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Jessica Seiden

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Jessica Seiden

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Title: Increasing Patient Safety by Permitting Generic Drug Manufacturers to Update Product Safety Labels

Part I: Introduction

Since 1984, the Food and Drug Administration (FDA) has approved over 8,000 generic drugs, which comprise approximately seventy-eight percent of currently filled prescriptions.¹ The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) has governed the approval of generic drugs.² The Act provides an expedited approval process for generic drugs that have an identical Reference Listed Drug (RLD). Provided a generic drug is the “same” as its listed drug counterpart, its manufacturer is permitted to forgo clinical testing, on the condition that the drug maintains the same label as the listed drug.³ The generic drug manufacturers have no authority to modify or update their own safety labels.⁴ The inability to independently update labels has led to issues concerning generic drug manufacturers’ liability for

¹ Fact Sheet: New User Fees for Generic Drugs Will Enhance American’s Access to Less Expensive Drugs and Generate Major Cost Savings, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm310992.htm> (last visited Nov. 5, 2014).

² See 21 U.S.C. 355(j) (1)-(2). See also, *Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) Before the S. Comm. on the Judiciary*, (2003) (statement of Daniel E. Troy, Chief Counsel, U.S. Food and Drug Administration).

³ *Examining Concerns Regarding FDA’s Proposed Changes to Generic Drug Leveling Before the Energy and Commerce Subcomm. On Health*, U.S. H.R., (2014) (statement of Ralph. G. Neas, President and CEO, The Generic Pharmaceutical Association).

⁴ *Id.*

failure to warn of safety concerns, which have been recently addressed by the U.S. Supreme Court.⁵

Congress has begun to address these concerns with the enactment of the Generic Drug User Fee Amendments of 2012 (“GDUFA”).⁶ The GDUFA recognizes the growth of the generic drug industry by expediting the approval process for generics, saving time and money for the industry, and ensuring Americans have access to low cost, quality medicine. In exchange for faster approval times, the generic industry must pay user fees, as the branded pharmaceuticals do.⁷ The GDUFA is the beginning of major reform for the generic drug industry, placing some of the same obligations and benefits on the generic industry that the brand name manufacturers have.

The growth of the generic industry and the issues presented in recent Supreme Court cases have prompted the FDA to reconsider current federal mandate and to suggest generic drug manufacturers be permitted to update their safety labels in response to safety issues that have been discovered.⁸ The proposed regulation would require generic-drug makers to update their labels in light of newly acquired safety information to avoid injury to consumers, which could result in legal liability.⁹ This Note argues that allowing generic-drug makers to update safety labels as soon as new information is received will increase patient safety and prevent injuries by

⁵ Jennifer M. Thomas, *FDA Proposes a Rule that Would Undercut Generic Drug Preemption*, FDA L. BLOG (September 2, 2014), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/11/fda-proposes-a-rule-that-would-undercut-generic-preemption.html

⁶ Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, §908, 126 Stat. 993 (2012).

⁷ Fact Sheet, *supra* note 1.

⁸ Joe Carlson, *FDA’s Generic-Drug Label Rule Draws Controversy*, MODERN HEALTHCARE (September 2, 2014), <http://www.modernhealthcare.com/article/20140628/MAGAZINE/306289979>.

⁹ *Id.*

providing timely updates to safety information.¹⁰ This would also allow generic drugs that no longer have a brand-name counterpart to update their labels.¹¹

These changes may also have an impact on manufacturer's exposure to failure-to-warn liability. Under the Supreme Court's 2011 ruling in *PLIVA v. Mensing*, generic drug makers are unable to add new side effect and safety information to product labeling and therefore should not be held accountable for any failure-to-warn claims.¹² Currently, access to the courts depends on whether an individual has been prescribed a brand-name or generic drug.¹³ Many fear that if the proposed regulatory change is approved, it may allow consumers to file failure-to-warn claims against generic drug manufacturers.¹⁴ Once generic drug makers have the right to change their label, they are responsible for knowing the full effects of the drugs they produce, and may be sued for failing to timely update their labels.¹⁵ The FDA notice of the proposed rule acknowledges the proposed regulation may also change generic drug manufacturer's liability.¹⁶ Although the proposed regulations may have a significant impact on generic drug makers' liability, such discussion is beyond the scope of this note.

Part II of this Note will introduce background legislation and regulations concerning the labeling of brand-name and generic drugs. It will describe the subsequent amendments to food

¹⁰ *Id.*

¹¹ *Id.*

¹² *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011); Silverman, Ed. *How Fast Should a Generic Drug Maker Update Labeling with New Safety Info?* THE W.S.J. PHARMALOT, (Sept. 3, 2014), <http://blogs.wsj.com/pharmalot/2014/09/03/how-fast-should-a-generic-drug-maker-update-labeling-with-new-safety-info/>; *See also Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466 (2013).

¹³ *Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling Before S. Comm. On Health, Comm. On Energy and Commerce, U.S. H.R.*, (2014) (statement of Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Service).

¹⁴ *Id.*

¹⁵ Carlson, *supra* note 8.

¹⁶ Freidman, Ezra and Abraham L. Wickelgren. *Who (if Anyone) Should be Liable for Injuries from Generic Drugs?* (citing 67986 Federal Register, Vol 78, No. 219, November 13, 2013).

and drug legislation in response to the growth of generic drugs over the past few decades. Part II will also introduce the 2013 proposed regulatory amendments which would provide generic manufacturers the ability to independently update safety labels. Part III of this Note will discuss the benefits of independent label changes to public policy and patient safety while keeping costs significantly lower than brand-name counterparts.

Part II: Background/Overview

A. Statutory Background

The Federal Food, Drug, and Cosmetic Act (“FD&C Act”) and the Public Health Service Act (“PHS Act”) “provide [the] FDA with authority over the labeling for drugs and biological products.”¹⁷ The Acts also authorizes the FDA to enact regulations to facilitate the review and approval of applications regarding the labeling for those products.¹⁸ Section 502(f) of the FD&C Act states that “a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage, methods, duration of administration, or application.”¹⁹ Section 502(j) of the Act mandates that “a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.”²⁰ These statutes created new standards for drug manufacturer’s products and facilities.

In 1984, the FD&C Act was amended to include the Drug Competition and Patent Term Restoration Act, more commonly known as The Hatch-Waxman Act.²¹ The Hatch-Waxman Act

¹⁷ See 21 U.S.C. 301. See also 42 U.S.C. 201.

¹⁸ Woodcock, *supra* note 13.

¹⁹ *Id.*

²⁰ *Id.*

²¹ Wolfman, Brian & Anne King, *Mutual Pharmaceutical Co. v. Bartlett and Its Implications*, U.S.L.W. (Sept. 19, 2014), available at <http://scholarship.law.georgetown.edu/facpub/1297>.

provided a less stringent approval process for generic drug makers. The generic manufacturer is now required to submit an abbreviated new drug application, showing the generic drug is the “same” as a previously approved brand-name drug, and the generic is “bioequivalent” to the brand name drug.²² Under the “sameness” requirement, the generic manufacturer must show that the generic drug provides the same safety and efficacy, by proving that the generic drug has the same active ingredient, is identical in strength, dosage and administration, and has the same safety label.²³ The Act exempted generic manufacturers from the “expensive, time-consuming, and ultimately repetitive clinical testing and trials that already had been performed on the innovator drug.”²⁴ In the twenty-two years preceding the Act, only fifteen generics had been approved by the FDA. One year after the Act, more than 1,000 drugs approvals were submitted to the FDA. The Act has resulted in billions of dollars of savings to the health care industry and consumers.²⁵

Currently, for most substantive changes to drug labeling, a brand-name manufacturer must submit an approval supplement and obtain FDA approval for the change.²⁶ FDA regulations also require manufacturers of pharmaceutical and biological products to submit reports of adverse drug experiences that occur after approval.²⁷ In promotion of public health, the FDCA permits certain labeling changes based on newly acquired safety information about the drug when the manufacturer submits a “changes being effected” (“CBE-0”) supplement

²² *Id.*

²³ Neas, *supra* note 4.

²⁴ *Id.*

²⁵ *Id.*

²⁶ Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67985 (proposed Nov. 13, 2013), *available at* <https://www.federalregister.gov/articles/2013/11/13/2013-26799/supplemental-applications-proposing-labeling-changes-for-approved-drugs-and-biological-products>

²⁷ *Id.*

describing the change.²⁸ Newly acquired safety information is defined by the FDCA as "information derived from a clinical trial, an adverse event report, a post approval study . . . peer reviewed biomedical literature, data derived from the post-market risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by [the FDA]."²⁹ When this information is received, the brand drug must update their warnings labels to reflect the new information.

The CBE-0 supplement regulations "allow application holders to comply with the requirement to update labeling promptly to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug"³⁰

According to the 2008 amended regulations governing the CBE-0 process, a CBE-0 labeling supplement is appropriate only to show new information. The 2008 amendments clarified that the supplement may be used to "add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the approved product."³¹ The FDA reviews all labeling changes proposed in a CBE-0 supplement and the underlying data and research supporting the change. The FDA then accepts, rejects, or requests modifications to the proposed changes as deemed appropriate, and can bring enforcement action if the information makes the product's label false or misleading.³² Also, if the newly acquired information causes the product to no longer meet FDA standards, the agency can take action by rescinding the drug's approval.³³

²⁸ *Id.*, See also 21 C.F.R. §§ 314.70(c) (6) (iii) and 601.12(f) (1).

²⁹ See 21 U.S.C. 505(o)(2)(C)

³⁰ See 78 Fed. Reg. 67985, see also 21 C.F.R. 201.57(c).

³¹ Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67985-02 (proposed Nov. 13, 2013) (to be codified at 21 C.F.R. pt. 314 and 601).

³² See 21 U.S.C. 352(a).

³³ See 21 U.S.C. 355(e), 355-1.

B. The 2012 Enactment of FDASIA/GDUFA: Paving the way for Generic Label Updating?

In 2010, seventy-eight percent of pharmaceutical prescriptions were filled with generic brands.³⁴ Today, the top ten drugs filled in America are all generic brands.³⁵ Over the past decade, generic drugs have provided a savings of over \$824 billion dollars to the nation's health care system in the last decade.³⁶ In response to the rapid growth of generic drugs over the past decades, Congress, in 2012, enacted the Generic Drug User Fee Act ("GDUFA") as a part of the Food and Drug Administration Safety and Innovation Act ("FDASIA").³⁷ GDUFA allows for more speed in approving generic drugs while ensuring safety and low costs by requiring generic manufacturers to pay fees to supplement the costs of reviewing generic drug applications and inspecting facilities.³⁸ As the FDA has explained "Recognizing the critical role generic drugs play in providing more affordable, therapeutically equivalent medicine, the Generic Drug User Fee program is designed to keep individual fee amounts as low as possible to supplement appropriated funding to ensure that consumers continue to receive the significant benefits offered by generic drugs..."³⁹

The FDASIA gives the FDA the authority to collect user fees from the pharmaceutical industry to "fund reviews of innovator drugs, medical devices, generic drugs and biosimilar

³⁴ Gary Gatyas, *IMS Institute Reports U.S. Spending on Medicines Grew 2.3 Percent in 2010, to \$307.4 Billion*, IMS HEALTH (April 19, 2011), <http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=1648679328d6f210VgnVCM100000ed152ca2RCRD>.

³⁵ von Koeckritz, Karen. *Generic Drug Trends- What's Next?* (April 11, 2012), <http://www.pharmacytimes.com/publications/issue/2012/April2012/Generic-Drug-Trends-Whats-Next>.

³⁶ *Generic Drug User Fee Act Program Performance Goals and Procedures*, (Nov. 10, 2014), available at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>

³⁷ Fact Sheet, *supra* note 1.

³⁸ *Generic Drug User Fee Amendments of 2012*. U.S. Food and Drug Administration, (Nov. 10, 2014), available at <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>. See 112 H.R. 3988, 2012 H.R. 3988, 112 H.R. 3988.

³⁹ *Supra* note 35.

biological products.”⁴⁰ The FDASIA also encourages innovation by providing a “breakthrough therapy” designation for certain drugs that may be substantially superior to current drugs on the market. This designation would allow for an expedited review and approval process through the collection of fees to create additional resources.⁴¹ The FDASIA was also implemented to protect the drug supply chain and to ensure patients have access to drugs they need by extending the FDA’s detention authority and increasing penalties for adulterated and counterfeit drugs.⁴²

The purpose of the GDUFA is to increase safety by requiring that any manufacturer who participates in the U.S. generic drug industry be inspected biennially.⁴³ It also will “deliver greater predictability and timeliness to the review of generic drug applications, slashing review times and saving industry time and money.”⁴⁴ The GDUFA also requires that any domestic or international facility involved in the manufacture of generic drugs and their ingredients be identified upon their sale in the United States to increase transparency in the complex, global pharmaceutical market.⁴⁵ All facilities and companies selling generic drugs must register annually with the FDA.⁴⁶ This includes manufacturers of active pharmaceutical ingredients whose products may be used in US products through another manufacturer or facility that repackages generic drugs.⁴⁷ The FDA has laid out guidance on which companies need to self-identify and what information they are required to provide to the FDA.⁴⁸ In its guidance

⁴⁰ Food and Drug Administration Safety and Innovation Act (FDASIA), (Jan. 1, 2015), *available at* <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendments/totheFDCAAct/FDASIA/>

⁴¹ *Id.*

⁴² *Id.*

⁴³ *Supra* note 35.

⁴⁴ Fact Sheet, *supra* note 1.

⁴⁵ *Id.*

⁴⁶ 112 H.R. 3988. *See also* Gaffney, Alexander. *FDA Releases Guidance on Facility Registrations, Payments under GDUFA*, (Jan. 21, 2015), <http://www.raps.org/regulatoryDetail.aspx?id=7435>.

⁴⁷ *Id.*

⁴⁸ *Id.*

documents, the FDA explained that “[t]he information provided through self-identification will enable quick, accurate and reliable surveillance of generic drugs and facilitate inspections and compliance.”⁴⁹

The GDUFA also aims to cut down the review time of generic drug applications from thirty-one months to about ten months. The funds collected from the user fees, which is stated to be one half of one percent of generic drug sales, will be used to assess the safety of generic drugs.⁵⁰

The user fees result in benefits to the public health by financing the FDA to carry out functions that it could not do previously. By cutting the review time of a generic drug applications, the GDUFA will increase savings in development time, while decreasing the costs of bringing a generic drug to the market.⁵¹ Therefore, this may also result in a decline in costs to consumers.⁵²

C. Recent Supreme Court Cases

Recent Supreme Court cases have addressed the issue of whether generic drug manufacturers should be liable for failing to provide adequate warnings on drug labels.⁵³ This wave of lawsuits began with *Wyeth v. Levine* in 2009.⁵⁴

⁴⁹ *Id.*

⁵⁰ Sullivan, Thomas. *The Food and Drug Administration Safety and Innovation Act (FDASIA): Summary of GDUFA, MDUFA, BsUFA and Pediatrics*, POLICY AND MEDICINE (NOV. 10, 2014), <http://www.policymed.com/2012/07/the-food-and-drug-administration-safety-and-innovation-act-fdasia-summary-of-gdufa-mdufa-bsufa.html>

⁵¹ *Supra* note 26.

⁵² *Id.*

⁵³ Woodcock, *supra* note 13.

⁵⁴ *Wyeth v. Levine*, 555 U.S. 555 (2009)

In *Wyeth*, the patient was injured by using a brand-name anti-nausea drug through an IV-push method. The patient claimed the drug's label was defective because it failed to instruct clinicians to use an IV-drip method, rather than the higher-risk push method.⁵⁵ The patient filed a failure-to-warn suit in state court against the drug manufacturer, Wyeth for failing to update the product's label with newly acquired safety information, even though the labels conformed to FDA regulations.⁵⁶

The Supreme Court determined that federal law does not preempt a state law failure to warn claim for brand name drugs.⁵⁷ The Court explained that “[i]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the contents of its label at all times.”⁵⁸ The court held that the manufacturer must create an adequate safety label and ensure it is up to date as long as the product is being sold.⁵⁹ The Court opined “Wyeth failed to demonstrate that it was impossible for it to comply with both federal and state requirements . . . the mere fact that the FDA approved . . . [the] label does not establish that it would have prohibited such a change.”⁶⁰ The Court held that Wyeth could have strengthened the warning labels under the FDA's CBE-0 regulation to comply with state law.⁶¹ The Court's holding in *Wyeth* sent a clear message to brand-name drug manufacturers that: “if they do not unilaterally

⁵⁵ See *Wyeth*, 555 U.S. 555. See also Boyd, Marie. *Unequal Protection Under the Law: Why FDA Should Use Negotiated Rulemaking to Reform the Regulation of Generic Drugs*, 35 *Cardozo L. Rev.* 1525, 1530 (2014).

⁵⁶Goldstein, Jacob. *Wyeth v. Levine: The Mother of All Preemption Cases*, W.S.J. BLOGS (Nov. 9, 2014), <http://blogs.wsj.com/health/2008/09/19/wyeth-v-levine-the-mother-of-all-preemption-cases/>

⁵⁷ *Supra* note 13.

⁵⁸ *Wyeth*, 555 U.S. at 570-71.

⁵⁹ *Id.*

⁶⁰ *Wyeth*, 555 U.S. at 573.

⁶¹ Boyd, *supra* note 55.

strengthen their labels when they know it is necessary, they will face liability in the state court system.”⁶²

In 2011, the Supreme Court distinguished *Wyeth* in the subsequent case *PLIVA v. Mensing*.⁶³ In *PLIVA*, the patients alleged they developed tardive dyskinesia after using the generic drug metoclopramide. The patients claimed the generic drug label did not contain adequate warnings of this adverse side effect.⁶⁴ The manufacturer of the drug argued that: “(1) FDA regulations require the warnings on generic pharmaceuticals to be the same as those of the brand-name product; and (2) they had no ability to unilaterally add or strengthen warnings without FDA approval.”⁶⁵ The Court agreed with the manufacturer, and held the claim was preempted because generic manufacturers cannot add further warnings without violating FDA regulations under the Hatch-Waxman Act.⁶⁶

The holdings in *Wyeth* and *PLIVA* suggest that “The Supreme Court has determined that generic manufacturer’s lack of independence with respect to drug safety labeling makes it impossible for them to comply with both Federal drug labeling requirements, and state tort law (failure-to-warn or design-defect) requirements.”⁶⁷ The holdings in *Wyeth* and *PLIVA* suggest that access to the courts depends on whether a consumer purchased a generic or a brand-name drug.⁶⁸

⁶² Sarah S. James, Note, *Generic Drug Manufacturer Liability: Achieving a Balance Between Consumer Affordability and Safety*, 38 Iowa J. Corp. L. 177, 182 (2013).

⁶³ See *PLIVA*, 131 S. Ct. 2567.

⁶⁴ *Id.*; Rose, Beth S., Charles J. Falletta & Vincent R. Lodato. *Pliva, Inc. v. Mensing—United States Supreme Court Holds That Failure To Warn Claims Against Generic Pharmaceutical Manufacturers Are Pre-Empted By Federal Law*, N.L.R. (Nov. 10, 2014), <http://www.natlawreview.com/article/pliva-inc-v-mensing-united-states-supreme-court-holds-failure-to-warn-claims-against-generic>

⁶⁵ *Id.*

⁶⁶ *Id.*

⁶⁷ Thomas, *supra* note 4.

⁶⁸ *Supra* note 13.

In 2013, the Supreme Court decided *Mutual Pharmaceutical Co. v. Bartlett*.⁶⁹ In *Bartlett*, the plaintiff suffered an adverse effect from taking the generic medication Sundilac.⁷⁰ The patient, who took the prescribed medication to alleviate muscle pain, developed Stevens - Johnson syndrome and toxic epidermal necrolysis and became extremely disfigured as a result.⁷¹ This side effect was originally listed as “a possible adverse reaction” on the safety label and was later moved to the “warnings” section of the generic label in conformance with the FDA’s recommendation.⁷²

The Supreme Court held in *Bartlett* that federal law preempts a state-law design-defect claim against a generic drug manufacturer under *PLIVA*.⁷³ The Court first decided that New Hampshire does not have a “pure” design-defect cause of action, which would require a jury to balance the risks and benefits of an FDA approved drug to determine if it is “unreasonably dangerous”.⁷⁴ As the FDA argued in its brief, this would undermine their assurance of approved drugs on a state-by-state and case-by-case basis, as well as Congress’s purpose that FDA approvals are made by experts applying science based judgment.⁷⁵ The Supreme Court determined that New Hampshire’s design defect cause of action includes an evaluation of the adequacy of the label.⁷⁶ Through the design-defect analysis, the Court determined that generic drug manufacturers should not be held accountable for failure-to-warn or design-defect claims

⁶⁹ See *Bartlett*, 133 S. Ct. 2466.

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² Wolfman, *supra* note 18.

⁷³ *Bartlett*, 133 S. Ct. 2466; Wolfman, *supra* note 18.

⁷⁴ *Bartlett*, 133 S. Ct. at 2470.

⁷⁵ *Id.*; Brief for the United States as Amicus Curiae, p. 25, *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466 (2013).

⁷⁶ See *Bartlett*, 133 S. Ct. 2466.

because generic drug makers are not permitted to independently update safety information on drug labeling.⁷⁷

A recent case contesting the issue of generic drug liability has been decided by California's highest court.⁷⁸ Here, the plaintiff was injured from her prolonged use a generic form of Fosamax.⁷⁹ She claimed Teva, the generic maker, had failed to update their warnings in compliance with the brand Fosamax's warnings.⁸⁰ The defense rebutted that the plaintiff's claim was preempted by *PLIVA*. The trial court held, and the appellate court affirmed, that since the brand-name drug maker made the safety update, the generics are at fault for failing to immediately update their labels to conform to the newly acquired information.⁸¹ This case raised issues about the scope of *PLIVA* and whether failure-to-update claims would be preempted by Federal law.⁸² The California Supreme Court declined to review the decision, therefore the pharmaceutical company appealed to the United States Supreme Court.⁸³ The subsequent petition was denied, leaving the decision about generic drug liability to the FDA.⁸⁴ The Supreme Court's denial of the petition to hear this case may pave the way for similar failure to warn claims to be brought against generic drug makers in state court.⁸⁵

⁷⁷ Silverman, Ed. *Lawmakers Ask White House to Review FDA Rule for Generic Label Changes*, PHARMALOT (Sept. 2, 2014), <http://blogs.wsj.com/pharmalot/2014/06/26/lawmakers-ask-white-house-to-review-fda-rule-for-generic-label-changes/>.

⁷⁸ *Teva Pharmaceuticals USA, Inc. v. Superior Court*, 217 Cal. App. 4th 96 (Cal. App. 4th Dist. 2013).

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ Silverman, Ed. *Supreme Court Declines to Review Case About Generic Labeling*. (Jan. 21, 2015). PHARMALOT, <http://blogs.wsj.com/pharmalot/2015/01/21/supreme-court-declines-to-review-case-about-generic-labeling/>.

⁸² *Id.*

⁸³ *Id.*

⁸⁴ *Id.* See also *Teva Pharm. USA, Inc. v. Superior Court*, 2015 U.S. LEXIS 687, 1 (U.S. Jan. 20, 2015).

⁸⁵ Kang, Y. Peter, *High Court Lets Teva Drug Labeling Suit Go Ahead*, LAW 360 (January 20, 2015), <http://www.law360.com/articles/612895/high-court-lets-teva-drug-labeling-suit-go-ahead>.

Similarly, the Alabama Supreme Court recently upheld a suit against brand name manufacturer for damages caused by the generic form under the concept of “innovator liability.”⁸⁶ Here, the court found brand drugs could be liable because the generic manufacturers relied on the warnings and labels of the brand drug.⁸⁷ The court relied on the holding in *PLIVA*, finding that the federal regulatory scheme made it foreseeable that the brand-name drug owed the generic version a duty of care.⁸⁸ The pharmaceutical industry fears that this precedent could cause a damaging trend throughout the U.S. economy.⁸⁹

D. Proposed FDA Regulation

Under the current federal regulations, a generic drug manufacturer may only use the CBE-0 supplement process to update its product labeling to conform to the approved safety label for the similar brand-name drug.⁹⁰ A generic drug manufacturer may not independently file a CBE-0 supplement to the FDA in light of newly acquired safety information or unilaterally change label its product’s label to add information that is different from the brand-name drug’s label.⁹¹

On November 13, 2013, the FDA proposed to add 21 C.F.R. 317.70(c) (8), which amends the current regulations and procedures that govern the ability to update and change generic drug safety labels.⁹² This proposed rule would allow generic drug manufacturers to independently

⁸⁶ See *Weeks v. Wyeth, Inc.*, No. 1101397, slip op. (Ala. Aug. 15, 2014).

⁸⁷ James W. Huston, Erin M. Bosman, and Julie Y. Park. *Weeks II: Innovator Liability Finds a Sweet Home in Alabama*, CLIENT ALERT (August 20, 2014), <http://www.mofo.com/~-/media/files/clientalert/2014/08/140820weeksIIInnovatorliability.pdf>

⁸⁸ *Id.*

⁸⁹ *The Threat of ‘Innovator Liability’*, WALL ST. J. (March 13, 2013), available at <http://www.wsj.com/articles/SB10001424127887323628804578346231780434760>

⁹⁰ See 21 U.S.C. 355(j) (1)-(2).

⁹¹ *Id.*

⁹² *Supra* note 26.

submit CBE-0 supplements to update labels in light of newly acquired safety information, regardless of whether this information may differ from the warnings on the brand name drug.⁹³ The generic manufacturer would be able to distribute updated safety labels after submitting a “changes being effected” (CBE-0) supplement to the FDA, as well as safety information supporting the change.⁹⁴ The CBE-0 will also notify the maker of the listed drug of the newly acquired safety information.⁹⁵

To make updated safety information readily available to the public and to avoid confusion, the FDA proposed to establish a webpage where the FDA will post new safety information acquired from the CBE-0 supplements.⁹⁶

This proposed rule would allow a generic drug to display a label that is temporarily inconsistent with the labels of the listed drug.⁹⁷ The FDA would then evaluate whether the change is justified and make a decision on the generic and listed drug change at the same time, and as a result, both drugs will have the same FDA approved label.⁹⁸ After the FDA has approved the safety label change, there will be a thirty day time frame in which all drug manufacturers of the “same” drug will have to submit a CBE-0 supplement with conforming label changes.⁹⁹

The amended regulations would also permit generic drugs which no longer have a brand name counterpart to update their own labels. Under current regulations, there is no technique to

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Id.*

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ Press Release, U.S. Food and Drug Administration, FDA Takes Action To Speed Safety Information Updates on Generic Drugs (Nov. 8, 2013) <http://fda.gov/newsevents/newsroom/pressannouncements/ucm374171.htm>

⁹⁹ *Supra* note 22.

accomplish such label change, and therefore, these drugs are being sold on the market with potentially incorrect or out-of-date safety information.¹⁰⁰ The FDA estimates approximately 420 drugs are sold only in the generic form, and the listed drug is no longer manufactured.¹⁰¹ Current FDA regulations also prohibit a generic drug manufacturer from sending a “Dear Doctor” letter which would inform physicians of updated and new safety warning information.¹⁰²

Part III: Reexamining the Current FDA Regulations to Permit Generic Drug Manufacturers to Update Safety Labels

FDA-approved drug labeling provides patients with essential information needed for the safe and effective use of a drug, and reflects the FDA’s findings of the safety and effectiveness under the labeled conditions of use.¹⁰³ Scholars argue that “[t]he primary purpose of labeling for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors.”¹⁰⁴ This safety information is used by practitioners and patients to make decisions about prescription drugs by weighing the stated risks against the benefits.¹⁰⁵

As of 2010, nearly 90% of pharmaceuticals in the United States are filled with a generic brand despite the availability of a substitute.¹⁰⁶ Despite the changes in the market, and the

¹⁰⁰ Carlson, *supra* note 8.

¹⁰¹ Zieve, Allison. *Guaranteeing Patient Safety*, U.S. NEWS (Sept. 22, 2014), <http://www.usnews.com/opinion/articles/2014/03/27/fdas-generic-drug-labeling-proposal-guarantees-patient-safety>

¹⁰² Boyd, *supra* note 55.

¹⁰³ *Supra* note 23.

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ HHS, *ASPE Issue Brief: Expanding the Use of Generic Drugs*, (Sept. 22, 2014), available at <http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.shtml>

evolution of the generic drug industry, the regulations concerning generic labeling have remained largely unchanged.¹⁰⁷

Generic drug makers may not always be able to quickly inform consumers of updated safety information, because they are not able to act under the same authority as their brand name counterparts.¹⁰⁸ Generic drugs must maintain an identical label to their brand-name substitutes, and are only required to update safety labels when the brand name has filed a CBE Supplement with the FDA and the change has been approved.¹⁰⁹

A. Public Policy Favors Informing Patients and Physicians of Changes in Drug Safety Information

The side effects and risks of taking a particular drug may not come to light until after the drug has been approved by the FDA.¹¹⁰ Therefore, both brand name and generic makers are required to have written procedures for the review, surveillance and reporting of adverse drug information, and any “serious and unexpected” drug experiences to the FDA.¹¹¹ Information obtained from any source, foreign or domestic, or any type of post-marketing study or investigation must be reviewed.¹¹² Both brand-name and generic manufacturers must comply with postmarketing reports by submitting an annual report to the FDA including a summary of information that may affect the drug’s safety, effectiveness, or labeling, as well as a description of the actions taken in response to the new information and proposed revisions to the safety labels.¹¹³

¹⁰⁷ Wolfe, Sidney M, Allison M. Zieve & Brian Wolfman. Citizen Petition (Aug. 29, 2011).

¹⁰⁸ Silverman, *supra* note 12.

¹⁰⁹ *Supra* note 23.

¹¹⁰ Boyd, *supra* note 55.

¹¹¹ *Supra* note 33.

¹¹² *Supra* note 23.

¹¹³ *Id.*

The Supreme Court ruling in *PLIVA* sparked the concern that generic labels are not sufficient to warn consumers of the risks associated with medications.¹¹⁴ Public policy favors informing health care practitioners and patients of safety information regarding the prescription medications. The public will benefit as a result of manufacturers updating drug safety labels in response to newly acquired safety information.¹¹⁵ Allison Zieve, head of the litigation group at Public Citizen, commented “[n]o drug is safe in all situations. A drug is safe when used in accordance with labeling that accurately reflects the known risks. The sooner generic drug companies are allowed to make safety updates, the better for public health.”¹¹⁶ The public is harmed when a regulatory delay allows a safety gap and relevant information is not readily available to the affected parties.¹¹⁷ The ability to update safety information ensures that patients have the most recent and reliable information about their medications, and can make an informed choice on whether to take a prescribed drug.

The proposed amendments to current FDA regulation will permit generic drug makers to update product labeling to “reflect data obtained through post-market surveillance.”¹¹⁸ Although the proposed amendment does not require generic manufactures to conduct new clinical tests, it will allow the manufacturers to inexpensively update labels when adverse information is received and investigated while keeping prices lower than brand-name counterparts.¹¹⁹ Some argue prices will increase due to the liability generic drug makers would face.¹²⁰ However,

¹¹⁴ Silverman, Ed. *FDA Delays Final Rule on Allowing Generic Drug Makers to Update Labels*, PHARMALOT, (Nov. 18, 2014), <http://blogs.wsj.com/pharmalot/2014/11/18/fda-delays-final-rule-on-allowing-generic-drug-makers-to-update-labels/>.

¹¹⁵ Woodcock, *supra* note 15.

¹¹⁶ Silverman, *supra* note 12 (statement of Allison Zieve, Public Citizen)

¹¹⁷ *Id.*

¹¹⁸ *Supra* note 13.

¹¹⁹ *See generally* note 23.

¹²⁰ Clarke, Toni. *FDA defends generic drug label proposal at U.S. House hearing*. (April 1, 2014), REUTERS, <http://www.reuters.com/article/2014/04/01/genericdrugs-idUSL1N0MT1IV20140401>.

proponents believe generic drug makers will not face an increase in litigation because lawsuits would be less likely to occur when generic drugs are able to update safety information, preventing injury from occurring altogether.¹²¹ The FDA states the proposed regulation will “provide incentive to generic drug companies to actively participate with the FDA in ensuring the timeliness, accuracy and completeness of drug safety labeling.”¹²²

“This proposal will help equip health care providers and consumers who depend on generic drugs with the best possible information to avoid adverse outcomes.”¹²³ The public will benefit because both brand-name and generic drug makers will have the obligation to give doctors and patients the information necessary to avoid injuries.¹²⁴ Through this amendment, the FDA will not only be able to preserve the principal of “sameness” between brand-name and generic drugs, but will also allow patients to have better information of a drug’s potential risks and benefits, regardless of the manufacturer.¹²⁵

Many opponents of the regulations claim that the time period where labels may differ will cause confusion and lead to over-warning.¹²⁶ However, under the current regulations when a brand-name drug has a safety label update, it can take several months before the generic drug manufacturers updates their labels with the new warnings.¹²⁷ Also, brand-name drugs have had

¹²¹ *Id.*

¹²² Neger, Peter C., *FDA Proposes New Change to Generic Labeling Rule*, (Nov. 13, 2013), http://www.martindale.com/products-liability-law/article_Bingham-McCutchen-LLP_2028576.htm

¹²³ Statement of Senator Matthew Cartwright, Press Release, U.S. Senate Committee on Health, Education, Labor, & Pensions, Harkin Welcomes FDA’s Release of Proposed Rules to Protect Consumers Using Generic Drugs (Nov. 8, 2013) available at <http://www.help.senate.gov/newsroom/press/release/?id=fdadb26d-2999-4a09-9766-a2a2f7546701>.

¹²⁴ Press Release, U.S. Senate Committee on Health, Education, Labor, & Pensions, Harkin Welcomes FDA’s Release of Proposed Rules to Protect Consumers Using Generic Drugs (Nov. 8, 2013) available at <http://www.help.senate.gov/newsroom/press/release/?id=fdadb26d-2999-4a09-9766-a2a2f7546701>.

¹²⁵ *Id.*

¹²⁶ Zieve, *supra* note 101.

¹²⁷ *Id.*

the ability to update their own safety labels for over thirty years, and there has never been a problem with over warning of safety information.¹²⁸

The confusion concerning the temporary differences in brand and generic labels will be outweighed by the benefit to public health.¹²⁹ Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research stated “It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for change to the labeling by the application holder for the corresponding brand drug, as well as other generic drug application holders.”¹³⁰ Therefore, it can be assumed when new safety information is acquired, all manufacturers will apply to change the label, reducing the amount of differing labels even before the FDA has approved the change. Further, the FDA will maintain a website tracking CBE-0 supplements so health care providers and patients will have access to the newest changes and updates. Once the FDA approves a CBE-0 supplement, it will continue to be posted on the site, and a thirty-day timeframe will be established for drug manufacturers to submit a CBE-0 supplement conforming to the label change.¹³¹ This will cut down the amount of time differing labels will be available on the market.¹³² Under the FD&C Act the FDA is authorized to “require and, if necessary [order] labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug.”¹³³ Therefore, the FDA can implement a rule allowing generic drugs to independently update warning labels, ensuring the

¹²⁸ *Id.*

¹²⁹ *Id.*

¹³⁰ Woodcock, *supra* note 15.

¹³¹ *Supra* note 23.

¹³² *Id.*

¹³³ U.S. Department of Health and Human Services, Guidance for Industry, Safety Labeling Changes- Implementation of Section 505(o)(4) of the FD&C Act, (July, 2013), *available at* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>.

newest warnings are available to consumers regardless of whether they take brand name or generic medication.

Senator Henry Waxman, co-author of the 1984 Hatch-Waxman Act, argued that allowing generic drugs to update their labels will ease customers' concerns about the danger of taking generic drugs because they will be aware of the latest risks and safety information. Waxman further argued it will aid in preventing consumers from believing generic drugs are not as safe as brand name drugs because generics will have more incentive to warn consumers about safety issues and will be able to get the information out to consumers.¹³⁴ Generic drug manufactures have already proven that generic drugs are equally as safe as the brand-name counterpart and the FDA has agreed.¹³⁵ Gary Beuhler, Director of the FDA's office of Generic Drugs argued "[m]ost people believe that if something costs more, it has to be better quality. In the case of generic drugs, this is not true. The standards for quality are the same for brand name and generic products."¹³⁶

As generic drugs' market shares increase, brand name drugs lose incentive to engage in safety monitoring.¹³⁷ Dr. Woodcock further argued "[t]he FDA cannot monitor all post-approval data by itself, drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share."¹³⁸ Because the generic drug has the majority of the market share, they will probably receive the

¹³⁴ Devaney, Tim. *FDA Raises Safety Measure for Generic Drugs*. The Hill, (April 1, 2014), <http://thehill.com/regulation/healthcare/202383-fda-raises-safety-measures-for-generic-drugs>

¹³⁵ FDA Ensures Equivalence of Generic Drugs, U.S. Food and Drug Administration, (August, 2002), <http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm134444.htm> (*quoting* Gary Beuhler, Director of FDA's Office of Generic Drugs).

¹³⁶ *Id.*

¹³⁷ *Supra* note 33.

¹³⁸ Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling, Association of American Physicians and Surgeons, (April 3, 2014), http://www.aapsonline.org/index.php/site/article/examining_concerns_regarding_fdas_proposed_changes_to_generic_drug_labeling

most reports concerning risks and adverse experiences using the drug.¹³⁹ Generic manufacturers therefore may be in a better position to update product safety labels because they serve a larger amount of the population.¹⁴⁰ Under the current system, the generic manufacturers cannot update safety information until the brand-name takes action.¹⁴¹

Allowing generic drug manufacturers to independently update product safety labels in light of newly acquired safety information will be a great benefit to public health by increasing patient safety and awareness, while keeping costs and confusion at a minimum.

B. Generic Drugs Will Continue to be an Affordable Alternative to Brand-Name Prescriptions

Generic drugs are more affordable because manufacturers do not need to spend money on costly clinical trials. Even if generics had more responsibility under the proposed regulation, the savings would still be apparent.¹⁴² The proposed rule would assist in keeping liability costs down by preventing injuries from occurring in the first place through efficient safety label updates.¹⁴³

Currently, generic drugs are shielded from liability because they cannot update their labels. If a generic drug maker becomes aware of a risk, they cannot change safety labels unless the brand name does so.

Critics of the proposed regulation fear that allowing generic drug makers to update their product safety labels will open them up to failure-to-warn lawsuits.¹⁴⁴ However, if the injuries

¹³⁹ *Id.*

¹⁴⁰ *Id.*

¹⁴¹ *See* 78 Fed. Reg. 67985

¹⁴² Boyd, *supra* note 55.

¹⁴³ Zieve, *supra* note 101.

¹⁴⁴ Friedman, *supra* note 17.

had never occurred, there would be no law suit.¹⁴⁵ Allison Zieve of Public Citizen testified in front of the House of Representatives Subcommittee on Health:

Because immunizing the companies from liability does not make the injured patients' costs go away. The medical expenses and lost wages from lost work time still exist; they are carried by the patients, health insurers, and taxpayers, through Medicare or Medicaid. Because the proposed rule will give generic manufacturers the tools and incentive to update safety labeling, any costs of the rule should be offset by cost savings—savings in medical care for the patients who will not be injured because physicians and patients are armed with updated labeling about safety risks.¹⁴⁶

Critics also fear that generic may over-warn to avoid liability. However, proponents have noted since the ruling in *Wyeth* there has not been a surge in CBE-0 supplements to update brand-name labels, therefore there should not be a worry for over warning by generic drug makers.¹⁴⁷

According to the FDA, "the main reason generic drug companies can market their drugs at lower prices is that they don't face the same development costs as brand-name companies."¹⁴⁸ Generic drugs are approved through an expedited process, and are permitted to skip costly clinical trials provided that the drug is the "same" and the "bioequivalent" of its brand-name counterpart.¹⁴⁹ The proposed regulation does not place any new requirements for generic drugs to undergo separate clinical trials and testing, therefore the costs to consumers should remain low.¹⁵⁰ Allison Zieve stated "[g]eneric competition [also] helps keep the cost of drugs down . . .

¹⁴⁵ *Id.*

¹⁴⁶ *Examining Concerns Regarding FDA's Proposed Changes to Drug Labeling: Hearing Before the Comm. On Energy and Commerce, S. Comm. Of Health*, (statement of Allison Zieve, Director, Public Citizen Litigation Group).

¹⁴⁷ Boyd, *supra* note 55 at 1543.

¹⁴⁸ Greater Access to Generic Drugs, U.S. FDA (Jan. 2006), <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143545.htm>

¹⁴⁹ Neas, *supra* note 4.

¹⁵⁰ *See generally*, *supra* note 97.

it also encourages the research based drug companies to keep finding new and better medicines that have patent protection.”¹⁵¹

An estimate published by the consulting firm Matrix Global Advisors stated the proposed rule would lead to approximately a 5% annual increase in spending on generic drugs.¹⁵² The FDA has examined the economic impacts of the proposed regulation and has determined:

the proposed rule would only impose new burdens on small generic drug manufacturers who submit CBE-0 supplements for safety-related labeling changes. The FDA believes the impact will not be significant due to the low-cost of submission, and the uncertainty of the amount of supplements that may be filed.¹⁵³

C. Allowing Generic Drug Makers to Update Product Safety Labels will Provide a Means for Generic Drugs which no Longer have a Brand Name Counterpart to Make Safety Updates

The FDA estimates there is approximately 420 drugs that are sold only in the generic form.¹⁵⁴ The Generic Pharmaceuticals Association states that number is even larger, estimating that about 45% of generic drugs have no brand-name counterpart.¹⁵⁵ There is a gap in the current regulatory system for generic drugs whose brand-name drug counterpart is no longer sold on the market. Since a brand name drug is only permitted to update safety warnings on product labels, the generic drugs that no longer have a brand-name counterpart are left without a means of updating safety label information.¹⁵⁶ Currently, there are no clear and efficient methods to

¹⁵¹ *Supra* note 97.

¹⁵² Carlson, *supra* note 8.

¹⁵³ *Supra* note 18.

¹⁵⁴ Zieve, *supra* note 101.

¹⁵⁵ *Id.*

¹⁵⁶ Boyd, *supra* note 55.

disseminate information to health care providers as well as the public about newly discovered safety risks.¹⁵⁷

This is concerning because serious drug risks may not be identified until after the generic drug enters the market, and several generic drugs no longer have a corresponding brand-name drug on the market.¹⁵⁸ Without a corresponding brand-name drug, there are no available resources to conduct on-going investigations as to the safety of the drug.¹⁵⁹ Therefore, drugs that are only available in generic form are not being continuously monitored and investigated, and there is no way to update the drug's label if new safety information were to come to their attention.

Part IV: Conclusion

The FDA has acknowledged the growth of the generic pharmaceutical industry, and its impact on the United States' health industry. Today, generic drugs fill almost 90% of all pharmaceuticals in the United States, yet consume only 27% of total drug spending, resulting in huge savings to American consumers every year.¹⁶⁰

The Hatch-Waxman Act of 1984 allowed for generic drugs to be approved through an abbreviated process, provided the generic drug was the "same" in ingredients, dosage, and administration, and was the "bioequivalent" of the brand-name drug.¹⁶¹ The enactment led to a greater number of generic drug approvals, and millions of dollars of savings in drug costs to American consumers.¹⁶²

¹⁵⁷ Carlson, *supra* note 8.

¹⁵⁸ *Id.*

¹⁵⁹ *Id.*

¹⁶⁰ Neas, *supra* note 4.

¹⁶¹ Wolfman, *supra* note 18.

¹⁶² *Id.*

The FDASIA and GDUFA were enacted in 2012 in response to the emerging generic drug industry. The GDUFA was enacted to increase safety and accessibility of generic drugs, and provide transparency by inspecting all generic drug facilities.¹⁶³ The Act was designed to expedite the approval process of generic drugs, and as a result, cut down the backlog of pending approvals.¹⁶⁴ As generic drugs continue to take an increasing amount of market share, the government has responded by imposing similar burdens and benefits on generics as brand name drugs through GDUFA. Allowing generic drugs to file CBE-0 changes and update labels would conform to this emerging trend.

The proposed regulation to permit generic drug manufacturers to update their safety labels without FDA approval, and independent of the brand-name drug's label will result in an increase of safety information that is beneficial to public health. Patients and physicians will be up to date with the newest safety information concerning generic drugs, which are used by the majority of Americans today.

Although this may create temporary differences between generic and brand-name drug labels, it will increase patient safety overall. Allowing generic drug manufacturers to independently update safety labels will also encourage them to monitor and research the safety of marketed drugs. It may also increase the quality of the drugs being manufactured by creating liability for generic products.

Updating the FDA's current regulations will also create an opportunity for generic drugs that no longer have a brand-name counterpart to keep patients up-to-date on the newest safety

¹⁶³ *Supra* note 24.

¹⁶⁴ Roth, Gil Y. *Generic Manufacturing: GDUFA & CMOs*, CONTRACT PHARMA, (NOV. 12, 2014), http://www.contractpharma.com/issues/2013-03/view_features/generic-manufacturing-gdufa-cmos/

information, and provide a consistent method for updating safety labels for all drugs and prescriptions in the United States.