

GENERIC MANUFACTURERS’ LABELING CATCH -22¹

Stacey B. Lee*

In Wyeth v. Levine, the Supreme Court eliminated brand-name manufacturers’ ability to use the preemption defense against state law failure to warn claims involving allegedly misbranded pharmaceutical drugs. Since that time, a heated debate has ensued among federal courts and legal scholars regarding that holding’s effect on generic manufacturers. Lost amid these judicial opinions and scholarly articles, however, is a more fundamental inquiry. Regardless of whether preemption is a viable defense, what type of legal and regulatory framework is needed to ensure generic manufacturers possess the necessary tools to fulfill their responsibility of providing consumers and the medical community with current and accurate labeling instructions for their products? This Article proposes such a framework.

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* Assistant Professor at the Johns Hopkins University Carey School of Business. Email:staceyb.lee@jhu.edu. Thank you also to: Brian P. Lee and Chester Chambers.

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INTRODUCTION

In many ways, the current challenge faced by generic manufacturers as they try to defend themselves against state law failure to warn claims is reminiscent of a conversation that takes place between two characters in Joseph Heller's Catch-22.²

Doc Daneeka: Catch-22 . . . says you've always got to do what your commanding officer tells you to.

Yossarian: But Twenty-seventh Air Force regulations say I can go home with forty missions.

Doc Daneeka: But they don't say that you have to go home. And regulations do say you have to obey every order. That's the catch. Even if the colonel were disobeying a Twenty-seventh Air Force order by making you fly more missions, you'd still have to fly them, or you'll be guilty of disobeying an order of his. And then the Twenty-seventh Air Force Headquarters would really jump on you.³

Essentially, generic manufacturers are being held responsible for the adequacy of warning labels that they did not write and that the Food and Drug Administration (FDA) maintains that they cannot alter.

The foundation of this precarious position was formed by the Supreme Court's decision in *Wyeth v. Levine*.⁴ This decision effectively sounded the death knell for brand name manufacturers' preemption defense to state law failure to warn claims. While the case did not directly reference generic manufacturers, the Court's ruling altered the landscape of generic labeling liability. As a result, a majority of courts, such as the Fifth, Eighth, and Ninth Circuits, have applied the preemption exclusion to generic manufacturers.⁵ Consistent throughout this line of cases is a heavy reliance on the regulatory framework the Supreme Court used in denying brand name manufacturers' preemption defense. The troubling aspect of that reliance is that the primary compliance

² JOSEPH HELLER, *CATCH-22* (Simon & Schuster 1996) (1961).

³ *Id.* at 68.

⁴ *Wyeth v. Levine*, 129 S.Ct. 1187 (2009).

⁵ *Actavis v. Demahy*, 595 F.3d 428 (5th Cir. 2010); *Mensing v. Wyeth*, 588 F. 3d 603 (8th Cir. 2009); *Gaeta v. Perrigo Pharm. Co.*, No 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011).

mechanisms the Supreme Court identified are largely unavailable to generic manufacturers.

The validity of the preemption defense for generic manufacturers has generated much scholarly debate, including analysis of such issues as: the preemption intricacies regarding the appropriate level of judicial deference to Agency pronouncements; the scope of states' authority to protect their citizens through the availability of liability lawsuits,⁶ and the existence of the factual predicates for drug manufacturers to claim preemption.⁷ Absent in this body of academic scholarship, however, is a practical legal framework for generic manufacturers to comply with the Supreme Court's mandate that "the manufacturer bears primary responsibility for their labeling."⁸

The need for such an examination is heightened by the consolidated Fifth and Eighth Circuit appeal pending before the Supreme Court.⁹ This case will more than likely quell the debate regarding whether generic manufacturers are preempted from state law failure to warn claims. The resolution of the preemption quagmire, however, is not synonymous with the articulation of a legal and regulatory framework that supports generic manufacturers' responsibility to provide the medical community and consumers accurate and timely product labeling information.

For example, the Eighth Circuit in the pending appeal held that preemption was not an applicable defense to state failure to warn claims.¹⁰ Yet, the court did so while refusing to take any position on the availability of key regulatory provisions that are critical for generic manufacturers to discharge their responsibility.¹¹ The Eighth Circuit based its ruling, in large part on the court's interpretation that the regulatory framework permits generic manufacturers to at least "take steps to propose a label change" through the Post Approval Supplement ("PAS") or suggest that the FDA send out warning letters to healthcare professionals.¹² In addition, the court noted that because a generic manufacturer can always choose to stop selling its product, preemption is an inapplicable defense.¹³ In its opinion, the Fifth Circuit substantively addressed the regulatory provisions glossed over by the Eighth Circuit. The court stated that Congress is silent as to generic manufacturer's post-approval labeling obligations.¹⁴ From that silence, the Fifth Circuit determined that nothing in the current regulatory labeling explicitly prevents generic manufacturers from unilaterally altering their labels to comply with state law warnings.¹⁵ As a result, the court rejected the preemption defense. This conclusion is

⁶ Margaret Gilhooley, "Drug Preemption and the Need to Reform the FDA Consultation Process," *American Journal of Law & Medicine*, Vol. 34 No. 4, 535, 536, (2008).; 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 (Summer 2009).

⁷ Lesley A. Stout, "Making Changes: Generic Drug Labeling and the Case Against Federal Preemption" 98 *KY. L.J.* 623 (2009-2010).

⁸ *Levine*, 129 S.Ct. at 1202.

⁹ *Pliva v. Mensing*, cert. granted (No.09-993) *Actavis v. Demahy*, 595 F.3d (5th Cir. 2010), cert. granted (No. 09-993);

¹⁰ *Mensing*, 588 F.3d at 614.

¹¹ *Id.* at 608.

¹² *Id.* at 609-10.

¹³ *Id.* at 611.

¹⁴ *Id.* at 436.

¹⁵ *Demahy*, 593 F.3d at 444-45.

curious in that it flies in the face of everything the FDA has ever said about the scope of generic manufacturers' labeling authority. Regardless of whether state law failure to warn claims are preempted, there needs to be a legal and regulatory framework that enables generic manufacturers to unilaterally meet their primary responsibility to address the underlying labeling concerns. This article proposes such a framework.

Section I provides an overview of the drug approval process. Part one of this section examines the regulatory framework that defines the *pre-* and *post-* approval process for brand name drugs. The next section provides similar background on the approval procedures for generic drugs. Section II offers a focused analysis of the regulatory framework that defines generic manufacturers' post-approval labeling responsibilities. Through the lens of federal preemption case law, this section examines how recent regulations and holdings combined to create a framework that is inadequate for generic manufacturers to fulfill their labeling responsibilities. Section III explores 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 IV articulates a practical framework in which generic manufacturers have the necessary tools to fulfill their responsibility of providing 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 drug approval process and how that process incorporates generic drugs. In 1938, Congress enacted the Food, Drug and Cosmetic Act (FDCA).¹⁶ This Act, granted the FDA exclusive authority to regulate the prescription drug industry.¹⁷ Accordingly, it is the FDA's responsibility to ensure that drugs are safe, effective,¹⁸ and not mislabeled.¹⁹ To that end, the FDA is the primary authority in establishing the regulations governing the manufacture, sale, and labeling of prescription drugs.²⁰

A. Brand Name Drug Approval and Labeling Process

1. Pre-approval

Pursuant to the FDCA, all drug manufacturers must receive FDA approval before they may introduce a new drug on the market.²¹ 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 that is supported by clinical trial

¹⁶ 21 U.S.C. § 393 (b)(1), (b)(2)(D) (2000 & Supp. III 2003).

¹⁷ 21 U.S.C. § 355 (a).

¹⁸ *Id.*

¹⁹ 21 U.S.C. § 355 (d).

²⁰ 21 U.S.C. §§321 (n), 331 (a)-(b), (k), 352, 355, 393 (b)(2)(B) (2000 & Supp. III 2003).

²¹ *Id.* § 355 (a).

data.²² The manufacturer must also provide proposed labeling that reflects the appropriate use and warnings about the drug's potential dangers and adverse reactions.²³

Under the FDCA, labeling comprises "all labels and other written, printed, graphic matter: (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."²⁴ Courts have also interpreted labeling to include product advertising attendant to the product.²⁵ A drug that contains labeling that is false or misleading or contains inadequate directions for use or inadequate warnings will be rejected by the FDA on the basis that that the drug is "mislabeled."²⁶

To avoid FDA rejection, brand name manufacturers work closely with the Agency during the NDA approval process to determine the appropriate labeling for the drug.²⁷ Side effects, contra-indications and relevant hazards are extensively discussed between the manufacturer and Agency in order to satisfy the FDA requirement that labels include warnings of "all known risks based on reliable scientific evidence."²⁸ During this process, the FDA also takes careful steps to omit risks that are inadequately supported by the scientific research.²⁹ Ultimately, the FDA determines what information is included in the labeling and the exact final version of the instructions, down to the type size and font.³⁰ 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 take years.³¹ Under federal law, therefore, the evaluation of a drug's safety and effectiveness is inextricably linked with the drug labeling.³²

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.³³ This ongoing responsibility is rooted in several factors. During the pre-approval phase, the drug is tested on relatively small groups of patients, generally between 600 and 3,000, and only for a limited period of time, rarely in excess of two

²² *Id.* §§355(a)-(b), (d).

²³ *Id.* 355 (b) (1) (F); *see also* 21 C.F.R. § 201.80 (2009) for detailed specifications for a drug's labeling.

²⁴ 21 U.S.C. §321(m).

²⁵ *Kordel v. United States*, 335 U.S. 350 (1948).

²⁶ 21 U.S.C. §352 (a), (f).

²⁷ Brief for Amicus Curiae in the United States of America, at 5, *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (No. 05 CV 05500-MMB) (noting that drug manufacturers and the FDA collaborate extensively regarding the content of proposed drug labeling) (hereinafter "Colacicco Amicus").

²⁸ 21 C.F.R. §§ 201.56(2), 201.57(c).

²⁹ *Colacicco Amicus*, *supra* note 27, at 5.

³⁰ *Id.*

³¹ Michael Dickson & Jean Paul Gagnon, Key Factors in the Rising Cost of New Drug Discovery and Development, 3 *NATURE REVS.* 417, 418 fig. 1 (2004) (estimating that research, development, testing, and FDA review of a new drug takes a minimum of three years).

³² 50 Fed. Reg. 7452, 7470 (1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.").

³³ 21 U.S.C. §331(a)-(b), (k) (2000).

years.³⁴ As a result, pre-approval testing cannot readily detect adverse effects that occur infrequently, have long latency periods, or affect populations that were under-represented.³⁵ Further, because under-represented subgroups rarely provide sufficient data to permit a degree of refined analysis, the FDA's assessment of a drug's risks is performed on a population wide rather than subgroup by subgroup basis.³⁶ In light of these limitations, the resulting FDA-approved labels cannot warrant that a drug will not cause serious adverse effects even if properly used for the approved purposes.³⁷ To monitor the unanticipated adverse events, the FDA requires all manufacturers to submit adverse event reports to the Agency.³⁸

In the pre-marketing phase, the FDA is the exclusive authority for determining the adequacy and approval of the drug's label.³⁹ The Agency's authority rests in part on its expertise in reviewing and evaluating the studies and information provided by the manufacturer.⁴⁰ However, in the post-market world, the burden rests more squarely on the manufacturer to ensure that its labeling is adequate. In part, this shift in responsibility reflects the decreased data the FDA receives on post-market drugs. 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.⁴¹ Even if such an ongoing obligation existed, the chronic resource constraints of the Agency calls into question whether the manpower exists to make meaningful use of the data.⁴²

³⁴ David A. Kessler and David C. Vladeck "A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims, 96 GEO LJ 461, 471 (2008).

³⁵ INST. OF MED. OF THE NAT'L ACADS., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 36 (Alina Baciú, Kathleen Stratton & Sheila P. Burke eds., 2006) [hereinafter IOM REPORT].

³⁶ Most clinical studies can detect drug-related injuries that occur at a rate between one and 500 and 1 in 1000. Yet, if the drug is used by 200,000 people . . . a serious adverse event and peering 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, at A35 (Mr. Schultz served as the FDA's Deputy Commissioner for Policy from 1994 to 1998).

³⁷ Jason Lazarou et al., Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta Analysis of Prospective Studies, 279 JAMA 1200, 1202 (1998) (The FDA recognizes that even the most up-to-date and informative labels cannot avert adverse reactions).

³⁸ 21 C.F.R. § 314.80 (b) (post-marketing reporting obligations for NDA applicants); 21 C.F.R. § 314.98 (post-marketing reporting obligations for ANDA applicants).

³⁹ 21 U.S.C. §355(n) (2006). The day that the FDA approves a drug is the one moment in time when it is in the best position to comment on the drug's safety and efficiency. During the approval process, the Agency has had access to and exhausted considerable resources in reviewing all available health and safety data pertaining to the drug.

⁴⁰ 21 U.S.C. 355 (b)(1) (Supp. V 2001-2006).

⁴¹ Kessler, *supra* note 34 at 492.

⁴² For example, the FDA's Office of Drug Safety, the unit responsible for monitoring adverse events that arise with the 3,000 prescription and approximately 8,000 OTC drugs the Agency has approved over the years, is 100 professional employees. FDA's Drug Approval Process: Up to the Challenge? Hearing Before the S. Comm. On Health, Educ., Labor and Pensions, 109th Cong. 11 tbl. (2005) In contrast, more than 1,000 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. At 42 (2005) statement of Dr. Bruce S. Patsy).

As the maker and seller of the product, the underlying responsibility to ensure that the drug is safe as well as effective should rightly be placed on the manufacturer.⁴³ To that end, there are detailed procedures that regulate post-market modifications to a drug's labeling.⁴⁴ For example, the brand name manufacturer is required to conduct extensive post-marketing surveillance.⁴⁵ This includes review and analysis of reported adverse events and published medical and scientific literature.⁴⁶ The FDA requires brand name manufacturers to disclose any relevant information discovered through this process including information contained in the adverse reports they received regarding any version of their product.⁴⁷ In addition, the Agency commonly requires brand name manufacturers to conduct follow-up Class IV clinical studies after they begin selling their product.⁴⁸ This analysis is conducted against the backdrop of the knowledge the manufacturer obtained during the clinical trials and other research conducted during the NDA approval process.⁴⁹

a. Mechanisms for Post-market 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" between the drug and the clinically significant hazard.⁵⁰ The procedure for making these changes are set forth in 21 C.F.R. §314.40 and include the Prior Approval Supplement ("PAS") and Changes Being Effected ("CBE") mechanisms.⁵¹ The PAS 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.⁵² While PAS provisions enable certain labeling modifications, they expressly exclude labeling changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction."⁵³ 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

⁴³ Brent R. Gibson et al., *The US Drug Safety System: Role of the Pharmaceutical Industry*, 17 *Pharmacoepidemiology and Drug Safety*, 110-114 (2008).

⁴⁴ Federal law requires brand name manufacturers to file "post-marketing reports" to the FDA, notifying the Agency 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.

⁴⁵ 21 C.F.R. § 314.80 (b).

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

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

⁴⁸ 21 C.F.R. §315.510; FDA, *Guidance for Industry: Post-marketing Studies and Clinical Trials - Implementation of Section 505(o) of the Federal Food Drug and Cosmetic Act at 2-3 & nn.3-4* (July 2009).

⁴⁹ *Id.* 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.

⁵⁰ 21 C.F.R. §314.98.

⁵¹ 21 C.F.R. §314.40.

⁵² 21 C.F.R. §314.70(b).

⁵³ PAS provisions expressly "except[s]" labeling changes "described in paragraph §314.70 (c) (6) (iii), (d) (2) (ix), or §314.70(b) (2) (2) (v) (A).

formulation of the drug product, including effective ingredients” that were listed on the original labeling.⁵⁴

b. Mechanisms for Post-market Modifications: Changes Being Effected

The Changes Being Effected mechanism also allows brand name manufacturers to make post-market modifications to their products' labeling.⁵⁵ This provision gives brand name manufacturers the ability to delete from any label “false, misleading, or unsupported indications” about the drug's use or effectiveness.⁵⁶ Upon learning of a clinically significant hazard, a drug manufacturer can unilaterally “add or strengthen a contraindication, warning, precaution, or adverse reaction” without first obtaining FDA approval.⁵⁷ This safety valve mechanism enables drug manufacturers to immediately make post-approval label changes to inadequately products and inform doctors and patients about the new information.⁵⁸

c. Mechanisms for Post-market Modifications: “Dear Doctor” Letters

A third way branded manufacturers can provide updated warnings about their products is through direct mailing to health care providers, commonly referred to as “Dear Doctor” letters.⁵⁹ These letters constitute a regulated “labeling” under the statute, regulations, and case law.⁶⁰ Accordingly, they are subject to the same standards that govern all labeling, including the “misbranding” label provisions.

This framework provides a regulatory scheme for brand name manufacturers to fulfill their primary responsibility to ensure the adequacy of their products' labeling. Moreover, in *Levine*, the Supreme Court determined this framework's mechanisms were sufficient to allow claims against brand name manufacturers who, while complying with federal regulations, failed to simultaneously address more stringent state law labeling requirements.⁶¹

⁵⁴ §201.57 (c) (12) (I) (c).

⁵⁵ 21 C.F.R. § 314.70(c) (3); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.); 21 U.S.C. § 356 (a) (2006). This longstanding practice was codified in 2004, following the passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

⁵⁶ *Id.* at §314.70 (c) (6) (iii) (A), (C).

⁵⁷ 21 C.F.R. §§ 314.601, 814 (2008).

⁵⁸ The regulations do however, require the manufacturer to immediately inform the FDA of the change and file a Supplemental New Drug Application at least thirty days prior to distributing the drug with the labeling changes.

⁵⁹ 21 C.F.R. §200.5 (setting standards for such correspondence); 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); Center for Drug Evaluation & Research, Manual of Policies and Procedure [“MAPPS”] § 6020.10 (July 2, 2003) (establishing protocols for FDA review of such correspondence).

⁶⁰ 21 U.S.C. §321 (m) (labeling includes “all labels and other written, printed, graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” *See also Kordel v. United States*, 335 U.S. 345,350 (1948) (“one article worth it is accompanied by another supplement works plaintiff to physical attachment one to the other is necessary.”); 21 C.F.R. § 202.1(a) (1) (2).

⁶¹ *Levine*, 129 S.Ct 1204.

B. Generic Drug Approval and Labeling Process

1. Pre-approval

In 1984, Congress passed the Hatch-Waxman Act to aid generic drugs in coming to market as quickly as possible after the expiration of a brand name patent.⁶² The Act 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.⁶³ The Act permits ANDA applicants to rely on the FDA’s approval of the original drug so long as the generic manufacturer establishes that the generic drug: is (1) bioequivalent to its branded counterpart; (2) has the same route of administration, active ingredients, strength and dosage form as the listed drug,⁶⁴ and (3) has labeling that is the same as the labeling for the approved drug.⁶⁵ By requiring generic manufacturers only to prove bioequivalency and maintain the same label as its branded counterpart, Congress intended a relatively inexpensive and stream line approval process.⁶⁶ The resulting regulatory framework eliminated the need to conduct clinical trials because as Congress noted they would not only be “unnecessary and wasteful because the drug has already been determined to be safe and effective,” but would be “unethical because [trials] would require that some sick patients take placebos and be denied treatment known to be effective.”⁶⁷

The 1992 regulations implementing the Hatch-Waxman Amendments’ ANDA requirements reiterate that labeling proposed for the generic must be essentially “the same as”⁶⁸ the label of its branded counterpart.⁶⁹ This provision of the 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.⁷⁰ The FDA places “a very high priority [on] assuring consistency in labeling,” so as to “minimize any cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name products.”⁷¹

As part of the ANDA approval process, a generic manufacturer submits: the proposed labeling for its product;⁷² proof that the “conditions of use prescribed, recommended, or suggested” in the labeling of the generic drug have been previously approved for the brand name drug;⁷³ materials for a side-by-side comparison of the

⁶² The Hatch-Waxman Act (the Act), also known as the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c).

⁶³ 21 U.S.C. §355(j).

⁶⁴ 21 U.S.C. 355 (j)(2)(A)(ii)

⁶⁵ 21 C.F.R. §314.94 (a)(8)(2008); *See Zenecca, Inc. v. Shalala*, 213 F. 3d 161, 164 (4th Cir. 2000) (citing 21 U.S.C. § 355 (j)(4)(C), (D), (H)).

⁶⁶ Pub. L. No. 98-417, 98 Stat. 1585 (1984).

⁶⁷ H.R. Rep. No. 98-857(I) (“The purpose of the bill is to make available more low-cost generic drugs by establishing a generic drug approval process for pioneer drugs. . .”)

⁶⁸ The FDA has defined “same as” to mean “identical”. 21 C.F.R. §314.92(a) (1).

⁶⁹ 21 C.F.R §314.914 (A) (8) (IV) (2008).

⁷⁰ 54 Fed. Reg. 28,884 (1989) (The purpose of 21 U.S.C 355 (j) is to ensure the marketing of generic drugs that are safe and effective as their branded counterpart.)

⁷¹ Division of Generic Drugs, FDA Policy and Procedure Guide 37 (1989); 57 Fed. Reg. 17,961 (1992).

⁷² 21 C.F.R. §314.94(a)(8)(ii)

⁷³ 21 U.S.C. §355(j)(2)(A)(I)

proposed labeling to the brand name drug;⁷⁴ and a statement affirming that the generic labeling is the same as the labeling of the approved drug.⁷⁵ 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 its branded counterpart. The scope of the FDA's labeling review of the ANDA is solely on whether the generic drug's labeling "is the same as the labeling approved for the [brand name drug]."⁷⁶ In fact, the FDA rejects ANDA applications that contain new warnings or safety precautions not present on the brand name drug's label.⁷⁷

2. Post-approval

Once the ANDA is approved, the generic manufacturer's labeling responsibilities expand from merely demonstrating that its product label's is identical to its the listed drug. As noted earlier, FDA labeling regulations reflect the reality that drug labels are subject to change.⁷⁸ In some cases, it is only after wide distribution and prolonged use that certain risks manifest.⁷⁹ 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.⁸⁰ 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" and a "description of the actions that applicant has taken or intends to take as a result of this new information."⁸¹

All manufacturers have post-market 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.⁸² Nor do FDA regulations require generic manufacturers to perform the same post-marketing surveillance, review, and data collection activities as brand name manufacturers.⁸³ Brand name manufacturers are required to review and analyze *all* reported adverse events.⁸⁴ That analysis is conducted based on the knowledge they obtained through the detailed clinical trials they conducted 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 the Agency adverse event

⁷⁴ 21 C.F.R. §314.94 (a)(8)(iv)

⁷⁵ 21 C.F.R. § 314.94 (a) (8) (iii).

⁷⁶ 21 U.S.C. § 355 (j) (4) (G); 21 C.F.R. 314.105(c).

⁷⁷ Proposed Rule, Abbreviated New Drug Application Regulations, 54 Reg. 28,872, 28,884 (July 10, 1989).

⁷⁸ *Mensing*, 588 F.3d. at 606.

⁷⁹ *Id.*

⁸⁰ 21 U.S.C. §355(k).

⁸¹ 21 C.F.R. 314.80 (a) and (c) (NDA holders); 21 C.F.R. § 314.98 (a) (ANDA holders).

⁸² *See* 21 U.S.C. §355(j) (2) (A) ("The Secretary may not require that it abbreviated applications include information in addition to that required by clauses (i) through (viii)").

⁸³ *Compare* 21 C.F.R. § 314.80 (b) (post-marketing reporting obligations for NDA applicants) *with* 21 C.F.R. § 314.98 (post-marketing reporting obligations for ANDA applicants).

⁸⁴ 21 C.F.R. §314.80.

reports *they* receive.⁸⁵ 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 a 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.⁸⁶ Regulations governing brand name manufacturers, however, state that they “must” notify the FDA about a change in safety information.⁸⁷

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.⁸⁸ Failure to comply with these regulations could render the drug “misbranded” and in violation of the FDCA.⁸⁹ 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. This section requires generic manufacturers to comply with 21 C.F.R. §§ 314.70 and 314.71 which address “major changes” and “moderate changes.”

a. Mechanisms for Post-market Modifications: Prior Approval Supplement

Major changes comprise a large portion of labeling modifications.⁹⁰ 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.⁹¹ However, for generic manufacturers this prior approval supplement only allows generic manufacturers to use the PAS to revise their product to mirror major changes that their branded counterparts implement.⁹² The overarching uniformity requirements contained

⁸⁵ 21 C.F.R. §314.98(a) (requiring generic manufacturers only to “the requirements of §314.80 regarding the reporting and recordkeeping of adverse drug experiences, rather than the “review” “scientific literature” and “post-marketing studies” provisions of §314.80. Generic drug manufacturers receive far fewer of the reports than their branded counterparts and FDA. See FDA, Center for Drug Evaluation and Research, Office of Generic Drugs, Manual of Policies and Procedures, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports 1 (2005) available at <http://www.fda.gov/downloads/AboutFDA/CentersCDER/ManualofPoliciesProcedures/ucm079791.pdf> (highlighting the Office of Generic Drugs receives fewer AERs because the reports frequently do not identify a generic manufacturer for the drug and since the safety profile of a drug is well-known prior to the generic version is approved).

⁸⁶ Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 179613 (Apr. 28, 1992) (to be codified at 21 C.F.R. pts. 2,5, 10, 310, 314, 320 and 433).

⁸⁷ 21 C.F.R. §314.70 (a)(2009).

⁸⁸ See 21 C.F.R. § 201.57(e) (2004) (generic drugs prior to June 30, 2006); 21 C.F.R. §201.80 (e) (2008) (generic drugs after June 30, 2006), 21 C.F.R. §201.57 (c) (6) (i) (2008) (NDA drugs).

⁸⁹ A drug is considered misbranded when its labeling is false or misleading, or does not provide adequate instructions for use and adequate warnings. 21 U.S.C.A. 321(n), 331(a), (b) and (k), 352 (a), (f), (j) and (n).

⁹⁰ Revisions to 21 C.F.R. §314.70 Supplement and Other Approved Changes to an Approved Application: PhRMA Perspective, FDA Public Meeting (Feb. 7, 2007) available at www.fda.gov/ohrms/dockets/dockets/.../06n-0525-ts00009-LLucisano.ppt.

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

⁹² *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels – Proposed Rule*, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000).

in the regulations prohibit a generic manufacturer from initiating independent labeling changes.⁹³

Even if a generic manufacturer could propose a label change through the Prior Approval Supplement process, it is questionable if a generic manufacturer would be in the position to evaluate the available data to determine whether or what types of labeling change is potentially needed. As noted previously, brand name manufacturers' reporting requirements necessitate the collecting and analyzing of all adverse event information associated with their drug.⁹⁴ From that information and the background knowledge brand name manufacturers acquired through the clinical trials and NDA approval process, they have the ability to assess the reported adverse events and discern the need for and wording of a major labeling change.⁹⁵ The regulatory framework that governs generic manufacturers recognizes that they lack the research base of brand name manufacturers. Consequently, the generic manufacturers submit to the FDA only adverse event reports they receive directly.⁹⁶ Given this limitation, the quality of their reports and any resulting major change request could be compromised by the lack of clinical trial data.⁹⁷ The FDA's Deputy Commissioner echoed this concern when he stated, "if 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're concerned about the adequacy of the reports we would receive."⁹⁸

b. Mechanisms for Post-market Modifications: Changes Being Effectuated

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."⁹⁹ Such changes are brought to the FDA's attention through the CBE process.¹⁰⁰ The flashpoint in the preemption debate is whether this process is available to generic manufacturers. On one side of the debate are those who argue that when the FDA adopted the regulations implementing Hatch-Waxman, the Agency included a provision

⁹³ 21 CFR §314.94 *See also* Guidance for Industry, Providing Regulatory Submissions in Electronic Format ANDA's Center for Drug Evaluation and Research, June 2006, ("Electronic Format Guidance"), p.6 (applying to "electronic submission of abbreviated new drug applications (ANDAs) and supplements and amendments to those applications" and advising ANDA holders that "you must provide a statement that your proposed label and this the same as the labeling of the reference listed drug except for differences explained in the indicated comparison of labeling 21 CFR §314 .94 (a)(8)(iii)). " After an 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." 57 Fed. Reg. at 17955.

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

⁹⁵ 21 C.F.R. 314.510 (Post approval requirements of the FDA typically include additional clinical trials to support new indications or formulations of drug or to satisfy safety and efficacy concerns raised by the Agency.); FDA Center for Drug Evaluation and Research, Guidance for Industry: Post-marketing Studies and Trials – Implementation of Section 505(o) of the Federal Food Drug and Cosmetic Act 2-3 & nn.3 – 4 (2009).

⁹⁶ 21 C.F.R. §314.94.

⁹⁷ Statement of Mark Novitch, M.D. Deputy Commissioner, FDA. Pliva Reply Br. 2010 WL 1789712 *6 quoting App. . 120a.

⁹⁸ *Id.*

⁹⁹ 21 C.F.R. §314.70(c).

¹⁰⁰ *Id.*

that requires 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.”¹⁰¹ 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.¹⁰² On the other side of the debate, are those, including the FDA, Eighth Circuit, and the Solicitor General who conclude 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.¹⁰³ Those regulations include the rule that ANDAs will not be approved unless the generic drug’s proposed labeling is the “same as” the brand name drug;¹⁰⁴ and that approval will be withdrawn unless the generic labeling *stays* the “same as” its branded counterpart.¹⁰⁵ Accordingly, under this interpretation, generic manufacturers cannot use the CBE process to change unilaterally their product labeling from wording used by their branded counterpart.

The FDA has long stressed the uniformity of brand name and generic labeling.¹⁰⁶ In response to FDA proposed regulations implementing the labeling requirements of the Hatch-Waxman amendments, several comments addressed whether a generic manufacturer could include warnings or precautions in addition to those listed on the branded drug.¹⁰⁷ The Agency summarily rejected each suggestion.¹⁰⁸ One comment, specifically addressing the labeling requirements of 21 CFR §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 contrary indications, warnings, precautions, or adverse reactions and other safety related information.”¹⁰⁹ 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 an approval.”¹¹⁰

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.”¹¹¹ Again, the FDA rejected the proposed change and reiterated that section

¹⁰¹ See e.g., *Stacel v. Teva Pharms., USA*, 620 F. Supp. 2d 899 (N.D. Ill. 2009), *Kellogg v. Wyeth*, 612 F. Supp. 2d 421 (D. Vt. 2008), *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009).

¹⁰² *Id.*

¹⁰³ Brief for United States as Amicus Curarie, *Pliva v. Mensing, Actavis v. Mensing*, 595 F.3d 428 (5th Cir. 2009) Nos 09-993 and 09-1039.

¹⁰⁴ 21 C.F.R. 314.94(a)(8)(iii); see 21 U.S.C. 355(j)(4)(g); 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 the generic drug is “no longer consistent with that for the listed drug”).

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

¹⁰⁶ *Id.* 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 [suggesting that ANDA applicants be allowed to deviate from the labeling for the brand name drug] ***. [T]he ANDA product’s labeling must [be] the same as the listed product’s labeling because the listed drug is the basis for ANDA approval.”).

¹⁰⁷ 57 Fed. Reg. at 17,961.

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ Abbreviated New Drug Application Regulations - Final Rule 57 Fed. Reg. 17950, 17961 (April 28, 1992) (codified at 21 C.F.R. § 314).

¹¹¹ *Id.* at 17953.

505(j)(3)(G) of the Act requires the applicant's proposed labeling be the same as that of the reference listed drug" and "that exceptions in sections 505(j)(2)(A)(v) and (j)(3)(G) of the Act are limited."¹¹² Similarly, the Agency disagreed with a suggestion that the FDA 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 better directions regarding how the drugs should be taken."¹¹³ The FDA admonished that "labeling differences are not proper subjects for a suitability petition" and "reminded 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."¹¹⁴

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 the Agency ultimately controls the labeling of generic drugs.¹¹⁵ The Guide reiterates that generic manufacturers cannot unilaterally revise their product labels' warning but instead must await FDA instructions before making any changes.¹¹⁶ Part of the FDA's rationale for this approach could be grounded in the recognition of the fragmented nature of the generics market. There are multiple generic competitors, each possessing only a portion of the accumulated safety data for drug. As a result, the FDA reasoned that generic drug manufacturers making unilateral changes could be both impractical and counterproductive:¹¹⁷

Each 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 the accomplishment of the revision process is important to ensure that consistencies down the labeling of all similar drug products.¹¹⁸

¹¹² *Id.*

¹¹³ *Id.* at 17957.

¹¹⁴ *See* 21 U.S.C. 355 (j) (3) (G).

¹¹⁵ Center for Drug Evaluation and Research, Guidance for Industry: Changes to and Approved NDA or ANDA (Nov. 1999).

¹¹⁶ FDA, Division of Generic Drugs, Changes in the Labeling and ANDAs Subsequent to Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling, Policy and Procedures Guide No. 8-89(1989).

¹¹⁷ Generic manufacturers generally only possess data required by the 21 C.F.R. §314.98 (ANDA post-approval requirements).

¹¹⁸ *Id.* at 1

By limiting the ability of brand name manufacturers to implement unilaterally changes and by requiring generic manufacturers 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).¹¹⁹

In 2008, the FDA once again affirmed its position regarding the availability of the CBE process for generic manufacturers. Specifically, the Agency stated that CBE changes are not available for generic drugs approved under an ANDA.¹²⁰ To the contrary, the proposed rule indicated that generic manufacturers’ ability to change unilaterally a label is confined to reflect “differences in expiration date . . . or omission of an indication or other aspect of labeling protected by patent.”¹²¹

To the extent that generic manufacturers may use the CBE mechanism to propose or effectuate certain labeling changes, the FDA has consistently held that such actions may be taken only to “conform” their product labeling to that of their branded counterpart.¹²² In short, the FDA has always made clear that generic manufacturers may not use the CBE process to craft independently their own warning labels. “[T]he Agency wishes to remind ANDA applicants that . . . the labeling for an ANDA product must, with few exceptions, correspond to that of the reference listed drug.”¹²³

These regulations leave generic manufacturers in a precarious position on two fronts. As discussed in the next section, the majority of courts interpret the current regulatory framework as providing a sufficient basis to reject the preemption defense against state failure to warn claims. Accordingly, generic manufacturers must choose between compliance with FDA regulatory guidance or possible liability under state failure to warn laws. On the other front, as discussed in Section III, the confluence of federal regulations, state law, and the specter of liability have stymied generic manufacturer’s ability to make necessary label changes in a timely manner.

SECTION II – THE FEDERAL PREEMPTION DEBATE’S AFFECT ON THE GENERIC LABELING FRAMEWORK

¹¹⁹ FDA, Division of Generic Drugs, Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling, Policy and Procedure Guide No. 8-89 at 1(1989).

¹²⁰ *Id.*

¹²¹ 21 C.F.R. §314.94 (a) (8); *see also* 57 Fed. Reg. 17950, 17953, and 17961 at n.1; 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. 49603 (Aug. 22, 2008).

¹²² *Id.* at 5-6 (explaining that “[t]he sponsor of an ANDA is . . . responsible for ensuring that the labeling contained in its application is the same as the currently approved labeling of the [brand drug],” and instructing ANDA holders to “submit revised labeling” when changes [are] needed because of changes to their [branded] labeling”).

¹²³ *Id.* *see also* at 17961 (“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.”); Center for Drug Evaluation & Research [CDER] *Guidance for Industry: Changes to an Approved in NDA or ANDA* [“Changes Guidance” at 24 (Apr. 2004) (“All labeling changes for ANDA products must be consistent with section 505(j) the Act.”); CDER, *Guidance For Industry: Revising ANDA Labeling Following Revision of the RLD Labeling* [“Revisions Guidance”] at 5-6 (May 2000) (explaining that the sponsor of the ANDA is . . . responsible for ensuring that the labeling contained in its application is the same as the currently approved labeling of the [branded drug],” and instructing ANDA a holders to “submit revised labeling” when “changes [are] needed because of approved changes to the [branded] labeling.”).

The preemption debate serves as a lens to examine the inadequacies of the regulatory framework that prescribes generic manufacturer's labeling responsibilities. Until recently drug manufacturers had successfully argued that the federal regulatory framework rendered it "impossible" for them to make labeling changes prescribed by state law.¹²⁴ 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.¹²⁵ However, the Supreme Court decision in *Wyeth v. Levine* extinguished this defense for brand name manufacturers. In addition, the reverberations of *Levine* have forced courts to rule on whether the current regulatory labeling framework permits generic manufacturers to comply with state law failure to warn laws. Currently pending before the Supreme Court is a consolidated appeal from the Fifth and Eighth Circuits that raises this issue.

A. *A Word on Wyeth v. Levine's Effect on the Generic Manufacturers' Regulatory Framework*

The Supreme Court decision in *Levine* called into question the continued viability of generic manufacturers' preemption defense. *Levine*, however, does not involve, or even reference generic manufacturers, the Hatch-Waxman Act or ANDA pre- or post-labeling regulations. Nevertheless, it is impossible to discuss the adequacy and contours of the labeling regulatory framework that governs generic manufacturers without starting with *Levine*.

In 2001, Diane Levine sued Wyeth for injuries she suffered after receiving a direct intravenous injection of Wyeth's nausea medication, Phenergan.¹²⁶ 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.¹²⁷ *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 health care professionals of the risk that an improper IV push could cause injuries like those she suffered.¹²⁸ 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.¹²⁹

¹²⁴ The following cases found pre-emption: *Horne v. Novartis Pharmaceutical Corp.*, 541 F. Supp. 2d 768 (W.D.N.C. 2008); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (Pa. 2006), aff'd 521 F.3d 253 (3d Cir. 2008), vacated 129 U.S. 1578 (2009).

¹²⁵ *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*, 2006 WL 2374742, at *6-*9; *Conte v. Wyeth, Inc.*, No. CGC-04-437382, 2006 WL 2692469, at *4-*6 (Cal. Super. Sept. 14, 2006); *Goudine v. Crews*, No. CAL 05-00480, 2006 WL 5277412 (Md. Cir. June 28, 2006), aff'd, 955 A.2d 766 (Md. 2008).

¹²⁶ 129 S.Ct. 1187, 1191-92 (2009).

¹²⁷ *Id.*

¹²⁸ *Id.* at 1191-92.

¹²⁹ *Id.*

In March 2009, the Supreme Court held failure to warn claims are not preempted against brand name manufacturers.¹³⁰ 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 interfere 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").¹³¹

According to the *Levine* Court, the manufacturer, and not the FDA, bears responsibility for the content of its label at all times."¹³² This point is underscored by the Court noting that the FDA did not even possess the authority to require a drug manufacturer to alter its label until 2007.¹³³ Circuits increasingly rely on *Levine*'s reasoning to reinterpret the requirements of the regulatory framework governing generic manufacturers. For example, the Fifth, Eighth, and Ninth Circuits have elevated generic manufacturers' labeling responsibilities to that of their branded counterparts. Imposing this type of responsibility on generic manufacturers is suspect for three reasons. First, the Supreme Court explicitly references manufacturers' use of the CBE regulations as the mechanism to fulfill their drug warning responsibilities.¹³⁴ Yet as the FDA and Solicitor General in the pending consolidated appeal readily acknowledge, the CBE process is not available to generic manufacturers.¹³⁵ Second, the Supreme Court states that this content labeling responsibility is premised on the "many amendments to the FDCA and FDA regulations."¹³⁶ While this statement is supportable in the case of brand name manufacturers, *Levine* makes no specific mention of generic manufacturers, let alone the intent behind the FDCA and FDA amendments affecting them.

Third, the Ninth Circuit justifies its elevation of generic manufacturers' responsibilities by referencing the *Levine* conclusion that because manufacturers have "superior access to information about their drugs than the FDA, especially in the post-marketing phase as risks emerge," they "bear primary responsibility for their drug labeling at all times."¹³⁷ The Supreme Court advanced this rationale in its discussion on compatibility of state law as a "complementary form of drug regulation."¹³⁸ Namely, given budgetary and personnel constraints on the FDA's ability to analyze the 11,000 drugs on the market, the Supreme Court reasons that state law failure to warn claims offer an "additional and important layer of consumer protection."¹³⁹ This article does not take exception with this Supreme Court's conclusion. Where the problem lies, is in the various ways circuits contort the FDA's labeling framework to find that generic manufacturers

¹³⁰ *Id.* at 1190 (Justice Stevens wrote for the majority and was joined by Justices Breyer, Ginsburg, Kennedy and Souter). Justice Thomas concurred in judgment but wrote a separate opinion. Justices Alito and Scalia and Chief Justice Roberts dissented. *Id.* at 1204-1231.

¹³¹ *Id.* at 1193-94.

¹³² *Id.*

¹³³ *Id.*

¹³⁴ *Id.* 1197-98.

¹³⁵ Brief for United States as *Amicus Curiae*, *Pliva, Inc. v. Mensing*, at (insert page #)

¹³⁶ 129 S. Ct. 1198.

¹³⁷ *Id.* at 1202

¹³⁸ *Id.*

¹³⁹ *Id.*

have “superior access” to information than that possessed by the FDA and brand name manufacturers.¹⁴⁰

Unlike the brand name manufacturers and the FDA, generic manufacturers neither conduct, nor have direct access to the clinical trial data submitted during the drug’s NDA approval process.¹⁴¹ Similarly, they are not provided the results of post-approval studies that the FDA may request, or the full spectrum of adverse event reports that brand name manufacturers submit to the FDA.¹⁴² Nevertheless, in *Gaeta v. Perrigo Pharmaceuticals, Co.*, the Ninth Circuit relied in part on that *Levine* reasoning to reject the generic manufacturer’s preemption argument.¹⁴³ This illustrates how courts err in their attempts to fit the square peg of the *Levine* holding into the round hole of the generic manufacturers regulatory frame work.

B. The Courts of Appeals’ Application and Reliance on *Wyeth v. Levine*

In *Demahy v. Actavis*, the Fifth Circuit acknowledges that “*Levine* is not the case before us.”¹⁴⁴ Nevertheless, the court relies heavily on the decision which in its view “carries important implications” for the implied preemption defense of generic manufacturers.¹⁴⁵ Likewise, the Eighth Circuit maintains that *Levine* “carries important implications” for generic manufacturers.¹⁴⁶ Both courts of appeals, however, failed to appreciate critical distinctions between not only *Levine* and the pending appeal, but also between the statutory and regulatory frameworks governing brand name and generic drugs.¹⁴⁷

Levine did not include a federal statute requiring that pharmaceutical manufacturers use labeling that was “the same as” the “labeling approved for” the bioequivalent drug by FDA.¹⁴⁸ It is this federal law mandate, absent in *Levine* that is the crux of generic manufacturers’ preemption argument. As confirmed in the Solicitor General’s invited brief, the regulatory requirements imposed on generic manufacturers are different from those at issue in *Levine*.¹⁴⁹ As the regulatory framework establishes, and the government confirms, a generic manufacturer may not use the CBE regulation to change its product’s labeling.¹⁵⁰ Yet it was precisely this capability – which generic

¹⁴⁰ See discussion *infra* Section II C and D.

¹⁴¹ Br. for Morton Grove Pharmaceuticals, as Amici Curiae in Support of Petitioners Pliva, Inc., v. Mensing, Nos. 09-993, 09-1039, 09-1501, 2011 WL 343070 (Jan. 31, 2011) *29-30. See also 21 C.F.R. § 314 (g) (ii). FDA’s safety and effectiveness findings are contained in the “Summary Basis of Approval that the Agency prepares and makes publically 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.

¹⁴² *Id.*

¹⁴³ *Gaeta v. Perrigo Pharm. Co.*, No 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011).

¹⁴⁴ *Demahy*, 595 F.3d at 433.

¹⁴⁵ *Id.*; see also *id.* at 434-35, 446, 449.

¹⁴⁶ *Mensing*, 588 F.3d at 607.

¹⁴⁷ The Ninth Circuit in *Gaeta v. Perrigo Pharmaceuticals, Co.*, also notes its reliance on *Levine*.

¹⁴⁸ 21 U.S.C. §355(j)(2)(A)(v),4(G).

¹⁴⁹ Brief for United States as *Amicus Curarie, Pliva, Inc. v. Mensing*, Nos 09-993 and 09-1039 at 11.

¹⁵⁰ *Id.*

manufacturers lack – that served as the basis for rejecting brand name manufacturers' argument for impossibility preemption in *Levine*.¹⁵¹

The courts continue their misunderstanding of the applicability of *Levine* with respect to the manufacturers' obstacle preemption arguments. *Levine* did not involve the Hatch-Waxman Act. Accordingly, it did not in any way implicate congressional purposes underlying that statute. It is these purposes that form the core of generic manufacturers' preemption arguments.¹⁵² The maintenance of the failure to warn claims in *Levine* in no way affected Congress' objective of ensuring the uniformity of approved brand name and generic drug labeling.¹⁵³ Nor did it undermine Congress' objective of reducing the cost of generic drugs for consumers¹⁵⁴ or implicate the FDA's regulatory aims designed to carry out these congressional objectives.¹⁵⁵

Finally, an argument could be made that *Levine*'s articulated responsibility that federal law charges manufacturers (thus implicitly generic manufacturers) with "primary responsibility for their drug labeling" is inapplicable.¹⁵⁶ Instead an argument could be made that federal law, (through the statute itself, FDA's duly promulgated regulations, and the Agency's repeated legal directives to applicants) charges generic manufacturers with the entirely different task of merely ensuring that their drug product labeling is "the same as" the latest FDA approved labeling fixed to the generic products brand name equivalent.¹⁵⁷ Notwithstanding the possible appeal of this argument, this article advances another approach. Given the Supreme Court's pronouncement, the charge is now one to reform the regulatory framework so that generic manufacturers possess the mechanisms to fully share in the responsibility of ensuring that their products are accurately labeled.

C. Mensing v. Wyeth- Eight Circuit Rejects Preemption Defense based on a "Steps Could have Taken" rationale

Mensing sued generic manufacturer Wyeth alleging that its metoclopramide warnings in-adequately disclosed the long term risk of tardive dyskinesia and asserted state law obligations to provide different warnings to avoid liability.¹⁵⁸ On appeal the Eighth Circuit acknowledged that "generic labels must be substantively identical to the name brand label even after they enter the market."¹⁵⁹ Nevertheless, the court rejected Wyeth's preemption defense by concluding that federal law at least would have allowed them to "propose a label change that the FDA could . . . enforce uniformly on all metoclopramide manufacturers if approved."¹⁶⁰

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 that it

¹⁵¹ 129 S.Ct. at 1204

¹⁵² See generally, *Mensing*, 588 F. 3d 603; *Demahy*, 595 F.3d 428.

¹⁵³ 21 U.S.C. §355 (j)(2)(A)(v)

¹⁵⁴ H.R. REP. No. 98-857(1), at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647.

¹⁵⁵ *Id.*

¹⁵⁶ *Wyeth*, 129 S. Ct. 1202.

¹⁵⁷ 21 U.S. C. §355(j) (2) (A) (v); 21 C.F.R. § 314.94 (a) (S) (iv); 73 Fed. Reg. at 49, 603-04.

¹⁵⁸ *Mensing*, 588 F.3d at 605.

¹⁵⁹ *Id.* at 608.

¹⁶⁰ *Id.* at 603.

may be marketing an unsafe drug.”¹⁶¹ 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.¹⁶² According to the court generic manufacturers are not permitted to “passively accept the inadequacy of their drug's label as they market and profit from it.”¹⁶³ In the court’s view, generic manufacturers can comply with this mandate through the PAS process. To justify this interpretation of the regulatory framework the court engages in a sleight of hand type of analysis. The court points out that the PAS process allows manufacturers to make major changes.¹⁶⁴ The court also acknowledges, however, that such changes are subject to “a few exceptions including permissible use of the CBE process for learning enhancements.”¹⁶⁵ The court attempts to minimize this restriction by noting that the PAS provisions state that permissible changes, “include but are not limited to” the ones described in the rule.¹⁶⁶ Thus the court concludes that the federal framework does not “specifically prevent generic manufacturers from proposing changes to a label’s warning through” a PAS.¹⁶⁷

The Eighth Circuit made short work of Wyeth’s impossibility defense based on FDA regulations that prohibit generic manufacturers from using the CBE process to make a unilateral change to their product.¹⁶⁸ Specifically, Wyeth argued that federal regulations requiring generic manufacturers to maintain warning labels identical to their branded counterparts prohibit them from altering their labels to comply with stronger state law requirements.¹⁶⁹ Rather than substantively addressing Wyeth’s CBE argument, the court rendered their defense moot by holding that:

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.¹⁷⁰

This approach is insufficient because a “proposal” that a generic manufacturer forwards the FDA, does not make the labeling any more adequate under state law. Only a *change* in the labeling would satisfy the state law.¹⁷¹ More importantly, only a *change* in the inadequate labeling could potentially protect consumers from harm.

The district court determined that generic manufacturers “may seek to add safety information to the drug label” by requesting that the FDA send “Dear Health Care

¹⁶¹ *Id.* at 609.

¹⁶² *Id.* at 608.

¹⁶³ *Id.* at 609.

¹⁶⁴ *Id.*

¹⁶⁵ *Id.* at 610 *citing* 21 C.F.R. §314.70(b)(2)(v)(A)

¹⁶⁶ *Id.*

¹⁶⁷ *Id.*

¹⁶⁸ *Id.* at 608.

¹⁶⁹ *Id.*

¹⁷⁰ *Id.*

¹⁷¹

Professional” letters.¹⁷² The Eighth Circuit acknowledges that “Congress did not intend the generic manufacturer to send out ‘Dear Healthcare Provider’ letters [unilaterally].”¹⁷³ Nevertheless, the court surmised that the generic manufacturer “could have suggested that the FDA send out [such] a warning letter”¹⁷⁴ However, as pointed out by the Solicitor General, the Eighth Circuit “misunderstood the status of DHCP letters.”¹⁷⁵ Generic manufacturers “do not customarily send” Dear Doctor letters “without coordinating with [the] FDA”.¹⁷⁶ Moreover, if a generic manufacturer sent out a letter warning about “risks seemingly unique to its product” the letter “would likely be misleading” because it could “mislead consumers and providers into believing that the generic drug” and branded drug lack “therapeutic equivalence.”¹⁷⁷

To the extent that generic manufacturers still insist on asserting the impossibility of complying with state and federal regulations, the Eighth Circuit offers the following solution: 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.¹⁷⁸

Rather than provide generic manufacturers an intelligent interpretive framework from which to meet the responsibilities of ensuring a safe product, the court instead opted to turn the goal of the Hatch-Waxman Amendments on its head and essentially force generic drug manufacturers out of business.

The court next considered Wyeth’s obstacle defense. Namely, the court addressed whether state failure to warn claims were preempted because they “obstruct the purposes and objectives of federal law.”¹⁷⁹ In support of this defense, Wyeth claimed that the Hatch-Waxman Amendments, rather than the whole FDCA, provided the relevant statutory scheme and that “proposing a label change would necessitate expensive clinical studies, thwarting the goals of the Hatch-Waxman Amendments to bring low-cost generic drugs to market quickly.”¹⁸⁰ In response, the court noted that the level of scientific proof required to support a proposed label change does not require a generic manufacturer to conduct new tests.¹⁸¹ The court observed that multiple reports of adverse drug experiences might be sufficient to justify a manufacturer’s request for a labeling change.¹⁸²

¹⁷² *Id.* at 610.

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 611.

¹⁷⁵ Brief for United States as *Amicus Curiae*, *Pliva, Inc. v. Mensing*, Nos 09-993 and 09-1039 at 17-18

¹⁷⁶ *Id.*

¹⁷⁷ *Id.* (explaining that sending the “Dear Doctor” letter sought by Mensing “could have resulted in misbranding branding the drug in violation of federal law.”).

¹⁷⁸ *Id.* at 611.

¹⁷⁹ *Id.*

¹⁸⁰ *Id.*

¹⁸¹ *Id.* at 611.

¹⁸² *Id.* at 612.

The most noteworthy aspect of the decision is the question left half answered regarding generic manufacturers' post-labeling responsibilities. Specifically, does the federal regulatory framework requiring generic manufacturers to maintain "the same labeling" as their branded counterparts prevent them from fulfilling state law duties to maintain "adequate" labeling warnings and directions?¹⁸³ The Eighth Circuit chose to ignore the first part of this question. Rather it concluded that the Supreme Court's application of conflict preemption in *Levine* does not require courts to determine what duty federal law imposes on generic manufacturers. The only part of the question the court addressed was "Does federal law forbid generic manufacturers from taking steps to warn their customers?" In response, the court concluded that absent a specific federal prohibition, there can be no preemption.¹⁸⁴

D. Demahy v. Actavis – Fifth Circuit Rejects Preemption Defense based on a "No Explicit Prohibition" rationale

In *Demahy*, taking its cue from *Mensing*, the Fifth Circuit similarly extended to generic drug manufacturers the Supreme Court's ruling that state law failure-to-warn claims are not generally preempted by federal laws.¹⁸⁵ In facts similar to *Mensing*, the plaintiff was diagnosed with tardive dyskinesia after taking the manufacturer's generic metoclopramide for several years to treat her acid reflux.¹⁸⁶ In the wake of *Levine*, the generic manufacturer premised its opening argument on the inapplicability of the Supreme Court holding.¹⁸⁷ Specifically, Actavis tried to distinguish *Levine* by claiming that generic manufacturers, unlike brand name manufacturers, were prohibited from using the CBE regulations to change unilaterally the labeling of their products.¹⁸⁸ The court acknowledged that *Levine*'s preemption holding relied in part on the availability of the CBE process to brand name manufacturers.¹⁸⁹ Nevertheless, the court reasoned that despite some differences, *Levine* still had some bearing on the case at hand.¹⁹⁰

It was against this backdrop that the court considered the generic manufacturers' impossibility argument. Actavis contended that because federal law requires generic manufacturers' labeling to be the "same as" their branded counterparts, that generic manufacturers may not update their labels independently.¹⁹¹ The Fifth Circuit disagreed. Instead, the court noted that while the Hatch-Waxman Amendments require a generic drug's label to conform *initially* to the brand name drug's label in order to receive FDA approval, federal law does not bar the generic manufacturer from subsequently changing the label after approval.¹⁹² The court based this conclusion on its interpretation of alleged regulatory silence "as to the manufacturer's obligations after the ANDA is granted."¹⁹³

¹⁸³ *Id.* at 605.

¹⁸⁴ *Id.* at 609-10.

¹⁸⁵ *Demahy*, 595 F.3d 449.

¹⁸⁶ *Id.* at 430.

¹⁸⁷ *Id.* at 433.

¹⁸⁸ *Id.*

¹⁸⁹ *Id.* at 430.

¹⁹⁰ *Id.*

¹⁹¹ *Id.* at 433.

¹⁹² *Id.* at 437.

¹⁹³ *Id.* at 436.

In the absence of specific restrictions or requirements for generic manufacturers, the court took the view that mechanisms contained in the regulations regarding the ability to make major and moderate changes apply to all manufacturers.¹⁹⁴

The Fifth Circuit relies on its interpretation of the regulatory term “abbreviated application” as support for the conclusion that generic manufacturers may use the CBE process to make moderate changes to their labels. The court determined this term included only the document generic companies relied on to obtain an initial approval.¹⁹⁵ As such, after initial approval, the generic manufacturer is no longer required to maintain labeling that is identical to that of its branded counterpart.¹⁹⁶ Such an interpretation however, directly conflicts with FDA regulations. Specifically, in regulations not cited by the *Demahy* court, the Agency defined the term “abbreviated application” as “the application described under [21 C.F.R.] §314.94, which “includes all amendments and supplements.”¹⁹⁷ Accordingly, the “same as requirement” persists throughout the life of the generic product. The FDA has consistently maintained throughout its regulations that the requirement that ANDA holders are required to supplement a previously approved ANDA must be read in conjunction with the requirement that warning labels for generic drugs must be the same as their branded counterpart.¹⁹⁸ Not only does the plain language of §314.94 contradict the Fifth Circuit’s interpretation; it also seemingly fails a common sense analysis. FDA regulations allow for revocation of a prior approval if the generic manufacturers’ “labeling . . . is no longer consistent with that of the listed drug.”¹⁹⁹ This provision is only triggered after the initial Agency approval; there is no approval to revoke until one has been granted.

The court was not persuaded by Actavis’ argument that inherent deficiencies in the regulatory framework made meeting federal and state labeling requirements impossible. 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 if the Agency found “a lack of 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 the labeling.”²⁰⁰ 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.²⁰¹ Again relying on *Levine*, the Fifth Circuit responded it would be “difficult to accept” that the FDA would take punitive action against a manufacturer for strengthening a warning.²⁰² 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.²⁰³ 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

¹⁹⁴ *Id.*

¹⁹⁵ *Id.*

¹⁹⁶ *Id.*

¹⁹⁷ 21 C.F.R. §34.94 (emphasis added).

¹⁹⁸ *Id.* at §314.94(a)(8)(iv).

¹⁹⁹ *Id.* at §314.150(b)(10).

²⁰⁰ *Demahy*, 595F.3d at 438.

²⁰¹ *Id.*

²⁰² *Id.* at 439 quoting *Levine*, 129 S.Ct. at 1197.

²⁰³ *Id.*

warning health care providers directly.²⁰⁴ Relying on its statutory silence line of reasoning, the Fifth Circuit then went on to identify the CBE, Dear Doctor letters and PAS as mechanisms available to Actavis to fulfill its labeling obligations.

Specifically the court considered and rejected Actavis' argument that FDA commentary and amicus briefs support its argument that a generic manufacturer cannot use the CBE process.²⁰⁵ After a detailed review of FDA statements and regulations, the court concluded that the Agency does not expressly prohibit generic manufacturers from using the CBE process.²⁰⁶ 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."²⁰⁷ Next the court found that the PAS allows generic manufacturers "to propose any and all labeling changes – no matter the significance."²⁰⁸ Lastly, the court references the availability of "Dear Doctor" letters.²⁰⁹ These communications allow manufacturers to warn healthcare professionals about newly discovered risks.²¹⁰ The court conceded that while these letters require pre-approval by the FDA, nothing in the regulations prohibits generic manufacturers from at least proposing that the Agency send them out on their behalf.²¹¹

The *Demahy* court also asserted that the regulatory framework requires all drug manufacturers adhere to the requirement that their labeling be revised as soon "as there is reasonable evidence of an association of a serious hazard with a drug."²¹² Again the court identified the CBE process as an available mechanism for generic manufacturers to fulfill that alleged requirement.²¹³ 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 counterpart.²¹⁴ As *Levine* 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" by declaring that the brand name manufacturer must "revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with the drug.'"²¹⁵ The rationale for this requirement is the fact that brand name companies conduct the original clinical studies, form post-market studies, and are subject to extensive post-approval surveillance obligations.²¹⁶ As such, they are able to place information they acquire in context, review and analyze its significance, and craft the suitable labeling change based on "sufficient evidence of the standards [for which

²⁰⁴ *Id.* at 439,444,

²⁰⁵ *Id.* at 440.

²⁰⁶ *Id.* at 442.

²⁰⁷ *Id.* at 444.

²⁰⁸ *Id.*

²⁰⁹ *Id.*

²¹⁰ *Id.*

²¹¹ *Id.* at 445.

²¹² *Id.* at 437.

²¹³ *Id.* at 440.

²¹⁴ 21 C.F.R. §201.80(e).

²¹⁵ *Levine*, 129 S.Ct. at 1198 (quoting 21 C.F.R. § 208.80(e)).

²¹⁶ 21 C.F.R. § 314.80 (b) (post-marketing reporting obligations for NDA applicants).

changes] are met.”²¹⁷ By contrast, generic manufacturers lack the comprehensive data possessed by brand name manufacturers and lack the context to properly assess the limited post-approval information they have received.²¹⁸ In recognition of this, the FDA interprets 21 C.F.R. §201.80(e) as requiring generic manufacturers to conform their labeling to that of the brand name manufacturer in a timely manner.

It is worth contemplating drug warnings if the *Demahy* reasoning was universally followed and generic manufacturers were permitted to unilaterally deviate from their branded counterparts after approval. The result would produce a patchwork of distinct safety warnings for drugs that have the same safety profile. In theory, patients taking the same drug could receive different warnings if their prescribing health care professional relied on package inserts from different manufacturers. In addition, a single patient could receive different warnings if she switched physicians, or the same physician switched generic manufacturers in refilling a prior prescription. Taken to its logical conclusion, the Fifth Circuit embraces a framework that allows every generic version of a brand drug to bare its own unique warning. The practical effect being that essentially dozens of products with the *same safety profile* and will offer users a patchwork of *different* safety warnings. It is hard to reconcile that regulatory framework approach with the basic premise that underlines the FDA statute: as the FDA long ago recognized, only “consistent labeling will assure physicians, health professionals, and consumers the generic drug is as safe and effective as its branded counterpart.”²¹⁹

III. THE NEED FOR A NEW FRAMEWORK

A. *Putting the Need in its Proper Context*

To date, the legal wrangling over the availability of the preemption defense has been at the forefront of disputes with regard to generic manufacturers' labeling regulations. Despite its prominence, however, preemption is only one piece of the challenge involved in interpreting the regulations that define generic manufacturer's labeling responsibilities.

Since passage of the Hatch-Waxman Act, the impact of generic competition on overall drug prices has been dramatic. The Congressional Budget Office (“CBO”) reported that generic drug use in 2007 saved senior citizens and the federal government \$33 billion just on Medicare Part D prescriptions.²²⁰ Another recent study reported that dispensing generic versions of brand name drugs saved the American health care system more than \$829 billion over the past decade (2000-2009) and 139.6 billion in 2009

²¹⁷ Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, Medical Devices – Final Rule, 73 Fed. Reg. 49603, 49605 (Aug. 22, 2008).

²¹⁸ See e.g., 73 Fed. Reg. at 49604 (“[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.”); see also *Levine* 129 S.Ct at 1197 (noting that “risk information accumulates over time” and suggesting that “subsequent developments” might have meaning only in light of “reports previously submitted to FDA”) (quoting 73 Fed. Reg. at 49607).

²¹⁹ 57 Fed. Reg. at 1791; 21 U.S.C. § 355(j)(2)(A)(v)).

²²⁰ Congressional Budget Office, Effects of Using Generic Drugs on Medicare's Prescription Drug Spending 7-8 (2010). <http://www.cbo.gov/ftpdoc/6xx/doc655/pharm.pdf> (hereinafter CBO 2010).

alone.²²¹ Today, the average generic drug costs barely a quarter of its branded counterpart.²²² A 2009 IMS National Prescription Audit illustrates this saving by comparing the typical insurance or government formulary charges: \$6 for generic medications; \$29 for preferred brand name drugs and \$40 for non-preferred brand name drugs.²²³ The natural effect of the affordability of generic drug alternatives is a dramatic increase in their use. As the CBO noted in a 1998 study:

The Hatch-Waxman Act has increased the likelihood that generic copies will become available once the patent on a brand name drug expires. Before the Act (in 1983), only 35% of the top selling drugs no longer under patent had generic copies available. Today, nearly all do.²²⁴

All of this is to say that the ever-increasing foothold of generic drugs in the U.S. healthcare system requires us to reorient our focus. Bickering as to whether regulations permit generic manufacturers to escape liability for failure warn to claims is not the true issue. The truly pressing concern is how to fashion regulations so as to ensure generic manufacturers can strengthen their labels and prevent foreseeable harms from occurring.

B. The 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 post-marketing studies, and adhere to extensive post-approval surveillance requirements.²²⁵ Complying with these duties affords the brand name manufacturer access to the following: (1) virtually all clinical data on the branded as well as the generic version of its drug; (2) all world literature regarding the product; (3) and years of adverse reports from all sources since the drug's approval.²²⁶

By design, the FDA deters generic manufacturers' access to much of the comprehensive data that is readily available to brand name manufacturers.²²⁷ This exclusion begins during the initial ANDA submission to the FDA and persists through

²²¹ Generic Pharmaceuticals 2000-2009 1-2 (2010) available at http://www.gphaonline.org/sites/default/files/GPhaSavingsStudyBookUpdatedWebFINALJul2310_0.pdf.

²²² CBO 2010 at 8-9.

²²³ Aitken et al., Prescription Spending Trends in the United States: Looking Beyond the Turning Point, 28 Health Affairs, no.1, w151, w155(2009).

²²⁴ Congressional Budget Office, How Increased Competition From Generic Drugs Has Affected Prices and Return in the Pharmaceutical Industry at xii(1998) available at <http://www.cbo.gov/ftpdoc/6xx/doc655/pharm.pdf>

²²⁵ See brand name drug approval process discussed in Section I-A *supra*.

²²⁶ *Id.*

²²⁷ See generic drug pre and post approval processes discussed in Section I-B *supra*.

the post-surveillance requirements.²²⁸ 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, they are forced to rely on publically available literature and the FDA's prior findings of safety and effectiveness of an approved medication.²²⁹ Prior to submitting the NDA for Agency approval, the FDA's Center for Drug Evaluation and Research offers a consulting program to foster early communications between the manufacturer and the Agency. Through that program, brand name manufacturers receive guidance on the data necessary for submission as well as the regulatory requirements for demonstrating safety and efficacy.²³⁰ 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 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.²³¹

Once introduced into the market, the FDA cannot implement subsequent labeling revisions without first negotiating these changes with the brand drug manufacturer.²³² Generic manufacturers are not included in these negotiations. The data and knowledge exchanged during these negotiations are all beyond the reach of the generic manufacturer. In fact, the Agency notifies the generic manufacturer of FDA proposed changes only if the brand manufacturer is no longer marketing the product.²³³ Similarly, generic manufacturers cannot access the results of Phase IV clinical trials that brand name manufacturers conduct at the FDA's request.²³⁴ Perhaps it is in light of this systematized restriction from data, that the FDA limited the responsibility of generic manufacturers to ensuring that their product was the same as its branded counterpart. 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 post-market 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

²²⁸ Jane A. Fisher, *Disclosure of Safety and Effectiveness Data under the Drug Price Competition and Patent Term Restoration Act*, 41 Food, Drug Com. L.J. 268, 270 (1986) (setting down the historical basis of FDA's interpretation and implementation of the trade secrets doctrine to data) ("Since 1938, FDA has consistently interpreted section 301(j) of the FDCA as encompassing animal and human test data in an NDA, in spite of the law's literal limitation to 'methods and processes.'").

²²⁹ Some innovator manufacturers have filed citizen petitions against the use of the FDA's prior findings. These FDA findings often are based on findings 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 if that information can extend passed published literature. Some pharmaceutical manufacturers have argued that the intent of section 505(b) (2) was to allow referencing only of portions of an NDA application available in the published literature, not p r i e t a n y portions of data. The FDA has upheld its position that section 505(b)(2) permits reliance on previous FDA findings of safety and efficacy.

²³⁰ Brief for Amicus Curia the United States of America at 4-5, *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (No. 05 CV 05500-MMB).

²³¹ *Id.*

²³² FDAAA, tit. X Sec. 901(a) §505(o)(4)(c), 121 Stat. at 925.

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

²³⁴ *Id.*

that it receives directly.²³⁵ 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 FDA directly.²³⁶ In fact, adverse reports often fail to specify generic manufacturers of the products entirely.²³⁷ 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.²³⁸ It is ultimately up to the FDA to determine what and how information will be displayed to the public.²³⁹

To that end, the FDA requests that manufacturers not submit adverse reports unless specific criteria can be met: (1) an identifiable patient and reporter; (2) a suspect drug; and (3) an adverse event.²⁴⁰ The FDA is of the opinion that ‘reports without such information make the interpretation of their significance difficult, at best, and impossible, in most instances.’²⁴¹ The Agency has even 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 the nonserious and labeled.”²⁴² 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.²⁴³

In 2007, Congress passed the FDAAA, which strengthened the FDA’s authority to compel labeling changes and identify post-market risks.²⁴⁴ Specifically, 21 U.S.C. §355(o) (4) authorizes the FDA to require manufacturers to make certain labeling changes. Yet, as illustrated by the FDA in *Mensing*, some generic manufacturers are excluded from receiving Agency warning revisions.²⁴⁵ Specifically, the FDA did not send letters to all metoclopramide manufacturers. Only brand name manufacturers and generic manufacturers who relied on a brand name product that was on the market were contacted by the FDA.²⁴⁶

The data vacuum that the framework creates has taken on added significance for generic manufacturers in the post-*Levine* world. Various courts assert that generic

²³⁵ 21 C.F.R. §314.98.

²³⁶ MAPP §5240.8 (Nov. 1, 2005) (“OGD [FDA’s Office of Generic Drugs] receives few AERS [adverse event reports] or similar reports since the reports may not specify a generic manufacturer for the drug product”).

²³⁷ *Id.*

²³⁸ 21 C.F.R. 314.80(b).

²³⁹

²⁴⁰ Disclosure reg

²⁴¹ Adverse Drug Reaction Reporting Regulations Working Group, Center for Drug Evaluation & Research, Guidance for Industry, Post-marketing Adverse Experience Reporting for Human Drug & Licensed Biological Products: Clarification of What to Report 1-2 (Aug. 1992) available at

²⁴² *Id.*

²⁴³ 73 Fed. Reg. at 49604 (“[T]he causal relationship between product and adverse event is often difficult to establish and may require large trials, often specifically designed to assess the risk.”); 73 Fed. Reg at 49607 (“risk information accumulates over time” and reasoning that “subsequent developments” may only be relevant in light of “reports previously submitted to FDA”).

²⁴⁴ The Food And Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823

²⁴⁵ 21 U.S.C. §355(o)(4).

²⁴⁶ Petitioner Br. Pliva No. 09-993 2010 WL1626450*18.

manufacturers can support labeling changes simply by relying on medical literature alone.²⁴⁷ In particular, the Eighth Circuit relies on the fact that the FDA only identified three pieces of literature in its letter compelling a change to metoclopramide labeling.²⁴⁸ What the Eighth Circuit overlooked is that the FDA evaluated those three pieces of literature against the background contained in the original clinical data, all the world literature regarding the drug, and 29 years of data from adverse reports submitted by all brand name and generic manufacturers of the drug since it was approved.²⁴⁹ In short, the Agency relied on nearly three decades of information, only a small portion of which was publicly available.²⁵⁰

As interpreted by the Eighth Circuit, the regulatory framework places generic manufacturers in the untenable position of having to amass a knowledge base equal to that of the FDA and the branded manufacturer as soon as their drugs are marketed. Essentially, the day after the generic manufacturer's application is approved, it becomes responsible under state law for information Congress exempted it from acquiring the day before.²⁵¹ On that day, and throughout the generic drug's life cycle it is difficult to see how generic manufacturers, in comparison to the FDA and brand name manufacturers, possess the "superior access" to knowledge that undergirds the *Levine* Court's conclusion that manufacturers bear the primary responsibility for ensuring adequacy of their labeling at all times.²⁵² At the time of approval, generic manufacturers possess only the data from the bioequivalence studies they must conduct to obtain approval for their ANDA.²⁵³ To procure the scientific substantiation to support changes in the risk benefit analysis reflected in the drugs' labeling requires the generic manufacturers to either generate or have access to the scientific data necessary to construct their labels. The time and expense necessary to generate such data effectively negates the Hatch-Waxman Amendments of their overriding purpose of providing Americans consumers and state and federal governments with low-cost generic drugs. Consequently, other options must be made available.²⁵⁴

2. Lack of Appropriate Mechanisms for Generic Manufacturers to Change their Drug's Label

Another problem posed by the current regulatory framework is the difficulty regarding which mechanisms are available for generic manufacturers. Here generic manufacturers' good intentions of ensuring the adequacy of their labeling arguably could be stymied by conflicting federal and state law demands. This Article takes the position that the FDA's regulatory framework does not permit generic manufacturers to make unilateral changes through the CBE process or implement any changes that would take a

²⁴⁷ *Mensing*, 588 F.3d at 611; *Demahy* 595 F. 3d at t443.

²⁴⁸ *Mensing*, 588 F.3d at 611.

²⁴⁹ *Pliva, Inc.*, Petition for Certiorari., No. 09-993, 2010 WL 638478*21

²⁵⁰ *Id.*

²⁵¹ 21 U.S.C. §§355(j) (Generic companies are only required to establish that the drug is bioequivalent to its branded counterpart.)

²⁵² *Levine*, 129 S.Ct. at 1202.

²⁵³ 21 U.S.C. §355(j)(2)(A); 21 C.F.R. §314.94(a).

²⁵⁴ New Drug Application: Hearings on H.R. 3605 Before the Subcomm. On the Health and the Environment of the House Comm. on Energy and Commerce, 98th Cong. 1st Sess. (1983).

label out of strict uniformity with its brand name counterpart.²⁵⁵ That overarching uniformity requirement similarly precludes generic manufacturers from sending out Dear Doctor letters or using the PAS mechanisms. Whether one adopts the opinions expressed in this Article or not, differing minds can still agree that without full access to these mechanisms, generic manufacturers cannot meet their elevated labeling responsibilities.

As illustrated in the consolidated Fifth and Eighth Circuit pending appeal, courts recognize the necessity of label changing tools. In fact, courts have gone so far as to test the bounds of logic in their attempts to make them, at least in theory, available. An illustration of this is apparent in the “step could have taken” line of reasoning the Fifth and Eighth Circuits relied on in the pending appeal. In determining the availability of Dear Doctor letters the courts concede that federal law does not allow generic manufacturers to send such correspondence because it would effectively alter the warnings on their generic labels.²⁵⁶ Yet, both courts held that generic manufacturers at least “could have suggested” that the FDA send Dear Doctor letters. Similarly, the courts held that generic manufacturers could have at least requested the FDA change the labeling for branded and generic drugs through the PAS even if they could not implement such a change themselves.²⁵⁷

The difficulty with the “steps could have taken” rationale is multifold. First, the Supreme Court long ago recognized that federal law preempts state law claims that depend on speculation about how a federal agency would exercise its power in hypothetical regulatory proceedings.²⁵⁸ Preemption is predicated on the fact that such claims necessarily impinge on an agency's authority.²⁵⁹ In the generic drug context, there is a critical gap in a failure to warn claim alleging that the generic manufacturers should have “taken steps” to alter their product warnings. Simply “suggesting” that the FDA consider a warning change that might apply to both brand name and generic products would not itself satisfy the state law duty to provide adequate warning. There is no way to determine whether the suggestion would have been accepted by the FDA, and even if approved, whether the modified warning would have reached the consumer before he or she was prescribed the medication.²⁶⁰

Another problem is that federal law explicitly prohibits generic manufacturers from modifying their warnings without prior FDA approval (regardless of whether the change is through the PAS procedure or otherwise). For state law claims predicated on the “taking steps rationale,” courts must therefore presume that the FDA would approve the proposed new warnings. Yet such an assumption requires a court to usurp a prerogative that belongs solely to the FDA.²⁶¹

²⁵⁵ See discussion Section II *infra*.

²⁵⁶ See discussion Section II C and D *infra*.

²⁵⁷ *Id.* While both courts identified steps of federal law would've allowed petitioner's to take, neither court cited authority for the proposition that state law would have found such steps to patient the film the duty to provide warnings.

²⁵⁸ *Arkansas La. Gas Co v. Hall*, 453 U.S. 453, 578-579; see also *Nantahala Power & Light Co. v. Thornburg*, 476 U.S. 953, 963-964(1986).

²⁵⁹ *Arkla*, 453 U.S. at 480-82.

²⁶⁰ *Whitmore v. Arkansas*, 495 U.S. 149, 159-60 (1990) (“It is just not possible for a litigant to prove in advance that the judicial system will lead to any particular result in a case.”)

²⁶¹ *Id.* at 480-82 (“the Supremacy clause will not permit” state law claims that are “necessarily supported by the assumption” that a federal Agency “would approved [a request],” because such claims “usurp[] a function that Congress has assigned to a federal regulatory body.”).

Litigation predicated on the “taking the steps” rationale would essentially topple the currently teetering regulatory framework. In effect, despite not having access to the data necessary to frame and substantiate a labeling change request, the threat of potential liability would be a powerful incentive for generic companies to submit anything to the FDA after receiving even a single adverse report simply so that they could claim that submission as a defense to possible state tort litigation. The Supreme Court commented on the harmful effects of such conduct in *Buckman*, “Applicants would then have an incentive to submit a deluge of information that the administration neither wants nor needs resulting in additional burdens on the FDA.”²⁶² While the FDA is mired down in processing the unprecedented deluge of potentially meritless labeling change requests from companies seeking to avoid state law liability, “the comparatively speedy [ANDA] process would encounter delays, which would, in turn, impede competition among prescription drugs and delay healthcare professionals’ ability to prescribe these products.”²⁶³

Another drawback of the approach is that it compromises generic manufacturers’ ability to discharge their responsibility of ensuring safe and effective labeling for their products. Instead of thoughtful analysis of available data and potentially adverse events, manufacturers could be tempted to resort to a strategy of defensive labeling, a practice the FDA has repeatedly cautioned against. As the FDA stated in its 2006 regulations, including too much information in a label could “result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.”²⁶⁴ Even for these regulations, the Agency observed that “it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation in which the agency has no part.”²⁶⁵

In addition, this approach overlooks many of the practical burdens that it would place on the FDA’s ability to carry out its public health mission. To litigate the question of how the FDA might have responded to a hypothetical request would necessitate access to the materials before the Agency at the time the request allegedly should be made.²⁶⁶ The FDA would be embroiled in a flurry of subpoenas from across the country seeking Agency records, internal deliberations and memoranda containing Agency officials’ states of mind.²⁶⁷ Further, the FDA’s scarce resources they should be devoted to fulfilling Congress’ health mission, not wading through piles of private discovery requests. Nor should the Agency expend valuable man hours, as subpoenaed witnesses

²⁶² *Buckman Co., v. Plaintiff’s Legal Comm.*, 531 U.S. 341, 351 (2001).

²⁶³ *Id.*

²⁶⁴ 71 Fed. Reg. 3922, 3935 (Jan. 24, 2006) (“over warning, just like under warning, can . . . have a negative effect on patient safety and public health.” W. Kip Viscusi, *Individual Rationality, Hazard Warnings, and the Foundations of Tort Law*, 48 Rutgers L. Rev. 625, 665-66 (1996) (“Excessive warnings are not innocuous . . . [I]f warnings are included for any consequential risks, they will serve to further dilute the warnings for the real hazards that should be identified to consumers.”)

²⁶⁵ Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37, 434, 37, 435 (June 26, 1979).

²⁶⁶ See e.g. Transcript of Record at 25, Warner Lambert (No. 06 – 1498), 2008 WL495030 [“Warner – Lambert Tr.”].

²⁶⁷ *Id.* at 21-22.

speculating in court over what the Agency would have done in response to hypothetical proposed warnings.²⁶⁸

Since the FDA issued its preemption preamble asserting the incompatibility of federal regulations and state law failure to warn requirements, litigation against drug manufacturers has grown at an alarming rate.²⁶⁹ As a result of the Supreme Court's *Levine* holding, virtually all preemption cases center on the role of generic manufacturers. The asserted allegations and defenses are nearly identical: plaintiffs allege the manufacturers breached their duty to revise their products' labeling to include warnings required under state law and generic manufacturers assert that the federal regulatory framework makes it impossible to comply with state law or that to comply with state law would frustrate the purposes of federal law.²⁷⁰ Until recently neither side referenced the FDA's "solution" regarding how generic manufacturers should meet their duty to provide adequate warnings.²⁷¹ Specifically, in the preamble to the final rule implementing the ANDA application process the Agency stated the following:

If an ANDA applicant believes 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 drug should be revised.²⁷²

In the 23 years since implementing the ANDA process, the FDA has failed to promulgate any regulations to govern this procedure.²⁷³ 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 Office of Generic Drugs. The FDA provides no timeline for review, contact names for follow-up, specifications of what a concerned manufacturer should submit, or description on what happens after the proposed change is submitted. The only vague reference as to what type of investigation the Agency conducts after receipt is that "some labeling reviews" will require the Office of Generic Drugs to consult with various FDA components before any change can be

²⁶⁸ See e.g. Warner-Lambert Federal Br. At 22-23 ("In one recent products liability class action, *Walson v. Merck & Co.*, No. 3:04-cv-0027-GPM-DGW (S.D. Ill.) FDA devoted approximately 1300 employee hours to producing approximately 40,000 pages of documents in response to a third-party subpoena. Private litigation such as this would divert FDA's resources and create a substantial potential for distorting its mission."); *Buckman* (No. 98-1768), 2000 WL 136444] (Noting that such claims quote "invite highly intrusive discovery" and "therefore pose a real danger diverting FDA's resources from important health mission that Congress has assigned to it and distorting FDA's internal decision-making process").

²⁶⁹ See Drug Preemption Score Card <http://druganddevicelaw.blogspot.com/2007/09/drug-preemption-scorecard.html>.

²⁷⁰ *Id.*

²⁷¹ 57 Fed. Reg. at 17,961.

²⁷² *Id.*

²⁷³ Brief for United States as *Amicus Curiae, Pliva, Inc. v. Mensing*, Nos 09-993 and 09-1039 at 16

made.²⁷⁴ To date, the Agency has not identified what labeling reviews trigger that type of consultation or identified the other components within the FDA that participate in examining these requests. The Agency justifies this haphazard approach by stating that “such instances arise infrequently.”²⁷⁵

IV THE NEW FRAMWORK

A. *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 current preemption debate focuses on the availability of post-approval mechanisms, this article suggests a broader framework.

For generic manufacturers to possess the necessary data to make meaningful labeling suggestions they need complete access to the clinical, animal, and bioequivalency data submitted in the brand name manufacturer's NDA.²⁷⁶ The implementing language of the Hatch Waxman Act allows generic manufacturers to use brand-name drugs still under patent to obtain bioequivalency data.²⁷⁷ The Act also allows generic manufactures to use Agency safety and effectiveness findings and publicly available literature to reverse engineer the components of the referenced drug.²⁷⁸ When the FDA approves a generic equivalent developed through these indirect methods, the Agency 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.²⁷⁹ Giving generic manufacturers access to the actual clinical results submitted in NDAs provides them a more complete clinical base to evaluate the current and future performance of their product.

Another fundamental shift in the proposed framework would be generic manufacturers' post-approval responsibilities and access to data. All manufacturers bear the responsibility for the adequacy of their labeling. To that end, crafting adequate warning labels necessitates generic manufacturers' possessing “superior” access to information about their drugs.²⁸⁰ As noted by the Supreme Court, this need is particularly important in the post-marketing phase as new risks emerge.²⁸¹ A proper regulatory framework needs to reflect that corresponding responsibility and access. Compliance

²⁷⁴ *Id.*

²⁷⁵ *Id.*

²⁷⁶ These are the component that constitutes the bioequivalency necessary for ANDA approval. 21 U.S.C. §355(j).

²⁷⁷ 35 U.S.C. §271(e)(1).

²⁷⁸ 21 C.F.R. § 314 (g) (ii). FDA's safety and effectiveness findings are contained in the “Summary Basis of Approval that he Agency prepares and makes publically 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.

²⁷⁹ 21 U.S.C. §355(j).

²⁸⁰ *Levine*, 129, S.Ct. 1202.

²⁸¹ *Id.*

with FDA post-approval reporting requirements should provide generic manufacturers sufficient data to discern the need for and craft adequate labeling. 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 access and analyze post-approval safety activities including: reporting to worldwide regulators; post-approval safety studies; safety-focused epidemiologic activities; activities required for safety-related labeling changes; literature review for adverse-event information; and provision of safety information to health care professionals.²⁸²

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. The proposed framework does not suggest altering the core cost-saving tenet. Currently brand name manufacturers conduct and pay for the majority of post-approval safety analysis.²⁸³ Similar to the data generated in the NDA process, generic manufacturers should have access to that data. Post-approval studies could continue to be conducted by the brand name manufacturer or through a contracted laboratory. Regardless of how 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.²⁸⁴ Congress could mandate an "accessing data fee" that 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.

Throughout the pre-approval and post-approval marketing of NDA products, the brand name manufacturer and FDA engage in on-going conversations and negotiations regarding safety and labeling. 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 regarding the performance of their products and should contribute in the negotiations with the FDA brand name manufacturer regarding all post-approval labeling changes and

²⁸² David B. Ridley, Judith M. Kramer, Hugh H. Tilson, Henry G. Grabowski and Kevin A. Schulman, Spending On Post-approval Drug Safety *Health Aff.*, March 2006 vol. 25 no. 2 429, 429. (other information could include: summary report production of aggregate post-approval adverse-event information, safety department; safety surveillance activities, including those related to post-approval risk management, safety-related product quality complaints, including product recall for safety reasons, responses to safety questions from worldwide regulators) *Id.* at 431.

²⁸³ *Id.* at 429 ("drug manufacturers regarding safety efforts. Mean spending on post-approval 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.")

²⁸⁴ 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 alleviate some of these concerns.

be invited to consult with the FDA at critical junctures in the ANDA approval process and in response to adverse event reports.²⁸⁵

In addition to direct access to brand name manufacturer 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 would merely be the recipients of increased information. Similar to their branded counterparts, generic manufacturers' post-approval responsibilities would require them to conduct worldwide literature searches of their product. As noted by the Eighth Circuit, generic manufacturers should not be allowed to "sit passively by and profit from a product that may be dangerous."²⁸⁶ It was not Congress' intent for the FDA to carry alone the burden of ensuring safety and effectiveness of the pharmaceutical industry.²⁸⁷ The current resource constraints of the Agency only underscore the importance of generic manufacturers embracing their responsibility to ensure the adequacy of their products.²⁸⁸ More transparency in data will allow them to meet the elevated responsibility the Supreme Court is tasked them with.

Once brand name and generic manufacturers are on an equal footing regarding access to information, the next question is what mechanisms should be available to the generic manufacturers to suggest changes to ensure the safety of their product? Generic manufacturers require the clear and unequivocal access to the CBE, PAS, and Dear Doctor letters processes as is afforded their brand name counterparts. For example, to avoid FDA rejection of a change implemented in the CBE process, it is a common practice that brand name manufacturers meet and discuss with the Agency the proposed change before they implement it. To ensure generic manufacturers the same ability to use this consultation process, the regulations should be modified accordingly.

B. Addressing Anticipated Criticisms

There are several anticipated 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.²⁸⁹ The proposed framework's call to provide generic manufacturers with direct access to NDA information and results from ongoing clinical trials will trigger additional proprietary and

²⁸⁵ In the final rule implementing the ADA regulations, specifically requested the FDA incorporate provisions to provide ANDA applicants 90 day conferences and review conferences. The agency rejected such inclusions and indicated that those generic manufacturers request such conferences in case a 90 day conferences that will generally be unavailable and review conferences will be given a priority. 57 FR 17950 – 01 comment 62.

²⁸⁶ *Mensing*, 588 F.3d. at 609.

²⁸⁷ *Levine*, 129 S.Ct. 1196-97.

²⁸⁸ Pub. L. No. 110-85, 121 Stat. 823 (2007), "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." 153 Cong. Rec. SI 1832 (daily ed. Sept. 20, 2007) (Statement of Sen. Kennedy).

²⁸⁹ Lars Noah, *Law, Medicine, and Medical Technology: Cases and materials* 339 (Robert C. Clark et al. eds., 2nd ed. 2007).

intellectual property issues that are beyond the scope of this Article.²⁹⁰ These concerns, however, require careful balancing against the disclosures' ability to close potential gaps between generic and brand name drugs that the FDA had deemed to be the "same as" in terms of bioequivalency criteria but has made no determination in terms of whether the generic drug is "as safe as" its branded counterpart. Moreover, an argument can be made 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."²⁹¹ From this provision, it seems that Congress did not aim to bar the public from safety and effectiveness data.²⁹² The proposed framework furthers that intent by using it to foster one of Hatch-Waxman's goals of ensuring the availability of safe and effective generic drugs.²⁹³

Another probable criticism is that allowing generic manufacturers the ability to independently strengthen their labels erodes the FDA's mandate of uniformity among brand name and generic drugs. Further, 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 product would undermine the Congressional intent of the Act.²⁹⁴ Currently the Fifth, Eighth, and Ninth Circuit maintain that generic manufacturers possess such ability. While there is not complete uniformity among the circuits as to which mechanisms generic manufacturers are entitled to use, the courts have all held that generic manufacturers can change their warning labels.²⁹⁵ These pronouncements were not met with a sharp decline in consumer willingness to purchase generic drugs or an increase in consumer confusion regarding the safety and effectiveness of their prescribed generic. In the unlikely event that such unwillingness or confusion occurs, the FDA can easily use the public information platforms already in place to reassure and educate the American public.

²⁹⁰ 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) (explaining 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 the Act's strictures; see also Mustafa Ünlü, *It Is Time: Why the FDA Should Start Disclosing Drug Trial Data*, 16 Mich. Telecomm. Tech. L. Rev. 511 (2010), available at <http://www.mttl.org/volsixteen/unlu.pdf>

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

²⁹² 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 field 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.").

²⁹³ FDCA §§02(d), 76 Stat. 780.

²⁹⁴ See, e.g., FDA, *Facts and Myths About Generic Drugs*, www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (noting the "myths" that "[p]eople who are switched to a generic drug are risking treatment failure," that "[g]eneric drugs cost less because they are inferior to brand name drugs," and that "[b]rand name drugs are safer than generic drugs")

²⁹⁵ See note 5, *infra*.

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).²⁹⁶ As previously mentioned, it is a common practice for brand name manufacturers to consult with the Agency prior to making these proposed changes.²⁹⁷ 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 critics may raise.²⁹⁸ Essentially the proposed framework expands the process the Agency 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 the extent that generic manufacturers possess the unambiguous ability to change their labeling through the CBE, PAS, and “Dear Doctor” letter mechanisms, the need for courts to engage in the tortuous process of justifying the “steps could have taken” line of reasoning evaporates. Similarly, so do concerns about further overburdening the FDA’s limited resources with discovery requests and subpoenas to take part in litigation to determine how the Agency would have responded to hypothetically proposed label changes.

C. Reconciling the Proposed Framework with the Hatch-Waxman Intent

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.²⁹⁹ In determining how that balance should be struck, the Eight Circuit correctly noted that Congress did not intend the Hatch-Waxman Amendments to override “the fundamental requirement of the FDCA that all marketed drugs remain safe.”³⁰⁰ 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.”³⁰¹ Nothing in the Hatch-Waxman Amendments suggests that Congress intended to abandon that position. In enacting the Hatch-Waxman Amendments, Congress sought to make generic drugs available to American consumers, but not at the expense of drug safety.³⁰² Requiring generic manufacturers to bear the primary responsibility for ensuring the safety of their products

²⁹⁶ See note 125 *infra*.

²⁹⁷ Margret Gilhooly, *Drug Preemption and the Need to Reform the FDA Consultation Process*, *American Journal Law & Medicine*, 34 (2008) 535, 551.

²⁹⁸ The Agency could even consider expanding these pre-CBE change consultations to include both generic and brand-name manufacturers.

²⁹⁹ P.L. 98-417, Drug Price Competition and Patent Term Restoration Act, H.R. No. 857(I), 98th Cong., 2d Sess. (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647.

³⁰⁰ *Mensing*, 588 F. 3d at 612.

³⁰¹ FDCA §§02(d), 76 Stat. 780.

³⁰² *Gaeta v. Perrigo Pharms. Co.*, ___ F.3d ___, 2011 WL 198420, at *11 (9th Cir. Jan. 24, 2011); *see, e.g.*, Pub. L. No. 98-417, § 101, *codified at* 21 U.S.C. § 355(j)(2)(C)(ii) (providing that the Secretary can deny a petition to file an AND A for a generic drug with a different active ingredient than an approved drug if the drug “may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted” in the ANDA).

is directly in line with the intent of the Hatch-Waxman Act. To do so by requiring them to conduct their own clinical trials to acquire the knowledge base necessary to make meaningful label changes is not. Nor is the Eighth Circuit's solution of having generic manufacturers exit the industry if they maintain that it is impossible for their product to comply with state and federal labeling requirement. The solution proposed by this framework embraces the spirit of the Hatch-Waxman's disclosure provisions to provide generic manufacturers direct access to data necessary to craft adequate labeling changes. The framework also suggests increased transparency and open communication among generic manufacturers, their branded counterparts, and the FDA. Finally, the framework provides generic manufacturers unambiguous access to the mechanisms necessary to implement labeling changes on the same basis as do the brand name manufacturers.

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/preemption litigation. Several circuit courts have sought to shoehorn the distinct challenges faced by generic manufacturers into a *Levine* analysis. This Article offers several illustrations of why such reliance is misplaced. Despite key differences between the labeling frameworks for brand name and generic manufacturers, the *Levine* analysis is directly on point in one vital aspect. The Supreme Court properly identifies manufacturers as the starting point for ensuring the adequacy of their product's labeling. Proceeding from there, this Article advances a framework that incorporates the unique role generic drugs play in the American health care system while at the same time provides the necessary access to data and implementation mechanisms necessary to fulfill responsibilities common to all drug manufacturers.