FDA has more than doubled. During the same period, staffing levels have only increased by twenty percent.³⁰⁵ What is more, after the drug is approved, the FDA's responsibility for monitoring drug safety increases. The FDA received

301. Determination That Brethine (Terbutaline Sulfate) Injection Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 72 Fed. Reg. 39,629, 39,630 (July 19, 2007).

302. 153 CONG. REC. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy).

303. Bruce M. Psaty & R. Alta Charo, *FDA Responds to Institute of Medicine Drug Safety Recommendations – In Part*, 297 JAMA 1917, 1917-19 (2007).

304. FDA, FY 2010 PERFORMANCE REPORT TO THE PRESIDENT AND CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT at 103 (2010), *available at* <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf>.

305. *Id.* at 6, 82, 92.

over 524,000 adverse event reports in 2010.³⁰⁶ As reflected in three recent analyses of drug safety oversight, under these constraints, the FDA simply does not have sufficient resources for responding promptly to safety problems that are discovered after marketing approval.³⁰⁷ It also lacks adequate procedures for quickly and effectively communicating appropriate risk information to the public.³⁰⁸

Moreover, the FDA does not have the necessary competencies to interpret the data it receives. Its own Science Board found that the FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to assess the products it regulates or to guide sponsors to design valid and informative studies.³⁰⁹ The GAO recently has placed the FDA's drug safety program on its watch list of high-risk areas requiring attention by Congress and the executive branch:

Although improvements have been made, long-standing concerns remain regarding the effectiveness of the FDA's post-market oversight. FDA staff have expressed concern about their ability to meet the growing postmarket workload, with some maintaining that their premarket responsibilities are considered a higher priority. FDA is also encountering technological and staffing issues that limit its capacity to conduct drug safety studies.³¹⁰

These deficiencies reflect an agency that is ill equipped to fulfill its vital role in protecting the public from harm caused by inaccurately or inadequately labeled generic drugs. Ensuring the public's safety necessitates the addition of two critical components: (1) a regulatory framework that provides generic manufacturers with the tools necessary to fulfill the Supreme Court's charge that manufacturers bear responsibility for the labeling of their product at all times, and (2) a framework that can work in conjunction with state tort systems to

306. *AERS Patient Outcomes by Year*, FDA, (July 1, 2012, 4:28 P.M.), <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070461.htm> (reporting 471,291 "serious outcomes" and 82,724 reports of death).

307. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-11-278, HIGH-RISK SERIES: AN UPDATE 116-17 (Feb. 2011), *available at* <http://www.gao.gov/new.items/d11278.pdf> [hereinafter HIGH-RISK SERIES: AN UPDATE]; U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-68, DRUG SAFETY: FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED 34 n.75 (Nov. 2009), *available at* <http://www.gao.gov/assets/300/298135.pdf>; U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 18 (Mar. 2006), *available at* <http://www.gao.gov/new.items/d06402.pdf>.

308. See INST. MED. NAT'L ACAD., *supra* note 38.

309. FDA, SCIENCE AND MISSION AT RISK: REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY 31-35 (Nov. 2007), *available at* http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf.

310. HIGH-RISK SERIES: AN UPDATE, *supra* note 307, at 116-17.

incentivize generic manufacturers to monitor their products and disclose adverse drug effects through the risk of adverse verdicts and the cost of resulting damage awards.

B. The New Framework

1. Necessary Tools for Generic Manufacturers

The framework providing generic manufacturers with the ability to label their products adequately requires access to all relevant data and the unambiguous authority to transform that information into adequate warnings. While the issue in *PLIVA* focused on the availability of post-approval mechanisms, a broader scope is needed. This Article suggests a framework that seeks to remedy the unfortunate hand that generic drug consumers were dealt in *PLIVA*, while preserving the Hatch-Waxman Act's policy objectives of "getting safe and effective generics quickly to the market" without sacrificing the Act's cost-saving aims.³¹¹

For generic manufacturers to possess the necessary data to make meaningful labeling suggestions, they need complete access to the clinical, animal, and bioequivalence data submitted in the brand-name manufacturer's NDA.³¹² The implementing language of the Hatch-Waxman Act allows generic manufacturers to use brand-name drugs still under patent to obtain bioequivalence data.³¹³ Hatch-Waxman also allows generic manufacturers to use FDA safety and effectiveness findings, and publicly available literature, to reverse engineer the components of the referenced drug.³¹⁴ When it approves a generic equivalent developed through these indirect methods, the FDA does not render final judgment that the drug is safe. Rather, the FDA is merely concluding that the generic drug does not differ significantly in the rate of absorption when administered in the same dose as its branded counterpart.³¹⁵ Giving generic manufacturers access to the actual clinical results submitted in NDAs provides them a more complete clinical base with which to evaluate the current and future performance of their product.

This Article proposes another fundamental shift in the current framework in terms of generic manufacturers' post-approval responsibilities and access to data. All manufacturers bear the responsibility for the adequacy of their labeling. To

311. H.R. REP. NO. 98-857, pt. 2, at 9 (1984).

312. 21 U.S.C. § 355(j) (2006) (describing the components necessary to constitute bioequivalency for ANDA approval).

313. 35 U.S.C. § 271(e)(1) (2006).

314. 21 C.F.R. § 314(g)(ii) (2011). FDA's safety and effectiveness findings are contained in the "Summary Basis of Approval" that the Agency prepares and makes publicly available. This document is prepared in compliance with the safeguards against public disclosure of proprietary and confidential information contained in 21 C.F.R. § 210.

315. 21 U.S.C. § 355(j)(8)(B).

this end, crafting adequate warning labels necessitates that generic manufacturers' possessing "superior" access to information about their drugs.³¹⁶ As noted by the Supreme Court, this need is particularly important in the post-marketing phase. As new risks emerge, compliance with FDA post-approval reporting requirements should provide generic manufacturers with sufficient data to discern the need for adequate labeling improvements. Currently, they do not. To close that gap, generic manufacturer post-approval labeling regulations should be the same as the regulations for brand-name manufacturers. Accordingly, the proposed framework requires generic manufacturers to have access to and analyze: (1) post-approval safety activities, (2) reports to worldwide regulators, (3) safety-focused epidemiologic activities, (4) activities required for safety-related labeling changes, (5) literature review for adverse-event information, and (6) safety information provided to healthcare professionals.³¹⁷

A primary reason for the low cost of generic drugs is that the FDA does not require generic manufacturers to replicate costly clinical trials for approval.³¹⁸ The proposed framework does not suggest altering this core cost-saving tenet. Currently, brand-name manufacturers conduct and pay for the majority of post-approval safety analyses.³¹⁹ As with data generated in the NDA process, generic manufacturers should have access to those data. Post-approval studies could continue to be conducted by the brand-name manufacturer or through a contracted laboratory.³²⁰ Regardless of how they are performed, the results would be distributed to all manufacturers of the product. A critical distinction between generic manufacturers' access to NDA information and access to the post-approval information is that generic manufacturers would share in the costs of generating the data.³²¹ Congress could mandate an "accessing data fee" that

316. *Wyeth v. Levine*, 555 U.S. 555, 578 (2009).

317. David B. Ridley et al., *Spending on Post-approval Drug Safety*, HEALTH AFF. 429, 430-31, 436 (2006). Other information could include "summary report production of aggregate post-approval adverse-event information[,] . . . safety surveillance activities, including those related to post-approval risk management, safety-related product quality complaints, including product recall for safety reasons, [and] responses to safety questions from worldwide regulators." *Id.* at 430-31.

318. H.R. REP. NO. 98-857, pt. 2, at 3 (1984).

319. Ridley et al., *supra* note 317, at 429 ("We surveyed drug manufacturers regarding safety efforts. Mean spending on postapproval safety per company in 2003 was \$56 million (0.3 percent of sales). Assuming a constant safety-to-sales ratio, we estimated that total spending on post-approval safety by the top twenty drug manufacturers was \$800 million in 2003.").

320. Contract laboratories can perform preclinical and clinical testing, post-approval studies, and pharmacovigilance aimed at identifying safety signals from all sources. The benefits of contract laboratories are that some generic manufacturers may not have laboratories or the resources within their existing laboratories to perform the necessary studies and the contract laboratory may have expertise that the generic manufacturer lacks. Donald Singer et al., *Contract Laboratory Partnerships: How To Make a Partnership Work With a Contract Pharmaceutical Testing Laboratory*, CONTRACT PHARMA (June 6, 2011), http://www.contractpharma.com/issues/2011-06/view_features/contract-laboratory-partnerships; see also 21 C.F.R. § 312.3(b) (2008).

321. The lack of patent protection in the post-approval world increases brand-name manufacturer concerns of free riding. Implementing a fee structure for post-approval studies would

keeps the costs of generic drugs low, compensates brand-name manufacturers for their data, and prevents generic manufacturers from getting a “free ride.” This fee should not prevent generic manufacturers from offering their products at a lower cost.

During the pre-approval and post-approval marketing of NDA products, the brand-name manufacturer and the FDA engage in ongoing conversations and negotiations regarding safety and labeling. Once the brand-name drug’s patent expires, the regulatory framework should include generic manufacturers in these discussions. Currently, no process exists for joint consultation and dialogue among the FDA, the brand-name manufacturer, and generic manufacturers to discuss appropriate steps or labeling revisions raised in adverse events or post-approval study results. In the absence of such communications, one questions the appropriateness of the resulting labeling changes. Generic manufacturers possess unique insight about the performance of their products and should contribute to the negotiations with the FDA and brand-name manufacturers regarding all post-approval labeling changes. Generic manufacturers also should be invited to consult with the FDA at critical junctures in the ANDA approval process and in response to adverse event reports.³²² These manufacturers are often in the best position to discover, assess, and take early action to address risks that come to light after the brand-name drugs patent exclusivity ends, because once generics become available, generic drug manufacturers often have the majority market share for the drug.

In addition to direct access to brand-name manufacturers’ data, the proposed framework allows for increased transparency and communication between the FDA and generic manufacturers. All proposed labeling changes should be sent to all manufacturers of the product. It is not anticipated that generic manufacturers merely would be the recipients of increased information. Similar to their branded counterparts, generic manufacturers should have post-approval responsibilities requiring them to conduct worldwide literature searches of their product.

It was not Congress’ intent for the FDA to carry the burden of ensuring safety and effectiveness of the pharmaceutical industry alone.³²³ The current resource constraints of the FDA only underscore the importance of generic manufacturers embracing their responsibility to ensure the adequacy of their products. More transparency in data will allow them to meet the elevated responsibility, which the Supreme Court assumes belongs to all manufacturers.

These proposals actually align with generic manufacturers’ characterization of their recognized responsibilities. After hearings on the Hatch-Waxman Act, representatives of the generic drug industry commented on their continuing

alleviate some of these concerns.

322. For a description of bioequivalence studies conducted for ANDA review, see *supra* Subsection I.B.1.

323. *Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009).

responsibility after their products' approval. For example, Kenneth Larson, the Chairman of the Generic Pharmaceutical Industry Association, asserted that generic drug companies were "sensitive to the importance of looking at adverse reactions."³²⁴ He further stated, "generic manufacturers of today will respond to those needs [I]f it demands a higher level of knowledge on our part, we are prepared to meet and respond to the need."³²⁵ In response to the question about whether the brand-name manufacturers are better able to correct problems than generic companies, Mr. Larson stated:

I can state for my company as well as I think I can state for the other generic companies that produce these products, that we will do and provide whatever is required to be performed to meet the regulatory requirement to provide for the safety and well-being of those that are using the drug, this is our role and responsibility. This is an obligation to be in the business.³²⁶

Once brand-name and generic manufacturers are on an equal footing regarding access to information, the next concern is which mechanisms should be available to the generic manufacturers to promote changes that will improve the safety of their labeling. Generic manufacturers require the clear and unequivocal access to the CBE and Dear Doctor letters processes that are afforded their brand-name counterparts. For example, brand-name manufacturers typically meet and discuss proposed warning label changes with the FDA before implementing them through the CBE process. Generic manufacturers should have a similar opportunity to not only use the CBE process, but also to discuss proposed warning labels with the FDA beforehand. The CBE regulation was enacted because the FDA wanted to provide a mechanism for manufacturers to amend their labels with new safety information that "required prompt corrective action" without forcing the products off the market until the FDA approved or rejected the amended label.³²⁷ The intent then was to protect patients.

The Supreme Court reiterated this same goal in *Wyeth*.³²⁸ Accordingly, consumers and their doctors need the most up-to-date information available. There is no reason why this same mechanism should not be made available to generic manufacturers. While generic drugs were not directly referenced in the

324. *Hearings on H.R. 1554 and H.R. 3605*, *supra* note 295, at 45.

325. *Id.*

326. *Id.* at 47-48; *see also id.* at 50-51 (statement of Bill Haddad, Executive Officer and President of the Generic Pharmaceutical Industry Association) ("We [generic drug companies] also put our money into research. Every single generic drug company that I know has a large research staff. It not only researches the drug that they are copying, or bringing into the market but it researches new drugs, researches adverse reactions.").

327. New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,635 (Oct. 19, 1982) (proposed rule).

328. *Wyeth v. Levine*, 555 U.S. 555, 568 (summarizing the intent of 21 C.F.R. § 314.70(c)(6)(iii)(A), (C)).

CBE process, this is only because the CBE regulations were first proposed in 1982,³²⁹ two years before the enactment of the Hatch-Waxman Act revolutionized the approval, marketing, and affordability of generic drugs. Therefore, it makes sense to interpret the absence of robust amendment procedures for generic drug labels as reflecting nothing more than a lack of foresight.³³⁰

Furthermore, despite the truncated nature of generic manufacturers' responsibilities, there is a strong argument that the regulatory basis for extending the applicability of the CBE process to generics already exists. Both brand-name and generic manufacturers are required to comply with regulations designed to ensure the post-approval safety of their drugs. They must "promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological surveillance studies, reports in the scientific literature, and unpublished scientific papers."³³¹ All reports of a "serious and unexpected" drug experience must be reported to the FDA within fifteen days and must be investigated promptly by the manufacturer.³³² Manufacturers are also obligated to submit quarterly adverse reports for the initial three years after their application (ANDA or NDA) is accepted.³³³ These regulatory requirements demonstrate an expectation that generic manufacturers, similar to their branded counterparts, are to actively participate in postmarket surveillance and take an active role in enhancing patient safety. The availability of the CBE process and Dear Doctor letters are vital to accomplishing this goal.

Notwithstanding the articulated tools above, it would be naïve to think that merely creating a regulatory framework that provides generic manufacturers with the ability to use the CBE process and send Dear Doctor Letters would dramatically increase the accuracy and adequacy of generic drug warning labels. For these measures to have real effect, generic manufacturers must also have an incentive to use them. As a result of *PLIVA*, generic manufacturers have no motivation to ensure that their labels accurately reflect the risks associated with a given treatment, because they cannot be held accountable if their drugs do not. Patient safety and generic drug integrity require that generic manufacturers be saddled with a more robust duty than just to maintain identical warnings labels to their branded counterpart. To promote accurate labeling, manufacturers must expeditiously provide full and clear information to physicians and the FDA about

329. *Id.*; see also New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7498 (Feb. 22, 1985) (final rule).

330. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355) (1984).

331. 21 C.F.R. § 314.80(b) (made applicable to ANDA holders by 21 C.F.R. § 98(a)).

332. *Id.* § 314.80(c)(1)(i)-(ii).

333. *Id.* § 314.80(c)(2)(i).

a drug's properties and adverse effects.

State tort liability can provide generic manufacturers the necessary incentive to fuel the federal regulatory machinery. It also forces generic manufacturers to produce known safety risk information under the microscope of the adversarial system. State tort trials help to uncover previously unavailable data on adverse events, questionable practices by manufacturers, and flaws in regulatory systems.³³⁴ These suits also serve to facilitate the rapid transmission of information regarding drug properties. Failure-to-warn suits also provide lawyers economic incentive to gather information about safety risks that may have been known to drug manufacturers, but which have not yet been acted on by national regulatory bodies. Without such litigation, the potential cost to generic manufacturers of concealing information, which is none, could encourage them to withhold critical safety information. As noted in literature that traces the social welfare benefits of dual regulation of risky technologies,³³⁵ "[t]he common law system's independence and private incentives to challenge the status quo are particularly valuable antidotes to complacency and ineffective regulation."³³⁶ Given the FDA's limited capacity to analyze the safety data it receives, state failure-to-warn suits are critical to support the FDA's regulatory mission. Simply put, generic manufacturers have sufficient scientific and financial resources to fulfill the reasonable demands of product liability law and state courts. Maintaining tort liability is essential to preserving the alignment of manufacturers' and consumers' interest in full disclosure of evolving risk information.

The articulation of this framework raises the question, "What about *PLIVA*?" Specifically, how does one address the Court's elimination of any generic manufacturer duty or ability to change its product labeling to protect consumers against inadequate warnings? Similarly, how could such a framework be integrated into the Court's elimination of state tort failure-to-warn remedies for injured consumers harmed by those products? One solution is for the FDA to amend its labeling rules to eliminate the impossibility identified by the Supreme Court. In other words, if the FDA were to amend its rules to authorize generic drug manufacturers to use the CBE regulation in the same manner as brand-name manufacturers, the federal regulatory basis upon which the Court rested its impossibility finding would cease to exist. This amendment would eliminate the bizarre consequences of having inconsistent state law duties for brand-name and generic manufacturers. Admittedly, however, this could produce a situation

334. Kesselheim & Avorn, *supra* note 259, at 308-11.

335. See generally C.F. LARRY HEIMANN, ACCEPTABLE RISKS: POLITICS, POLICY, AND RISKY TECHNOLOGIES (1997); Michael M. Ting, *A Strategic Theory of Bureaucratic Redundancy*, 47 AM. J. POL. SCI. 274 (2003).

336. William M. Buzbee, *Asymmetrical Regulation: Risk, Preemption and the Floor/Ceiling Distinction*, 82 N.Y.U. L. REV. 1547 (2007).

where consumers are offered multiple labels containing varying safety requirements for the same product. While this is a departure from the FDA's desire for uniformity in labels, this approach bolsters consumer safety by establishing uniformity of manufacturer responsibility. In effect, this places the responsibility to ensure the safety of a product on its manufacturer. The viability of bringing a failure-to-warn lawsuit no longer would hinge on the happenstance of whether the drug was produced by a brand-name or generic manufacturer. Rather, this approach directly attaches culpability to the manufacturer. Therefore, the generic or brand-name manufacturer that provides inferior labeling will be a viable target for a tort claim, precisely because it failed to provide the safest warning it could have.

Alternatively, Congress could decide to overrule *PLIVA* by amending the FDCA to state that neither the Act nor its regulations are intended to preempt state law. In this regard, the Supreme Court's observations in *Wyeth v. Levine* are instructive. The Court noted that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.³³⁷ In particular, Congress "determined that widely available state rights of action provided appropriate relief for injured [drug] consumers"³³⁸ and that "state-law remedies further consumer protection by motivating manufacturers . . . to give adequate warnings."³³⁹ Congress could enact legislation making explicit that it considers "state tort law as complementing, not obstructing, the goals of the FDCA."³⁴⁰ Given that Congress can expressly regulate the dividing line between state and federal law, and that Congress frequently has invoked such regulatory power in the past, this could be a viable approach.

It remains an open question which of these two options would be the more effective route. If the past is any indicator, the FDA alternative may prove to be more expeditious. Following the Supreme Court's 2008 decision in *Riegel v. Medtronic*,³⁴¹ in which the Supreme Court held that certain state laws against medical device manufacturers were expressly preempted by the 1976 Medical Device Amendments, Congress introduced the Medical Device Safety Act in an effort to nullify *Riegel*'s effects. To date, however, this legislation has yet to take effect. Accordingly, if Congress decided to overturn *PLIVA*, a bill likely would take years to work its way through the legislative process. Regardless of whether the solution comes from Congress or the FDA, it is clear that, after *PLIVA*, some kind of change is necessary in order to ensure patient safety and the integrity of generic drug warnings.

337. *Wyeth v. Levine*, 555 U.S. 555, 574 (2009).

338. *Id.*

339. *Id.*

340. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 612 (8th Cir. 2009).

341. 552 U.S. 312 (2008).

2. Addressing Anticipated Criticisms

One may anticipate several criticisms of the proposed framework. Under the current regulatory scheme, it is not unusual for brand-name manufacturers to file infringement challenges to prevent public disclosure of their NDA data.³⁴² The proposed framework's call to provide generic manufacturers with direct access to NDA information and the results from ongoing clinical trials will trigger additional proprietary and intellectual property issues that are beyond the scope of this Article.³⁴³ An argument can be made, however, that the proposed disclosures are in keeping with the intent of the Hatch-Waxman Act. Section 505 of the FDCA provides that NDA "safety and effectiveness data and information which has been submitted in an application . . . shall be made available to the public, upon request."³⁴⁴ From this provision, it seems that Congress did not aim to bar the public from safety and effectiveness data.³⁴⁵ The proposed framework furthers congressional intent to foster one of Hatch-Waxman's goals of ensuring the availability of safe and effective generic drugs.³⁴⁶

In response to reinstating tort liability, the Generic Pharmaceutical Association of American (GPhA) has asserted that increased responsibilities to monitor the safety of their products would "wipe out" more than one hundred billion dollars per year in savings under the Hatch-Waxman scheme.³⁴⁷ In making this argument to the Supreme Court, however, GPhA offered no support to substantiate the actual costs to generic manufacturers for reporting known health risks or monitoring widely available public information about a drug. Similarly, GPhA offered no explanation as to why such responsibilities would be so costly

342. LARS NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS 339 (Robert C. Clark et al. eds., 2d ed. 2007).

343. For a competent summary, see Holly Soehnge, *The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51 (2003), which explains the purpose of the Hatch-Waxman Act as an attempt to correct the perceived imbalances between brand-name manufacturers and generics, while decrying the abilities of both sides to bypass strictures. See also Mustafa Ünü, *It Is Time: Why the FDA Should Start Disclosing Drug Trial Data*, 16 MICH. TELECOMM. TECH. L. REV. 511 (2010), available at <http://www.mttlr.org/volsixteen/unlu.pdf>.

344. 21 U.S.C. § 355(l)(1)(2006) (emphasis added).

345. In practice, brand-name manufacturers have successfully used the last minute addition of Section 505's tempering "unless extraordinary circumstances are shown" provision to curtail the release of research data. James T. O'Reilly, *Knowledge Is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1, 6 (1985) ("Advocates of drug data disclosure acted quietly in attaching a full disclosure provision, buried amidst many unrelated and controversial provisions, to the pending legislation."); *id.* at 18 ("Maneuvering in a minefield of ambiguity and mutual mistrust, the drafters of the 1984 Act settled upon the term 'extraordinary circumstances' on the false impression that it represented current FDA policy on data disclosure of live data.").

346. H.R. REP. NO. 98-857, pt. 2, at 9 (1984).

347. Brief of the Generic Pharmaceutical Association as Amicus Curiae in Support of Petitioners at 3, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501), 2011 WL 343069.

as to undermine significantly the current level of savings consumers receive from the use of generic rather than brand-name drugs.³⁴⁸

Critics may argue that *PLIVA* merely returns individuals to their pre-*Wyeth* position, when the majority of courts held that state law failure-to-warn claims were preempted. Yet significant changes in the healthcare landscape render these *PLIVA* implications far more significant for consumers. Another probable criticism is that allowing generic manufacturers the ability to strengthen their labels independently erodes the FDA's mandate of uniformity across brand-name and generic drugs. Because this uniformity is crucial for public confidence in the safety and effectiveness of generic drugs, increasing the number of manufacturers who can unilaterally change their products would undermine the intent of the Hatch-Waxman Act.³⁴⁹

The issue of uniformity must be re-examined in the wake of *PLIVA*. The congressional intent of the Hatch-Waxman Act was to create a market of generic drugs equivalent in value to their branded counterparts.³⁵⁰ Holding brand-name and generic manufacturers to the same state law standards directly serves that aim. For generics to succeed, they must have equal value to branded drugs. In economic terms, they must be perfect substitutes, and, in safety terms, this requires a duty to disclose risks equal to that of its branded drug. A critical component of the value equation for any product is a consumer's recourse in the event the product is defective. Products sold "as is" are less valuable than one sold with an implied warranty of fitness and merchantability. Similarly, a product sold without a preemption of state law tort claim is more valuable than one sold with such a preemption. Barring a consumer from pursuing a product liability claim against a generic manufacturer, but not a brand-name manufacturer, undermines the goal of uniform value between generic and brand-name drugs.³⁵¹

A basic economic tenant is that the cost of accidents is lessened when society imposes such costs on "the 'cheapest cost avoider' or [the actor] who is in the best position to make the cost-benefit analysis between accident costs and accident avoidance costs and to act on that decision once it is made."³⁵² The Supreme Court endorsed this finding in *Wyeth v. Levine*, by holding that pharmaceutical manufacturers "have superior access to information about their

348. *Id.*

349. See, e.g., *Facts and Myths About Generic Drugs*, FDA (last updated June 22, 2012) <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm>.

350. See Brief of Rep. Henry A. Waxman as Amicus Curiae in Support of Respondents Urging Affirmance at 8, *PLIVA*, 131 S. Ct. 2567 (Nos. 09-993, 09-1039, 09-1501), 2011 WL 794113.

351. *Id.*

352. *Beshada v. Johns-Manville Prods. Corp.*, 447 A.2d 539, 548 (N.J. 1982) (citing Guido Calabresi & Jon T. Hirschoff, *Toward a Test for Strict Liability in Torts*, 81 YALE L.J. 1055 (1972)).

drugs, especially in the post-marketing phase as new risks emerge,”³⁵³ and that “state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.”³⁵⁴ Uniformity necessitates this same standard be applied to generic manufacturers.

Under the current regulatory scheme, generic manufacturers do not make label modifications until the FDA approves the proposed label (whether through the CBE or some other process).³⁵⁵ As previously mentioned, it is a common practice for brand-name manufacturers to consult with the FDA prior to making these proposed changes.³⁵⁶ Giving generic manufacturers access to the same CBE change consultation process, and not requiring any industry-wide change in the generic or brand-name drug until the FDA approves the change, addresses many of the uniformity and consumer confidence concerns that critics may raise.³⁵⁷ Essentially, the proposed framework expands the process the FDA uses to notify generic manufacturers of changes made to their branded counterpart to now include notifying the brand-name manufacturer of required changes originally proposed by their generic counterpart. To be clear, it is not the intent of this Article to take exception to the Supreme Court’s preemption and validity of the impossibility defense analysis. Rather, this Article addresses the adequacy of a regulatory framework that contributed to the Supreme Court’s ruling and the resultant safety implications for consumers.

3. Reconciling the Proposed Framework with the Intent of the Hatch-Waxman Act

A major challenge to the proposed framework is balancing two of the Hatch-Waxman Act’s primary goals: increasing the availability of quality medical care and lowering the cost of generic drugs.³⁵⁸ In determining how that balance should be struck, Hatch-Waxman must be read in the context of the FDCA, which it amends. The purpose of the FDCA is to protect the public health and “assure the safety, effectiveness, and reliability of drugs.”³⁵⁹ As the Supreme Court succinctly noted, “Congress enacted the FDCA to bolster consumer protection against harmful products.”³⁶⁰ Nothing in the Hatch-Waxman Act suggests that Congress intended to abandon that position. Similarly, there is no evidence that, when Congress passed Hatch-Waxman, “it intended the goal of delivering low-

353. *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009).

354. *Id.* at 574.

355. *See infra* Subsection I.B.2.

356. Gilhooley, *supra* note 6, at 551.

357. The FDA could even consider expanding these pre-CBE change consultations to include both generic and brand-name manufacturers.

358. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355) (1984).

359. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

360. *Wyeth v. Levine*, 555 U.S. 555, 574 (2009).

cost generic drugs to supplant the FDCA's overall goal of providing consumers with safe and effective drugs."³⁶¹ Accordingly, while Hatch-Waxman sought to quickly make low-cost generic drugs more accessible, it did not pursue this goal at all costs.³⁶² To impute such a single-minded cost focus into Hatch-Waxman would give short shrift to Congress' purpose of consumer safety.³⁶³ Isolating the Hatch-Waxman Act from the entirety of FDCA would violate the basic principle that statutes should be read as a whole. The Hatch-Waxman Act's success rests in large part on the assurance of "sameness" between brand-name and generic drugs. The ANDA system, which streamlined the process for initially bringing generic drugs to market, is premised on this very idea. This "sameness" principle however, does not mean that generics are to be sold without regard for whether consumers are properly warned about serious risks.³⁶⁴ Rather, this core "sameness" principle requires generic and brand-name manufacturers to be held to the same post-approval standards. For example, brand-name and generic manufacturers often receive important safety information once their drugs are on the market. They should be treated the same with respect to their responsibility to bring that relevant data to the FDA's attention. They also should have the same access to regulatory mechanisms to strengthen their products' warning labels to ensure patient safety. Finally, any violation of the standards should be addressed with the same tort liability.

Simply put, requiring generic and brand-name manufacturers to bear the same level of responsibility for ensuring the safety of their products is directly in line with the intent of Hatch-Waxman Act. The solution proposed by this framework embraces the spirit of Hatch-Waxman disclosure provisions by providing generic manufacturers with direct access to the data necessary to craft adequate labeling changes.

CONCLUSION

The issue of whether the current regulatory framework adequately promotes safe and effective generic drugs has gotten lost amid state law failure-to-warn litigation. *PLIVA* effectively called a halt to circuits shoehorning generic manufacturers' regulatory responsibilities into a *Wyeth* analysis. In doing so, the Supreme Court clarified, for courts and consumers alike, "that federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully

361. *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225, 1395 (9th Cir. 2011).

362. H.R. REP. NO. 98-857, pt. 1, at 14 (1984).

363. See 130 CONG. REC. 15847 (June 12, 1984) (statement of Sen. Hatch) ("This is a good bill. *Without compromising the public safety or welfare in the least* it will significantly lower the price of off-patent drugs, by many times in some cases, through increased generic competition.") (emphasis added).

364. See *State Consumer Education Efforts*, GENERIC PHARM. ASS'N (GPHA), <http://www.gphaonline.org/issues/state-consumer-education-efforts> (last visited Aug. 1, 2012).

different than those that apply to generic drug manufacturers.”³⁶⁵ According to the Court, these differences have divergent safety and legal implications for consumers. For example, these differences preempt the ability of generic drug consumers to sue generic manufacturers for failure to warn. They also prohibit generic manufacturers from taking any steps to strengthen inadequate warning labels unilaterally or to disseminate publicly additional warnings on their own. Given that generic drugs constitute seventy-five percent of all prescriptions in the United States, the Court’s ruling has broad implications. By immunizing generic manufacturers against state law failure-to-warn claims, the Court arguably has reduced the incentive of generic manufacturers to provide comprehensive information about their products’ properties and associated risks. Generic manufacturers also may have less incentive to fulfill their duty to propose label changes under FDA regulations. All of these responsibilities are necessary components in ensuring that labels accurately reflect the risks associated with them. Without these controls, consumers may lose confidence in generic drugs and physicians may be reluctant to prescribe them. Additionally, as protectors of the health and welfare of their citizenry, states may reassess substitution laws.

Despite key differences between the labeling frameworks for brand-name and generic manufacturers, the *PLIVA* analysis loses sight of the most essential function of drug regulation: consumer safety. In the Court’s finding of “impossibility,” it essentially abandons a central premise of drug regulations. The framework advanced by this Article addresses what *PLIVA* neglected. While incorporating the unique role generic drugs play in the American healthcare system, this Article advances a framework that remains committed to Hatch-Waxman’s goals of providing safe, but less expensive, generic drugs. This is achieved through regulations that provide all manufacturers with increased access to data pertaining to the safety of their drugs. It also offers a structure for open communication among generic manufacturers, their branded counterparts, and the FDA. Finally, the framework grants generic manufacturers unambiguous access to label-changing mechanisms that are available to brand-name manufacturers.

365. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2582 (2011).